Access Monitoring Is Worthwhile and Valuable

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Abstract

During the past several years, a limited number of small clinical trials have questioned the role of surveillance in the management of vascular accesses, since the prolongation of access longevity until replacement was not altered. Although prolongation of access life span is an important endpoint, it is not the only one. Reduction in thrombotic events reduces the risks to the patient resulting from loss of access patency. The body of evidence suggests that the detection of stenosis and prevention of thrombosis are valuable. When a test indicates the likely presence of a stenosis, venography or fistulography should be used to definitely establish the presence and the degree of the stenosis. In most cases, angioplasty should be performed if the stenosis is greater than 50% by diameter. The value of routine use of any surveillance technique for detecting anatomic stenosis alone without concomitant functional assessment by measurement of access flow, venous pressure, recirculation, or other physiologic parameter has not been established. Stenotic lesions should not be repaired merely because they are present. If such correction is performed, then intra-procedural studies of access flow or intra-access pressure prior to and following percutaneous translumi-

nal angioplasty should be conducted to demonstrate a functional improvement with a 'successful' percutaneous transluminal angioplasty.

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Introduction

Hemodialysis is the most widely used mode of treatment of renal failure in the United States and Europe. Adequate vascular access for hemodialysis is the most important component determining the success or failure of dialytic therapy. A vascular access that reliably and consistently delivers a blood flow sufficient to meet the prescribed Kt/V, while at the same time has few complications, needs little maintenance, and no monitoring or surveillance, would be the ideal for every patient. Such an access does not exist; however, the autologous arteriovenous fistula (AVF) comes closest [1, 2].

Access problems are a daily occurrence in busy dialysis units. Low blood flow rates and loss of patency limit dialysis delivery, extend treatment times, and, in too many cases, result in underdialysis that leads to increased morbidity and mortality [3]. Between 1991 and 2001, the incidence of vascular access events in patients undergoing hemodialysis rose by 22% [4]. Thrombosis is the leading cause of loss of vascular access patency. Thrombosis increases health care spending [5, 6] and adversely affects quality of life [7]. Vascular access-related complications account for 15–20% of hospitalizations among end-stage

renal disease patients undergoing hemodialysis [5]. Prevention of access dysfunction by maintaining adequate flow translates into a policy of 'dialysis dose protection', whereas preventing thrombosis reduces risks to the patients and improves their quality of life. Thrombosis is associated with additional risks to the patient not presented with simple percutaneous transluminal angioplasty (PTA) [8]. One of the most common patient fears is access thrombosis.

Failure to detect access dysfunction has consequences on morbidity and mortality [3, 4]. In a recent study of 721 randomly selected patients from all 22 chronic hemodialysis units in northeast Ohio (USA), barriers found to significantly ($p < 0.001$) and independently relate to inadequate dialysis dose delivery were patient noncompliance, low dialysis prescription, catheter use, and access thrombosis [9]. Every 0.1 decrease in Kt/V was independently and significantly ($p < 0.05$) associated with 11% more hospitalizations, 12% more hospital days, and a USD 940 increase in Medicare inpatient expenditures. Vascular access-related complications accounted for 24% of all hospital admissions [10]. The reader is referred to the Kidney/Dialysis Outcomes Quality Initiative (K/DOQI) Hemodialysis Adequacy guidelines [11] for additional information on the importance of achieving the prescribed dialysis dose with regard to mortality.

K/DOQI and Vascular Access

In 1997, the National Kidney Foundation published the K/DOQI guidelines for the improvement in renal care [12]. The two major recommendations that came from the vascular access workgroup with the initial [12] and the subsequent revision in 2000 [13] were to (1) augment the construction of autologous native AVFs, and (2) detect hemodynamically significant stenosis likely to produce thrombosis of the access. The current workgroup believes that the goals still apply (guidelines to be published in spring 2006).

Through the year 2003, several analyses have shown that we have been very slow to change and have even fallen short of our own expectations in constructing AVF [14]. Although the National Vascular Access Improvement Initiative driven by the Center for Medicare and Medicaid Services and emphasizing a fistula first approach has increased the rate of construction of AVF in the USA, I am unsure whether the rate can be increased to reach a prevalence rate of 66% quality AVF by 2009, as desired by the Center for Medicare and Medicaid Services [15].

The same lack of progress applies to access surveillance. Once an access has been constructed, most dialysis centers *do not* employ a multifaceted quality assurance program to detect vascular accesses at risk for thrombosis, track access complication rates, and implement procedures that maximize access longevity. Even at centers that try, the responsibility is frequently placed into the hands of one individual. It is not feasible for any individual to manage all aspects of access care. Multidisciplinary teams must be formed at each dialysis center [16, 17] with a vascular access coordinator if possible. The lack of consensus as to 'which test is best' and the lack of investment into surveillance by large dialysis organizations has made the dynamic pressure test the choice by default [18], even though the original thresholds for referral which are still used are not appropriate in modern high-efficiency dialysis using large bore needles.

The current workgroup has developed explicit guidelines regarding which surveillance tests are best used to evaluate a given access type and when and how to intervene to reduce thrombosis and underdialysis. Surveillance/monitoring (S/M) using specific assessments must be combined with regular assessment of clinical parameters of the arteriovenous access and dialysis adequacy. Data from the clinical assessment and dialysis adequacy measurements should be collected and maintained for each patient's access and made available to all the staff. The data should be tabulated and tracked within each dialysis center as part of a Quality Assurance/Continuous Quality Improvement program. Whatever the size and composition of the team, its most important function is to work proactively to ensure the patient's delivery of the adequate dialysis dose by maintaining access function and patency.

Despite the strong position taken by the workgroup concerning the importance of access S/M, recent studies have challenged the value or efficacy of such S/M. The basic purpose of all S/M is to detect 'asymptomatic' stenoses before they are severe enough to produce inadequate dialysis or lead to thrombosis. Such stenoses are defined as being 'hemodynamically significant'. Although there is a consensus that monitoring of the access blood flow (Q_A) or pressures is useful in predicting stenosis or thrombosis [13, 14, 18, 19], several studies have reported that the use of these S/M techniques may not alter the outcome [20–22]. If early diagnosis and intervention for stenosis with angioplasty does not alter the 'life expectancy' of the access [23], what is the purpose? More intervention may increase the costs of care but not the useful duration of any given access (i.e. its useful lifespan until

replacement). Do we need to look at other methods for preventing thrombosis in our patients besides those of access longevity? Is reduction in thrombosis itself a reasonable goal? It is incumbent on us to review our methods of evaluation, placement, use, and repair of dysfunctional vascular access and evaluate what the data say.

However, in order to have a rational discussion, we must first define our terms.

Definitions

The following definitions will be used throughout this paper.

Monitoring. Physical examination (look, touch, listen) of the vascular access to detect physical signs that suggest the presence of dysfunction [24]. These basic skills have been lost at most centers in favor of technology and need to be retaught to all individuals who perform hemodialysis procedures.

Surveillance. Periodic evaluation of the vascular access by means of specialized tests that may involve special instrumentation, for which an abnormal test result suggests the presence of dysfunction. Such tests include Q_A , access resistance, intra-access pressure (P_{IA}), and access recirculation. These tests measure the adequacy of access function. Measurements such as the urea reduction ratio (URR) and Kt/V measure the effect of inadequate access function on the delivery of dialysis. Duplex Doppler ultrasound (DDU) is unique among the tests since it is not only able to measure Q_A but also visualize and quantify the severity of any stenoses present [25]. Surveillance and monitoring are complementary.

Diagnostic Testing. Specialized testing that is prompted by some abnormality or other medical indication specifically undertaken to diagnose the cause of the vascular access dysfunction. The current gold standard is angiography, but DDU can be used for this function as well [25, 26]. In most cases, the individual is sent to a radiologic center where contrast visualization can occur [27]. In some cases, intra-access angioscopy and ultrasound can be performed [28]. Magnetic resonance angiography can also be used to characterize the anatomic presence of stenosis [29–31], as well as to quantitate flow [32]. A variety of Q_A measurements are available; currently, dilution ultrasound is the ‘gold standard’.

Intervention. Performance of a procedure that dilates a stenosis, stents it, bypasses it, or resects it. The most common procedure performed for stenosis is PTA using high-pressure balloons with burst limits above 30 atm. If

Fig. 1. Flow diagram depicting a continuous quality surveillance/intervention process in which a pressure or flow technique is used, accesses with abnormality are studied, stenoses identified and corrected prior to thrombosis, and the measurement is repeated to assure that the PTA/surgical procedure was successful.

the access is thrombosed, a variety of techniques are available to remove the clot. Special devices have been developed for this procedure. Thrombolytics may or may not be used depending on the type of access.

The S/M Process

In a proper operational program, asymptomatic but hemodynamic stenoses are detected through a systematic S/M program, then referred for study, intervened upon, and checked to verify that the hemodynamics or functional abnormality has ‘improved’ (fig. 1). A functionally significant stenosis is currently defined as a reduction greater than 50% in normal vessel diameter, accompanied by hemodynamic or clinical abnormality, such as abnormal recirculation values, elevated venous pressures, decreased blood flow, swollen extremity, unexplained reduction in Kt/V , or elevated negative arterial prepump pressures that prevent increasing to acceptable blood flow [33]. This definition evolves from an analysis of hemodynamics and clinical correlation. Prospective M/S should provide the ability to salvage vascular access sites through planning, coordination of effort, and elective corrective intervention rather than through urgent procedures or replacement [34]. A number of surveillance methods are available: sequential Q_A , sequential dynamic or static pressures, recirculation measurements, physical examination, and combinations.

Fig. 2. Access pressure/mean arterial pressure ratios and Q_A of a 73-year-old diabetic male; tapered graft, 4–6 mm at the arterial (brachial artery) anastomosis increasing to 7 mm at the venous anastomosis (axillary vein). Changes in a vascular access graft over time depicting the reciprocal changes in pressure and flow until a threshold is reached at which a PTA restores the original function of the graft.

Basic Physiology/Basic Tenant for S/M

The basic tenant for vascular access monitoring and surveillance is that stenosis develops at variable intervals in the great majority of vascular accesses, and if detected and corrected, underdialysis can be minimized or avoided and the rate of thrombosis reduced. The rationale for surveillance depends on the ‘dysfunction’ hypothesis: stenosis produces graft dysfunction lowering Q_A and/or altering pressure profiles, and this dysfunction *reliably* precedes and accurately predicts thrombosis [35]. The usefulness of flow or pressure surveillance depends on the accuracy of the measurements themselves so that accurate confirmation of hemodynamic dysfunction is proven prior to correction of the stenosis. Unfortunately, both Q_A and pressure vary in patients during and, more importantly, between dialysis sessions. This makes a single measurement an inaccurate predictor of stenosis, and therefore, also of thrombosis. The only rational means to detect an evolving lesion is to perform analysis using multiple repetitive measurements so that inappropriate referrals are not made. Currently, there is very little quality assurance of ‘success’ of an intervention other than an anatomical one.

Knowledge of the ‘best function of a given access’ is crucial to the interpretation of any S/M technique. For an arteriovenous graft, this is typically shortly after the first use, since neointimal hyperplasia progressively increases

Fig. 3. Effect of graft venous outlet stenosis. Relationship between Q_A and P_{IA} in grafts. Note the inverse relationship. As venous out-flow stenosis secondary to neointimal hyperplasia develops, Q_A decreases while static pressure increases. Note that access recirculation is a very late manifestation of access dysfunction.

resistance with time. The pressure drop across the access from artery to vein is set by the mean arterial pressure minus the central venous pressure. Q_A results depend on many variables, including those of the graft diameter and the patient’s ability to augment cardiac output in response to the fistula. As shown in figure 2, use of an arterial taper to reduce Q_A and avoid ‘steal’ produces a relatively low Q_A and relatively low P_{IA} . A flow <800 and <500 ml/min occurred within 5 and 10 weeks, respectively, as neointimal hyperplasia developed. However, the best flow in this access was <900 ml/min when measured 3.5 weeks after creation. Stenosis is manifested by both a decrease in Q_A as well as progressive increases in arterial and venous segment P_{IA} . PTA is successful, but the rapidity of the initial dysfunction and the small reserve forecast repeated and frequent procedures in this access. However, the S/M approach in this marginal access is likely to differ from that of a ‘very good’ access, which is one whose initial ‘best flow’ was in excess of 1,500 ml/min when first evaluated.

As shown in figure 3, the relationship between Q_A and P_{IA} is inverse. If an outflow stenosis develops from neointimal hyperplasia and increases resistance, pressure will increase and flow decrease. An initially well-functioning graft with an Q_A approaching 2 l/min (usually in the upper arm) will manifest decreasing flow, as both the ar-

terial and venous pressure slowly increase with the development of outflow tract stenosis. Since the intimal hyperplasia process progresses variably with time, its detection requires sequential measurements of flow or pressure or both to detect a threshold at which action should be taken. The frequency of measurements depends on the rate of progression. Note that the graft thrombosis region by flow shown in the hatched area is reached long before a graft would show recirculation, and therefore, affects the delivered dose of dialysis. The relationship between flow and degree of stenosis is distinctly non-linear. Hemodynamic simulations indicate that flow decreases by less than 20% as the stenotic process grows and decreases the luminal diameter by 40–50%. Thereafter, flow decreases rapidly as the degree of stenosis increases to 80% [36]. The hyperbolic relationship between Q_A and both access pressures would be expected to occur within a given access if the outflow were the only source of stenosis. Unfortunately, this is not the case. Lesions in the inflow and within the body of the access do occur, and on average, the typical access has nearly two lesions/access locations at the time of referral [37, 38]. The lesions change the relationship between flow and pressure. As shown in figure 4, mid-graft lesions are associated with lower pressures at the venous limb, but the arterial pressure remains elevated. PTA accomplishes the same effect, increasing flow and restoring the profile 'toward' normal. With a dominant inflow lesion, both pressures would be 'low'. Stenosis at the arterial anastomosis of both grafts and fistulas causes P_{IA} to decrease. Thus, a high basal P_{IA} can be observed in the absence of stenosis when the flow delivered by a healthy artery is in excess of the initial capacitance of the venous system to accommodate to the flow. Because of these confounders due to anatomic factors and the location of stenosis, there is little, if any, correlation between a single measurement of flow and P_{IA} [39]. None would be expected.

The above considerations have two practical applications. First, it is immediately apparent that the quality and physical dimensions of the artery and vein will determine the initial access function; the major determinant of Q_A in a given patient will be determined by the capacity of the artery to dilate, its general 'health', and the patient's general cardiovascular health. In general, arteries at more distal sites have less capacity to deliver flow than more proximal sites, i.e. radial < brachial < axillary < femoral. Arteries that are calcified or affected by atherosclerosis will result in lower Q_A , whether autologous fistulas or graft. If the artery is healthy, the flow capacity will be determined by the characteristics of the vein used

Fig. 4. Depiction of the effect of the location of stenosis on hemodynamic (functional) parameters of Q_A and static pressures. Stenosis always reduced flow, but the location is important in interpreting static pressures (see text for details). PTA restores flow and normalizes the pressure profile.

in access construction. Too small a vein will limit the flow in both AVF and arteriovenous graft. Unfortunately, arterial disease is not uncommon; access inflow stenosis occurs in one third of the cases referred to interventional facilities with clinical evidence of venous stenosis or thrombosis [40]. This is much higher than the 5% rate that has been traditionally reported [41].

Second, serial measurements of pressure or flow within each patient are more valuable in detecting a stenosis than any isolated measurements of either absolute P_{IA} , normalized ratio, or Q_A . I will not discuss the various modalities available to measure Q_A or access pressures. As illustrated in figure 5 (many more pressure measurements were made than actually shown), it is important that measurements be made repeatedly and that criteria be developed for when to act with intervention. In the case illustrated, two PTAs (arrows) were performed based on an increase in the normalized systolic pressure ratio above 0.40 [42] but could have been just as easily driven by an absolute flow rate of <800 ml/min. How-

Fig. 5. An illustrative case depicting the inverse relationship between flow and static pressure ratio in a graft vascular access. VP0 = Venous pressure at zero dialyzer blood flow; BP = blood pressure.

Fig. 6. Compilation of studies that used historical controls showing the effect of S/M on thrombosis rates. Note that in each study implementation of an S/M technique reduced thrombosis rate by at least 40% and often by over half compared with the historical period. The reduction in thrombosis rate is independent of the S/M technique chosen.

ever, a criterion using a decrease in flow of 30% [43] would have led to premature PTA a year before it was necessary.

It is not clear whether Q_A measurements performed at a monthly frequency provide sufficient data stability to

make decisions. Until additional studies are performed to determine the optimal frequency, more frequent measurements are recommended.

What Are the Issues in the Efficacy/Value of S/M?

Does S/M Prevent Thrombosis? Yes

The usefulness of S/M depends on the accurate prediction of thrombosis so that stenosis can be corrected prior to thrombosis; the goal of any surveillance method is to detect access stenosis in a timely way so that appropriate correction can be undertaken prior to thrombosis. This lead time may be measured in weeks or months. A large body of evidence indicates that prospective S/M to detect stenosis reduces the rate of thrombosis, although at the expense of increased procedures [16, 42, 44–48]. As shown in figure 6, S/M reduced the thrombosis rate by 41 to 67%. Note that in the studies cited, the historic thrombosis rate ranged from 0.5 to 0.7 events per access-year at risk. The study by Schwab et al. [44] included both grafts and autologous AVF; the others analyzed only grafts. Although none of these studies were randomized, they do indicate that surveillance, and even monitoring, when performed well [49], can reduce the event rate.

The approach and role of S/M in AVF may differ. Since autologous fistulas maintain patency at lower flows than grafts, the criteria for intervention in AVF are not as well established. One study has established the value of Q_A surveillance in AVF, the positive predictive value, negative predictive value, sensitivity, and specificity of the ultrafiltration Q_A method for vascular access stenosis (OABF CritLine III) being 84.2, 93.5, 84.2, and 93.5%, respectively. The vascular access thrombosis rate in 50 Q_A surveillance patients was lower (2/50, 4%) than in 94 patients who were not followed with flow measurements (16/94, 17%) ($p = 0.024$) [50]. However, the urge to intervene with PTA to prevent thrombosis must be balanced by the observations that PTA almost invariably triggers repeated need for the same procedure. The optimal care of such patients requires individualization and not rigid application of protocols.

In general, when using flow, the period over which the prediction of thrombosis is made shortens as the absolute Q_A decreases, i.e. approximately 950–1,000 ml/min when forecasting 3–6 months [51, 52], and <600 ml/min if forecasting less than 2 months [53]. This is illustrated in our own work in which we measured flow by dilution ultrasound every 2 weeks for the first 3 months (6 data points)

Fig. 7. Probability of a vascular access thrombosis occurring within a 3-month period is dependent not only on the absolute flow at any time but also on the rate if there is a change in flow.

following new graft construction and monthly thereafter to determine the probability of thrombosis [54]. The decrease in flow from the initial value was obtained by regression analysis. As can be seen in figure 7, the likelihood of thrombosis during the second 3-month observation period increased with lower initial 'best' flow and with the decrease in flow per month. An access with an initial flow of 600 ml/min and a 20-ml/min decrease in flow per month has a lower probability of thrombosis (22%) than an access with an initial flow of 1,200 ml/min and a decrease in flow of 100 ml/min (38%), even though the absolute flow is much lower in the former (540 ml/min) than in the latter (900 ml/min) at the beginning of the observation period. Our results are in keeping with results by others [55, 56].

The above figure provides data on the probability, not the certainty, of an event, and the action level has to be determined by other considerations. Over a 3-month period observation, grafts can clot in the absence of any stenosis and often do so at flows equal to those that remain patent, usually in excess of 1,100 ml/min. P_{IA} in these cases remains unchanged. Grafts that require intervention or thrombose due to an anatomical lesion have much lower Q_A , i.e. 656 and 609 ml/min, respectively. Others have found that even at flows above the threshold (>800 ml/min), the incidence of thrombosis may be as high as 20% per 6-month period [57]. Similarly, even with flows in the highest quartile ($>1,395$ ml/min) a thrombosis rate of 9% over a period of 3 months (annualized risk would be 36%) was detected in these grafts [51]. These observations clearly imply that stenosis per se with its ac-

companying low flow is not a sufficient substrate to produce thrombosis in a predictable fashion. Other factors such as inflammation [58], procoagulant dysfunction [59], presence or absence of diabetes, and the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [60] all contribute to the process. Thrombosis rates in grafts in the absence of S/M have been noted to vary from 0.5 to over 2.0 episodes per access-year at risk. Such differences emphasize the role of these factors including cannulation techniques by the staff. The efficacy of S/M cannot be demonstrated if these other factors produce a high basal thrombosis rate in the absence of stenosis.

Does S/M Prolong Access Longevity? We Do Not Know! Is It Relevant?

The statement that 'it is widely accepted that surveillance with correction of stenosis before thrombosis prolongs hemodialysis graft survival' is incorrect. There have been virtually no large studies addressing this important aspect. The study by Lumsden et al. [61] initially refuted the concept that prophylactic or pre-emptive PTA would decrease graft thrombosis. In a study of 64 patients with a stenosis of 50% by diameter (50%D) identified by DDU and confirmed by angiography, pre-emptive PTA produced no change in 6- or 12-month patency. Because of confounding issues, a subanalysis was performed on 21 'virgin' grafts that had not previously clotted or required any intervention [62]. Pre-emptive PTA from the time of diagnosis of stenosis reduced the thrombosis rate from 0.44 to 0.10 episodes/patient-year at risk. Both rates were much lower than the rate of 0.91 in patients without virgin grafts.

The small sample size in this and all other prospective studies has limited assessment of efficacy. One prospective study using static pressure has been performed [20]. Although the study itself was well designed, it was flawed by the surveillance technique. The methodology for deriving the P_{IA} ratio differed from that originally described [42]. The net effect of the error was to 'falsely elevate' the fraction meeting the criterion for referral and intervention. Not surprisingly, receiver operating characteristic analysis yielded curves with areas <0.64 (very poor). Subsequently, 64 patients with 'elevated static venous pressure' measured in an upper extremity arteriovenous graft were randomized to intervention (they underwent angiography and repair of identified stenoses) or observation (they underwent stenosis repair only in the event of access

Table 1. Effects of access failure*Thrombosed vascular access is a major problem*

For dialysis staff

- Rearrange dialysis schedule
- Arrange for transportation
- Interface between patient and physicians
- Assist patient in coping

For the nephrologist

- Deal with unhappy patient and family
- Oversee logistics of resolving failure

For the patient

- Cope with discomfort, pain, anxiety, and fear
- Decreased quality of life
- Schedule disruption
- Delay of dialysis
- Situation aggravated if condition precludes delay of dialysis

thrombosis or clinical evidence of access dysfunction) with the primary endpoint being access abandonment. No difference in access abandonment (14 patients in each group) during the 3.5-year study period or in the time to access abandonment was found. However, the proportion of patients with a thrombotic event was greater in the observation group (72%) than in the intervention group (44%) ($p = 0.04$). The number of PTA performed in the two groups is not stated.

Two randomized studies have examined the role of access surveillance using Q_A in arteriovenous grafts. In the first, Moist et al. [22] found that stenotic lesions are more commonly detected by Q_A or a decrease in Q_A of 20% than by 'routine surveillance' using physical exam and dynamic venous pressure surveillance (>150 mm Hg) in a total of 112 patients. Elective PTA for lesions $>50\%D$ did not alter the thrombosis rate, rate of graft loss, time to graft loss, and overall thrombosis rate between the two groups. However, interventions increased by 30% in the intervention group. In the second study, 101 patients were randomized to 3 groups: control, flow surveillance Q_A (Transonics) monthly, or stenosis detection by DDU quarterly [21]. Referral for angiogram was based on clinical characteristics in all, on <600 ml/min in the Q_A group, and on $>50\%D$ in the DDU stenosis group. Q_A was measured in all 3 groups but only used for referral in the flow surveillance group. The baseline thrombosis rate was 0.7 and 0.9 per patient-year in control and Q_A groups, respectively. Q_A marginally increased the PTA rate (from 0.22 to 0.33/patient-year) and had no effect on the thrombosis rate. Stenosis surveillance increased the PTA rate to 0.65/patient-year and reduced the thrombosis rate to 0.5/pa-

tient-year, but as in the other trial, did not have an effect on the 2-year survival rate. In those grafts that clotted (overall 11/60), a $Q_A < 600$ was found in 4/18, 4/31, and 3/11 of the control, Q_A surveillance, and stenosis groups, respectively. However, 26 of 35 patients in the stenosis group had PTA for 'stenosis'. Stenosis was present much more commonly than the action level for flow surveillance. In both studies, 20–25% of access clotted without a surveillance abnormality, which was totally unexpected.

The overriding conclusion of the studies was that surveillance using Q_A and PTA in response to a threshold value of Q_A did not alter graft survival which has to be tempered by the small sample size of the studies. Graft survival studies require a sample size of approximately 700 patients to detect an increase in graft survival of 1 year or a 33% difference in survival by 3 years [H. Feldman, University of Pennsylvania, Philadelphia, Pa., USA, pers. commun.]. The current study of the National Institutes of Health assessing the effect of Aggrenox on decreasing and thus prolonging time to first event (thrombosis or need for PTA) has a target of over 1,000 subjects in order to detect a 25% improvement in primary unassisted patency. To date, none of the published studies on grafts have included even a fifth of the required number of subjects. Smaller studies may be able to provide data on rates of intervention, economic costs, effect on patients, but not on graft longevity with or without S/M or PTA.

From the perspective of the patient, the focus on the longevity of grafts is inappropriate. The effect of thrombosis on the patient and on the staff is frequently minimized or overlooked (table 1). A dysfunctional access is a real concern to patients, since almost 60% of patients cite thrombosis of the access as one of the most feared problems associated with hemodialysis, ranking it second only to pain [63]. A clotted access if not resolved within 24 h alters the quality of life of not only the patient but the dialysis staff as well, due to the heightened urgency present with thrombosis as opposed to elective repair. A retrospective analysis of an incident cohort of 88 hemodialysis patients, of whom only 32% had a permanent access placed at least 14 days prior to the need for hemodialysis, demonstrated a 24% primary access failure rate due to complications [64]. During the mean study follow-up period of 487 days, 51% of patients had at least one access complication, resulting in the requirement for 25 fistulograms (0.21 per patient-year of risk) and 116 additional temporary access placements (0.97 per patient-year of risk) [64]. A total of 2.43 inpatient days and 1.05 outpatient encounters per year of patient risk were di-

rectly attributed to admissions solely for such access complications.

Thus, prevention of thrombosis itself without prolongation of overall longevity is a worthy outcome.

Results of prospective surveillance in native fistulas have been more positive. In Italy, a 5-year randomized, controlled, open trial blood flow surveillance and pre-emptive repair of subclinical stenoses (angioplasty, open surgery, or both) with standard monitoring and intervention based upon clinical criteria alone was carried out [65]. Surveillance with blood pump flow monitoring during dialysis sessions and quarterly Q_A or recirculation measurements identified 79 AVFs with angiographically proven, anatomically significant ($>50\%D$) stenosis that were then randomized to either a control group (intervention done in response to a decline in the delivered dialysis dose or thrombosis; $n = 36$) or to a pre-emptive treatment group ($n = 43$). Kaplan-Meier analysis showed that pre-emptive treatment reduced the failure rate ($p = 0.003$), and the Cox hazards model identified treatment ($p = 0.009$) and higher baseline Q_A ($p = 0.001$) as the only variables associated with a favorable outcome. Access survival was significantly higher in pre-emptively treated than in control AVFs ($p = 0.050$), a higher post-intervention Q_A being the only variable associated with improved access longevity ($p = 0.044$). This study provides evidence that active blood flow surveillance and pre-emptive repair of subclinical stenosis reduce the thrombosis rate and prolong the functional life of mature forearm AVFs, and that $Q_A > 350$ ml/min prior to intervention portends a superior outcome with pre-emptive action in AVFs.

Finally, a prospective controlled open trial was performed to evaluate whether prophylactic PTA of stenosis not associated with access dysfunction improves survival in native, virgin, radiocephalic forearm AVF [66]. Sixty-two stenotic, functioning AVFs (able to provide an adequate dose of dialysis) were examined: 30 were allocated to control and 32 to PTA. Kaplan-Meier analysis showed that PTA improved AVF functional failure-free survival rates ($p = 0.012$) with a 4-fold increase in median survival and a 2.87-fold decrease in risk of failure. The Cox proportional hazard model identified PTA as the only variable associated with the outcome ($p = 0.012$). PTA increased Q_A by 323 ml/min ($p < 0.001$), suggesting that improved AVF survival is the result of increased Q_A . PTA was also associated with a significant decrease in access-related morbidity, halving the risk of hospitalization, central venous catheterization, and thrombectomy ($p < 0.05$). Since prophylactic PTA of stenosis in functioning fore-

Fig. 8. Summary of figures [35, 51, 55] depicting the receiver operating curves for various surveillance techniques in grafts. Note that an absolute flow of 25% is the least predictive of the occurrence of thrombosis (poor performance). Direct detection of stenosis by duplex Doppler sonography is best. Both a change in flow and static pressure have shown good performance in detecting stenosis (the precursor for thrombosis in most cases). SP = Static pressure ratio.

arm AVF improves access survival and decreases access-related morbidity, it supports the surveillance program for the early detection of these stenoses.

Is Stenosis Detection What We Should Be Evaluating? We Do Not Know

As important as is the accuracy of a method to detect stenosis, the goal of any surveillance method is to detect access stenosis in a timely way so that appropriate correction can be undertaken prior to thrombosis. A hemodynamically significant stenosis is the substrate for thrombosis by reducing flow, increasing turbulence, increasing platelet activation and residence time against the vessel wall. However, as previously discussed, it is not sufficient since accesses without major stenoses do thrombose and accesses with stable stenoses sometimes do not. No currently available physiologic technique is able to identify an anatomically significant 50% stenosis with a sensitivity of 90% and a specificity greater than 80% [35]. As is reflected by the data in figure 8, DDU is most accurate because it can directly visualize the degree of stenosis.

Because of the accuracy of DDU in detecting the presence of a 50%D stenosis [67], in some studies, DDU has been used as the reference method rather than angiography to avoid invasive procedures. Whatever method is used to document the degree of stenosis, the prevalence of a 50% stenosis is found much more frequently than a hemodynamic abnormality in static pressure or Q_A . In the study by Ram et al. [21], DDU found $\geq 50\%D$ stenotic lesions in over 70% of patients with grafts, but a $Q_A < 600$ ml/min was a poor predictor of its presence or of thrombosis occurring. Our findings are similar. In a study in which all 71 grafts were angiographed to determine the prevalence and degree of stenosis, 49 were found to have at least one 50%D stenosis. Of these, 37 were associated with an increase in static pressure ratio. Overall sensitivity and specificity of an increase in static pressure in detecting a 50% stenosis were 91 and 76%, respectively [68]. Paradoxically, when DDU was used to measure flow rather than to identify anatomical stenosis, sensitivity and specificity decreased. As stated previously, stenosis degree cannot alone predict the flow present or the actual P_{IA} due to other factors.

This raises the very important issue of whether stenosis detection alone is sufficient. In the study by Ram et al. [21], detection of stenosis followed by its correction reduced the thrombosis rate. Although promising at present, there are inadequate data to answer this question. In the Canadian study, the PTA rate increased without reducing the thrombosis rate. Of importance, the two studies had significantly differing baseline thrombosis rates, i.e. 0.9 versus 0.5 events/patient-year, and the ultimate rate of thrombosis regressed toward a common mean. Differences in rates among different centers due to unknown differences in the populations (Caucasian vs. Afro-American) or in the skill sets of the dialysis staff may be a major determinant of efficacy. At the present time, I believe that a lesion which is not progressing and in which hemodynamic parameters are stable over time should not be intervened, particularly in AVF.

Are Our Tools for Detection Good Enough? Yes for Now, but We Can Learn to Use Them Better

The available data suggest that the utility of dynamic venous pressure at flows of 150–225 ml/min to predict stenosis or thrombosis is quite limited or absent in grafts [69]. Studies are needed to determine if it retains any utility in native accesses. By contrast, flow measurements,

DDU assessment for stenosis, and static pressure measurements (direct or indirect) can detect hemodynamically significant stenosis in grafts and native fistulas. Although the location of stenosis in fistulas (inflow) favors Q_A over P_{IA} , no direct comparisons have been made using DDU anatomical imaging or contrast angiography to determine the accuracy of the techniques in this access type. If the prescribed Kt/V is not delivered in a patient who is using a native fistula, the recommended urea-based method or one of the non-urea methods (ultrasound dilution, glucose pump test) are used as the measurement of access recirculation.

The current K/DOQI workgroup feels that there is insufficient evidence from the literature to suggest one preferred surveillance technique of those listed in the guidelines as ‘preferred or acceptable’, as the choice at a particular site is affected by many variables, mainly access type, technology, effect of operator, and cost (usually labor) [70]. Although Doppler studies are predictive of access stenosis and the likelihood of failure [71], frequency of measurement is limited by expense. In addition, in some instances, interobserver variability in flow can reduce the reliability of Doppler flow measurement [72]. Variation in the internal software used for calculating Doppler flow measurements by different manufacturers is also a factor preventing standardization. Magnetic resonance flow is accurate but expensive. Both Doppler flow and magnetic resonance are difficult to perform during dialysis sessions.

In contrast, flow measurements performed by dilution ultrasound (Transonic) and other techniques can be done on-line during dialysis, thereby providing rapid feedback. The same applies for P_{IA} . Both flow and pressure techniques have been validated in prospective observational studies [42, 43, 48, 49, 69, 73]. Measuring venous pressure is the least expensive method of surveillance for stenosis [43, 74]. For these reasons, Q_A measurement and P_{IA} are listed as preferred. Online Q_A measurements are available but require further improvements in accuracy and replicability.

Recirculation is a relatively late predictor of access dysfunction. Urea measurement for the calculation of recirculation must be done under standardized conditions. Non-urea-based recirculation measurements are very accurate but require specialized devices. Unexplained decreases in delivered dialysis dose, as measured by Kt/V or URR, are frequently associated with venous outflow stenoses [75]. However, many other factors influence Kt/V and URR, making them less sensitive and less specific for detecting access dysfunction. Inadequate deliv-

ery of dialysis dose is more likely to occur with AVFs than with arteriovenous grafts.

In primary AVFs, inadequate flow through the access is the primary functional defect predictive of thrombosis and access failure (defined as thrombosis or failure to provide an adequate dialysis dose). It is currently unknown whether indirect measures of flow, such as static venous dialysis pressure, are less predictive of thrombosis and access failure in AVFs compared with arteriovenous grafts. However, combining the measurements with prepump pressures to assess for adequacy of inflow may be as effective as flow measurements. In the context of proper needle position, an elevated negative arterial prepump pressure that prevents increasing the blood flow rate to the prescribed level is also predictive of arterial inflow stenoses. Prospective comparative studies are needed. On the other hand, measurement of recirculation becomes a more useful screening tool in AVFs compared with arteriovenous grafts because flow in AVFs, unlike in arteriovenous grafts, can decrease to a level less than the prescribed blood pump flow (i.e. less than 300–500 ml/min), while still maintaining access patency [76, 77]. Doppler ultrasound may be useful in AVF despite its increased cost [78]. Comparative studies using hemodynamic monitoring (Q_A , P_{IA}) and DDU need to be performed before firm recommendations can be made as to the most cost-effective test.

Regular assessment of physical findings (monitoring) may enhance an organized surveillance program to detect access dysfunction. Specific findings predictive of venous stenosis include edema of the access extremity, prolonged bleeding after venipuncture (in the absence of excessive anticoagulation), and changes in the physical character-

istics of the pulse or thrill in the graft [79, 80]. Physical examination is a useful screening tool to exclude low flow (<450 ml/min) in grafts with impending failure [24].

Conclusions

The body of evidence suggests that detection of stenosis and prevention of thrombosis are valuable. When a test indicates the likely presence of a stenosis, venography or fistulography should be used to definitively establish the presence of and the degree of the stenosis. Currently, there is agreement with the recommendations of the Society of Cardiovascular and Interventional Radiography that in most cases angioplasty should be performed if the stenosis is greater than 50% by diameter. However, there have been no large-scale trials to determine whether correction of only 'hemodynamically' significant lesions (those associated with 'low' Q_A or 'high' pressures or a change in Q_A or pressure) is superior to correction of all stenoses greater than 50%.

Until such studies are conducted, the value of routine use of any technique for detecting anatomic stenosis alone without concomitant measurement of Q_A , venous pressure, recirculation, or other physiologic parameters has not been established. Stenotic lesions should not be repaired merely because they are present. If such correction is performed, then intraprocedural studies of Q_A or P_{IA} prior to and following PTA should be conducted to demonstrate a functional improvement with a 'successful' PTA.

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