Vascular Access Surveillance With Angioplasty: A Halfway Technology?

The role of access surveillance combined with angioplasty to achieve the goal of reducing vascular access thrombosis and prolonging access survival in hemodialysis patients.

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Vascular access dysfunction remains a major cause of morbidity and mortality in patients with end-stage renal disease. The vascular access circuit, composed of the inflow artery, the outflow vein, and the conduit that directly connects the two, begins at the heart and returns to the heart. An understanding of vascular access hemodynamics is important in order to interpret the different methods used to detect vascular access dysfunction. The primary cause of vascular access failure is thrombosis caused by the development of neointimal hyperplasia. The development of neointimal hyperplasia often leads to a stenosis within the vascular access circuit and may lead to thrombosis.

Observational studies have shown a benefit with surveillance when combined with preemptive angioplasty, whereas most randomized controlled trials have failed to demonstrate such a benefit. This article examines the role of access surveillance combined with angioplasty in achieving the goal of reducing vascular access thrombosis and prolonging access survival in hemodialysis patients.

VASCULAR ACCESS HEMODYNAMICS

An understanding of vascular access hemodynamics is fundamental in order to interpret the different methods used as surveillance tests for vascular access dysfunction. The vascular access circuit, starting at the heart and returning to the heart, is composed of the inflow artery, the conduit, and the outflow vein. The inflow artery must be capable of dilating and thereby increasing flow in response to the creation of a direct conduit to the outflow vein. This vein must then be able to adjust compliance as a result of the change in flow through the conduit. The heart must also be able to respond to this newly created circuit by increasing cardiac work.

A functioning upper arm autogenous fistula based on the radial artery as the inflow typically has a blood flow between 700 and 1,100 mL/min. Upper arm fistulas with brachial artery inflow normally have much higher flows of 1,100 to 2,000 mL/min.[1-3] Brachial cephalic fistulas may have even higher flows of 3 L/min or more and result in cardiac high-output failure.[4,5] Blood flow in normally functioning grafts also reflects the inflow artery, with radial artery-based forearm straight grafts having flows on the order of 600 to 800 mL/ min, forearm loop grafts with flows of 1,000 mL/min, and 1,000 to 2,000 mL/min or more in upper arm grafts with the brachial artery as the inflow artery.[6]

Although the range of blood flows is similar in fistulas and grafts, the relationship between pressure and flow within the dialysis conduit is different. Given that a graft has less compliance and only one outflow vein anastomosis, most of the inflow artery pressure is dissipated across the two anastomoses, making the measured pressures higher compared to an autogenous fistula.[7] Thus, a graft outflow stenosis will result in an increase in intragraft pressure and a corresponding decrease in graft blood flow.

Intra-access pressure in an autogenous fistula is lower compared to intra-access pressure in a polytetrafluoroethylene graft.[8] This intra-access pressure difference appears to be secondary to lower inherent resistance and possibly to the presence of collateral veins. Most of the pressure drop for a native fistula is across the arterial anastomosis.[7] The development of an outflow stenosis in a native fistula may not result in a decrease in blood flow with a proportionate increase in intra-access pressure.

This relationship is important if pressure measurements are used to detect stenosis in native fistulas.[9] It is important to note that there are no contemporary data on the intra-access pressure relationship to blood flow for transposed upper arm fistulas, which is likely to be similar to the intra-access pressure and blood flow relationship of grafts.

Vascular access blood flow may be measured by several different methods. The ultrasound dilution technique (Transonic Systems Inc., Ithaca, NY) has been extensively validated as a vascular access blood flow measurement method.[10,11] This method, as it is currently used, minimizes operator error, provides a direct measurement of venous line blood flow, and is recognized as the gold standard.[12] Other blood flow measurement methods include electrical impedance, optical properties, temperature, and the glucose pump test.

VASCULAR ACCESS SURVEILLANCE

Observational Studies

Although venous stenosis had been recognized as a frequent cause of access thrombosis before 1989,[13] the pivotal study by Schwab et al was the first to use a systematic approach of measuring and correlating elevated venous dialysis pressures with the presence of a significant venous stenosis.[14] The treated group had a thrombosis rate of 0.15 episodes per patient-year, similar to the patients without elevated venous pressures. This group was then compared to retrospective data obtained from chart reviews of patients from a period before the study. These retrospectively reviewed patients had a thrombosis rate of 0.6 episodes per patient-year. Based on these results, the investigators concluded that "elevated venous dialysis pressure is a reliable method of detecting fistula stenoses and that the elective treatment of these stenoses significantly decreases fistula thrombosis and fistula loss."[14]

For the next 7 years, there were a few studies using access pressure elevation or duplex ultrasound as surveillance techniques to identify vascular accesses at risk for thrombosis. The study by May et al was the first to compare several different surveillance techniques examining the short-term (3-month) thrombosis rate prospectively during two time periods. This observational study found that access blood flow was a reliable indicator of the relative risk of thrombosis.[15]

In a further observational study by the same group of investigators from Vanderbilt, a time-dependent decrease in dialysis access flow was found to be predictive of an increased risk of thrombosis. Ultrasound dilution flow of grafts and fistulas was measured every 6 months for a study period of 18 months. However, 10 dialysis vascular accesses had a thrombosis before a second blood flow measurement and were not included in the study. Furthermore, four patients who had two different accesses in the study period were included. The investigators concluded that a > 15% decrease in dialysis vascular access blood flow was associated with a high risk of thrombosis.[16]

The basis of the Kidney Dialysis Outcomes Quality Initiative (KDOQI) recommendations in 2000 were based on these and other observational studies. Specifically, that "prospective surveillance of grafts for hemodynamically significant stenosis, when combined with correction, improves patency and decreases the incidence of thrombosis." The KDOQI recommendations also defined the differences between monitoring and surveillance. Although the words "monitoring" and "surveillance" are frequently used interchangeably, they have distinctly different meanings related to vascular access. *Monitoring* is "the examination and evaluation of the vascular access by means of physical examination to detect physical signs that suggest the presence of dysfunction." *Surveillance* is "the periodic evaluation of the vascular access by using tests that may involve special instrumentation and for which an abnormal test result suggests the presence of dysfunction."[12] The recommendations would become clinical performance measurements and most recently have become incorporated into the Centers for Medicare & Medicaid Services updated Conditions of Coverage that appear to mandate surveillance of vascular access.[17]

These observational studies supported the conclusion that surveillance could identify a dialysis vascular access with a significant stenosis; however, the accurate prediction of access thrombosis is the ultimate goal of any surveillance method. In a prospective study, McDougal and Agarwal studied both venous pressure and graft flow surveillance for predicting graft thrombosis. They concluded that a single static or dynamic venous pressure could not predict graft thrombosis. This study did find an increased risk of graft thrombosis in grafts with decreased access blood flow when a risk factor analysis was used, similar to the study by May et al. These investigators found that dialysis access blood flow failed as a useful clinical test when receiver-operating characteristic (ROC) curves were used to evaluate the capability of access blood flow to predict graft thrombosis because of the high false-positive rate.[18]

ROC curve analysis is a plot of sensitivity or true-positive rate versus the false-positive rate (1-specificity). ROC curve analysis is the more relevant test of diagnostic decision making. Paulson and colleagues had reached a similar conclusion that single or repeated graft blood flow surveillance measurements fail to predict graft thrombosis based on ROC curve analysis.[19,20]

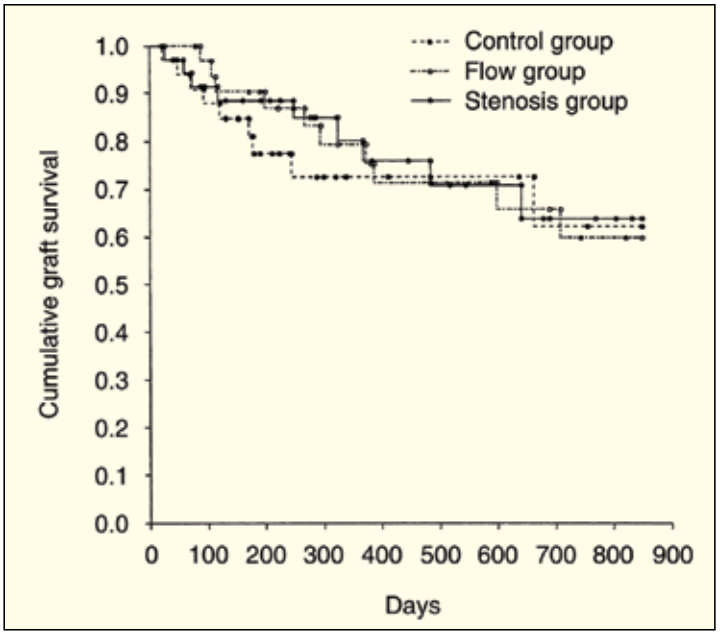

Figure 1. Kaplan-Meier comparison of cumulative graft survival. Reprinted from Ram SJ et al. A randomized controlled trial of blood flow and stenosis surveillance of hemodialysis grafts. Kidney Int. 2003;64:272–280.[21]

In a similarly designed prospective study, Dember and colleagues used monthly static venous pressure measurements to predict graft thrombosis. Using ROC curve analysis, these investigators found that static venous pressure measurement was a poor predictor of subsequent thrombosis. They found that different thresholds for referring patients for potential preemptive intervention would lead to many patients being misclassified—that is, many patients would undergo an unnecessary invasive intervention, and others would fail to have a necessary intervention to prevent thrombosis. They concluded, "Not all venous anastomosis stenoses lead to graft thrombosis." They further concluded, "There is currently no method to discriminate between nonproblematic stenoses and those that will result in thrombosis."[22] These surveillance methods, which are good at identifying grafts with stenoses, are poor at predicting graft thrombosis. The consequence of this is that many patients may undergo unnecessary and expensive procedures.

Randomized Controlled Trials

Randomized controlled trials (RCTs) are considered to be the most reliable form of scientific evidence because they reduce spurious causality and bias.[23] RCTs are therefore considered as providing the highest level of evidence (level I) in the development of evidence-based clinical decision-making guidelines. Lumsden and coworkers completed the first RCT addressing this important clinical question by first identifying patients who had graft stenoses > 50% detected by duplex ultrasound surveillance and confirmed by angiography. They were then randomized to either percutaneous transluminal angioplasty (PTA) or to a control group that received no intervention. The study endpoints were graft thrombosis, graft dysfunction that prevented dialysis, and six or more PTA procedures within 18 months. Six-month patency rates were 69% ± 7% in the treatment group and 70% ± 7% in the control group, with 12-month patency rates for treatment and control groups of 51% ± 6% and 47% ± 4%, respectively. There was no significant difference between these two groups. Lumsden concluded that PTA to treat all grafts with stenoses > 50% does not result in prolonged patency.[24]

The nephrology community overlooked the Lumsden study, perhaps because it was published the same year that the KDOQI Vascular Access Guidelines were published; these guidelines enthusiastically endorsed surveillance based on the multitude of observational studies that demonstrated a significant reduction in the frequency of graft thrombosis.[12] An additional factor may be that publication in the *Journal of Vascular Surgery* missed the audience, namely nephrologists, that needed to be aware of the study's conclusions.

The next RCT to address this issue was not published until 6 years later in 2003. Ram and colleagues randomly assigned 101 patients with grafts to one of two surveillance groups (blood access flow or duplex ultrasound) or to a control group following the CONSORT statement for documenting RCTs. All patients had monthly dialysis access flow measurements by ultrasound dilution (Transonic) and every 3-month stenosis measurement by duplex ultrasound. Referral for angiography was based on assigned randomization group: control group referred only based on clinical criteria, flow group only if access flow was under 600 mL/min or clinical criteria, and stenosis group only if a stenosis of > 50% (duplex ultrasound measurement) or clinical criteria. In all groups, PTA was performed for a stenosis of 50% or greater on angiography. The preemptive PTA rate was lowest in the control group and highest in the stenosis group. The stenosis group had the highest rate of preemptive angioplasty, and this was associated with a lower thrombosis rate. There were no significant differences in survival.

Possible reasons for the failure of surveillance when coupled with preemptive angioplasty to improve graft

TABLE 1. REASONS FOR FAILURE OF SURVEILLANCE TO IMPROVE GRAFT SURVIVAL

- Timely intervention may reduce thrombosis rates without ultimately influencing graft survival.
- Surveillance may provide an improvement in graft survival that is modest at best and requires a larger sample size to detect.
- Monthly blood flow measurements do not accurately detect progressive stenosis.
- Quarterly stenosis measurements are not sufficiently frequent to detect progressive stenosis in many grafts.
- Unnecessary or premature PTA may adversely affect graft survival.
- Aggressive clinical monitoring may provide most or all of the benefit provided by preemptive intervention.
- The benefit of surveillance may be limited to a subset of grafts.

Reprinted from Ram SJ et al. A randomized controlled trial of blood flow and stenosis surveillance of hemodialysis grafts. Kidney Int. 2003;64:272–280.[21]

survival are listed in Table 1. Although stenosis surveillance (duplex ultrasound measurement) did reduce thrombosis, graft survival was not prolonged compared to clinical monitoring in the control group (Figure 1). Flow surveillance failed to reduce thrombosis or prolong graft survival when compared to the clinical monitoring in the control group. The investigators point out that clinical monitoring may provide "most of the benefit that may follow from preemptive intervention."[21]

Moist et al compared monthly access monitoring, which included dynamic venous pressure, to access flow surveillance by ultrasound dilution and dynamic venous pressure. Patients were randomized to the control group or to the access flow surveillance group. The graft thrombosis rate per patient-year at risk was not different between the control group and the access flow surveillance group. There were more interventions in the access flow surveillance group versus the control group. Importantly, this study showed no difference in the time to graft thrombosis or time to graft abandonment between the control group and the access flow surveillance group.[25]

Two additional RCTs arrived at the same conclusion that surveillance coupled with preemptive angioplasty did not result in prolonged graft survival compared to a control group. Dember et al assessed monthly static venous pressure measurements as the surveillance method. During the 3.5-year study period, the same number of patients in the intervention and control groups had their accesses abandoned due to an inability to restore patency by radiologic or surgical intervention. Time to access abandonment was not different between groups. Although static venous pressure surveillance reduced the incidence of thrombosis, surveillance failed to prolong graft survival compared to the control group.[26]

Robbin and colleagues used duplex ultrasound surveillance in addition to clinical monitoring and compared it to clinical monitoring alone. In the duplex ultrasound surveillance group, 24% of patients referred for preemptive angioplasty were for clinical reasons; the remainder was referred based on the duplex ultrasound surveillance. The positive predictive value of identifying a significant stenosis using physical examination, part of the clinical monitoring arm of the study, was 80%. This was the same as the positive predictive value of duplex ultrasound.

Similar to other RCTs, they found the duplex ultrasound surveillance group had a higher frequency of preemptive graft angioplasty; however, the frequency of thrombosis was not different. The median time to graft failure and the median time to graft abandonment were similar in the two groups. The investigators concluded that routine duplex ultrasound surveillance coupled with clinical monitoring was effective at detecting graft stenosis, but the increase in preemptive angioplasties failed to translate into improved graft survival.[27]

Several surveillance techniques including static venous pressures, access flow, and duplex ultrasound are able to identify grafts with stenosis. However, currently, grafts that are at risk for thrombosis cannot be distinguished from grafts that are not destined to thrombosis. The failure to be able to make this important distinction leads to unnecessary preemptive angioplasties. The KDOQI recommendations in 2006 were changed based on these observations along with the negative results of the five RCTs. The guidelines now state: "Prospective surveillance of fistulas and grafts for hemodynamically significant stenosis, when combined with correction of the anatomic stenosis, may improve patency rates and may decrease the incidence of thrombosis."[28] Using graft surveillance to detect stenoses is a reasonable strategy only if an effective intervention is also available that provides meaningful prolongation of graft survival.

PREEMPTIVE ANGIOPLASTY

The rationale supporting preemptive angioplasty is based on the observation that patency after elective angioplasty of a stenosis in a functioning graft is considerably better than angioplasty of a thrombosed graft. Lilly et al have elucidated the clinical and radiologic predictors of graft survival after either elective angioplasty or angioplasty after thrombectomy. Stenotic grafts that were treated with preemptive angioplasty had significantly longer intervention-free survival compared to grafts that had thrombosed and underwent angioplasty. Predictors of graft survival for both preemptive angioplasty and postthrombectomy angioplasty included residual stenosis and postangioplasty intragraft to systemic systolic pressure ratio.[29]

Maya and colleagues used the same predictors as in the Lilly study, evaluating preemptive angioplasty outcomes in both grafts and fistulas. They found that for both fistulas and grafts, the degree of residual stenosis and intra-access to systemic systolic pressure ratio > 0.4 were predictors of shorter access patency after preemptive angioplasty.[30]

The effect of angioplasty on short-term blood flow has been examined in a study of both grafts and fistulas. The short-term effects, estimated at 1-week postprocedure for both grafts and fistulas, demonstrated a significant increase in blood flow. Degree of stenosis was also measured and demonstrated a significant decrease. However, there was no correlation between the change in stenosis and blood flow. Blood flow before preemptive angioplasty and the increase in blood flow after angioplasty correlated with improved long-term outcomes. However, intervention-free survival was only 25% for grafts and 50% for fistulas.[31]

Murray et al found that after preemptive angioplasty, blood flow increased almost twofold the first month after the procedure but decreased thereafter. They concluded that blood flow increased immediately after a successful preemptive angioplasty, but the effect is temporary, with the average blood flow returning to preprocedure values by 3 months.[32] Angioplasty appears to result in no more than a short-term benefit.

Although preemptive angioplasty outcomes are better than angioplasty postthrombectomy, the results remain dismal, with 6-month intervention-free patency between only 50% and 60%. Angiographic results fail to predict outcomes, and intra-access pressure to systemic systolic pressure ratios add little to identifying optimal angioplasty outcomes. In the study by van der Linden et al, multiple angioplasty procedures were required in a substantial number of grafts, and the time interval to repeat angioplasty was less with each subsequent intervention, suggesting that the treatment itself, namely angioplasty, accelerated the decline in blood flow.[31] This initial stenosis and the restenosis after angioplasty result from neointimal hyperplasia.[33]

Similar to the graft study by van der Linden et al, Chang et al found that the time to restenosis after angioplasty was shorter than the time to primary stenosis in fistulas.[34] As Diskin has pointed out: "Our procedures for reversing stenosis is the model for creating stenosis" and is "the same angioplasty procedure on healthy blood vessels that is used as a model to produce the development of intimal hyperplasia and stenosis."[35]

Arteriovenous Fistulas

Given the highly successful Fistula First Initiative (> 60% of United States patients using a fistula as of April 2013, according to FistulaFirst.org), surprisingly, there are limited surveillance studies focusing on fistulas only. There are only four RCTs, and these studies are limited at best but do suggest that surveillance decreased the risk of access thrombosis. However, in the studies that also included frequency of access abandonment, there was no significant difference in the surveillance and control groups. The primary issue with arteriovenous fistulas is failure to mature.

CONCLUSION

Dialysis vascular access surveillance using a variety of techniques including access blood flow, static venous pressure, and duplex ultrasound can identify grafts and fistulas with stenosis. However, surveillance fails to predict which grafts will develop a thrombosis. Surveillance failed to predict prolonged graft survival in RCTs. Clinical monitoring appears to provide equivalent benefit in terms of graft survival to surveillance programs when coupled with preemptive angioplasty.

Graft patency after preemptive angioplasty in a stenotic graft is significantly longer compared to angioplasty in a graft that has thrombosed. However, the benefit of preemptive angioplasty is poor, with an intervention-free 6-month patency rate of only 50% to 60%. This failure of surveillance and preemptive angioplasty may reflect other factors at play, such as lead-time bias or ineffective therapies. Indeed, the treatment of a stenotic lesion with preemptive angioplasty may induce aggressive neointimal hyperplasia. Taken together, the current use of surveillance coupled with preemptive angioplasty may decrease the thrombosis rate in fistulas, but there is currently no evidence that it prevents fistula loss; in the case of grafts, unfortunately, neither graft thrombosis nor graft survival is improved and likely leads to unnecessary and costly interventions.

As described by Lewis Thomas, vascular access surveillance combined with preemptive angioplasty is a "halfway technology."[36] This "level of technology is, by its nature, at the same time highly sophisticated and profoundly primitive." Unfortunately, it is the only approach available until we develop a genuine understanding of the pathobiology involved in the development of neointimal hyperplasia and develop solutions that eliminate it. ■

Note: Lewis Thomas, a physician, educator, and essayist who died in 1993, was invited to write regular essays in the New England Journal of Medicine*. One of his essays, entitled "The Technology of Medicine," describes three distinctly different levels of medical technology. Lewis called the first level a "nontechnology" in that this level does not alter the natural course of a disease or its outcome and is often referred to as "supportive care." Although absolutely necessary, this level is not a technology per se, because it fails to be directed at the underlying mechanism of the disease. This "nontechnology" involves both a great deal of health care provider time and significant health care costs. An example is intractable cancer or cerebral vascular strokes.*

A second level of medical technology is the "real high technology of medicine," which is the result of a "genuine understanding of disease mechanism" and, in terms of health care costs, is "relatively inexpensive, relatively simple, and relatively easy to deliver." A good example is polio. Lewis' last level was termed "halfway technology." Halfway technology "represents the kinds of things that must be done after the fact, in efforts to compensate" for the lack of understanding of the mechanisms involved in a disease process. Our current approach to vascular access dysfunction using surveillance combined with angioplasty may therefore be viewed as a halfway technology.

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