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NEPHROLOGY FORUM

Vascular access for hemodialysis

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CASE PRESENTATION

A 62-year-old black woman with end-stage renal disease secondary to type-II diabetes mellitus began hemodialysis 2 years ago. She presented to the Nephrology Service at Duke University Medical Center with a serum creatinine of 8.6 mg/dl; vascular access for hemodialysis was achieved via an internal jugular, cuffed, Silastic catheter. A brachiocephalic, primary arteriovenous (AV) fistula was attempted but failed to mature. A left upper arm PTFE graft was subsequently placed. Hemodialysis proceeded uneventfully, and she entered into a hemodialysis vascular access monitoring protocol with dynamic venous pressure testing. On two later occasions, she underwent percutaneous transluminal angioplasty of a stenotic lesion 2 cm superior to the vein/graft anastomosis. In both instances, venous dialysis pressure above the monitor threshold indicated the presence of the lesion. Four months ago, venous dialysis pressure monitoring was changed to monitoring with ultrasound dilution access flow. Her access flow rates continued to decrease on monthly readings, from 1020 ml/min to 750 ml/min over a 4-month period. Fistulography showed recurrence of the same stenotic lesion. Angioplasty was attempted, but the lumen was not successfully reconstituted. She was offered elective surgical revision but declined. One month later, her access flow had decreased to 680 ml/min, and she presented with a thrombosed arteriovenous graft. Pulse spray thrombolysis revealed a residual 95% outflow stenosis. The patient then elected surgical revision. Her access flow one month post revision was 980 ml/min.

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Key words: PTFE graft, AV fistula, AV graft, angioplasty, access thrombosis, tunneled, cuffed catheter, end-stage renal disease.

DISCUSSION

DR. STEVE J. SCHWAB (*Vice-Chairman, Department of Medicine, Duke University Medical Center, and Professor of Medicine, Duke University School of Medicine, Durham, North Carolina, USA*): This case exemplifies the current state of the art for the management of vascular access for hemodialysis. The predominant form of vascular access currently in the United States is the polytetrafluoroethylene (PTFE) graft, constituting some 70% of the total permanent access. Primary arteriovenous fistulas, although generally preferred, are used less often because of late referral of patients to nephrologists, and because an aging and diabetic population with a limited number of suitable sites for the formation of primary AV fistulas limits their formation. They currently constitute less than 20% of the prevalent hemodialysis access in the United States. This case also provides me an opportunity to discuss the current role of the tunneled cuffed catheter in hemodialysis vascular access.

Complications of vascular access are not only a major cause of morbidity in hemodialysis patients, but a major cost for the end-stage renal disease program. In its latest report, the United States Renal Data System (USRDS) estimated that the costs for access morbidity approach $8000/patient/year at risk [1]. Remarkably, conservative estimates suggest that this figure represents 17% of the total spending for hemodialysis patients. Feldman [2, 3] and others [4–6] have reported that access-related morbidity accounts for almost 25% of all hospital stays for ESRD patients and may contribute to as much as 50% of all hospitalization costs [2–7]. Using the prospectively collected data from the Dialysis Outcome Practice Patterns Study (DOPPS), Held has confirmed Feldman's observations [6]. Indeed, managed care organizations planning for a capitated payment environment estimate that as much as one-quarter of the total cost of end-stage renal disease is spent on the maintenance of vascular access in hemodialysis patients [7]. Thus, the maintenance of access to the circulation is not only a major

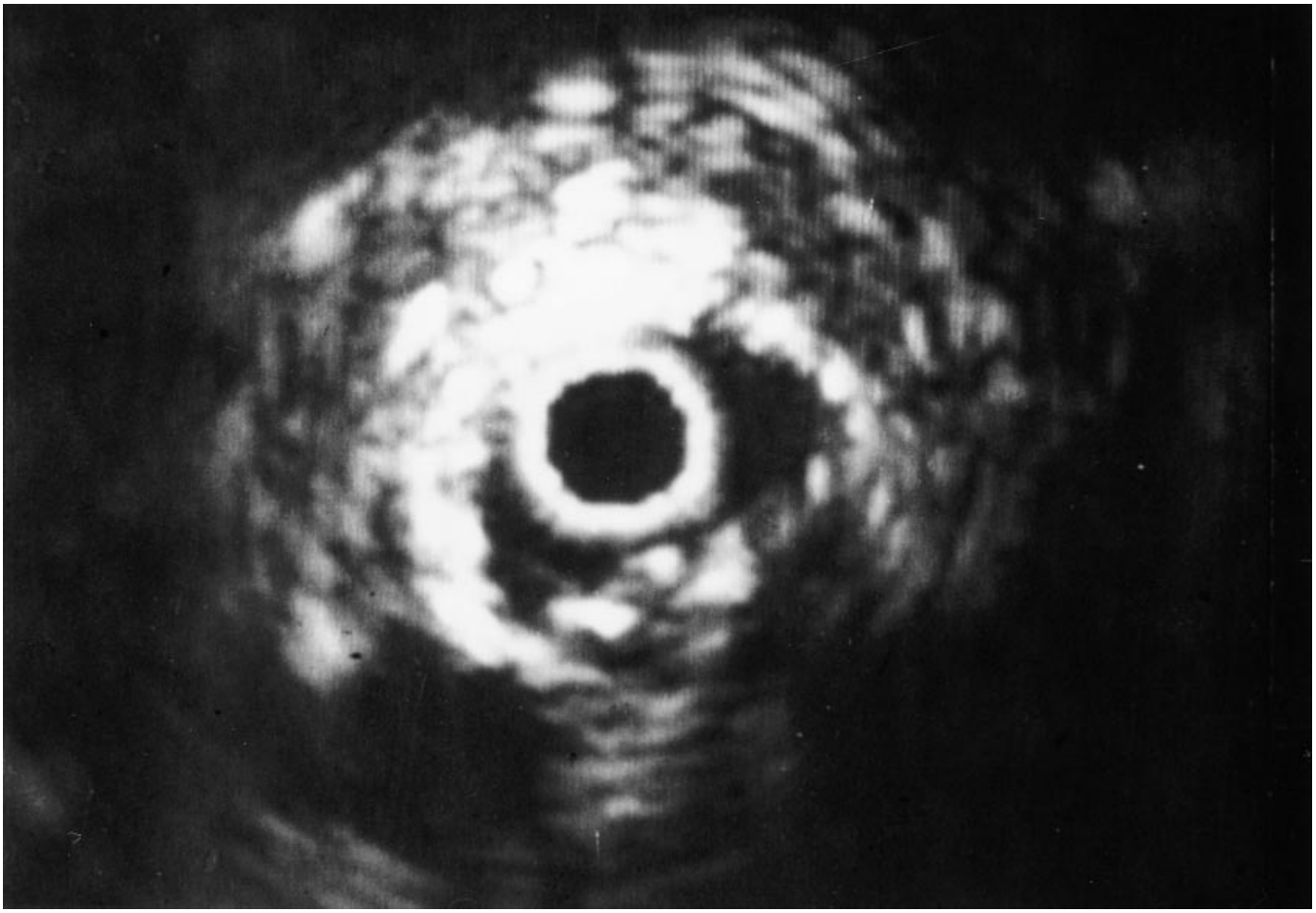

Fig. 1. Intravascular ultrasound of fibromuscular hyperplasia in brachial vein at the vein graft anastomosis. Sphere in center of vein is the head of the ultrasound catheter.

patient care concern, but also an enormous fiscal drain on the end-stage renal disease program.

Types of vascular access

The first described, and still the best, form of permanent vascular access is the native arteriovenous fistula [8–10]. This access, constructed by the anastomosis of a native artery with a native vein, can be created in either a side-to-side or an end-to-side fashion. Three types of native AV fistulas can be formed. The radiocephalic fistula is formed by the anastomosis of the radial artery with the cephalic vein to form a large forearm vein suitable for venipuncture [8]. An alternative type, which can be successfully placed in many patients in whom venous and arterial structures are not suitable for a radiocephalic approach, is a brachiocephalic AV fistula. This access is formed by the anastomosis of the brachial artery with the cephalic vein above the elbow. Thus, the vein runs over the anterior surface of the bicep and is suitable for cannulation [11–13]. The third type of primary AV fistula, a brachiobasilic AV fistula, is formed by the anastomosis of the brachial artery with the basilic vein. The disadvantage of this approach is that the vein runs on the undersurface of the arm and is very difficult to cannulate. Native AV fistulas have the disadvantage of requiring a long maturation time (3 to 6 months) and of not developing sufficiently in many older patients, especially diabetics. Thus, early referral, well before the need for dialysis, is required to successfully create native AV access in most patients.

Synthetic internal AV fistulas, termed "AV grafts," can be placed in numerous positions in the arms and legs and across the anterior chest wall. The synthetic portion of the graft is usually composed of PTFE [11, 14–16], a compound synthesized by many manufacturers and formed into both reinforced and nonreinforced configurations. Advantages of using PTFE grafts are the short maturation time (3 to 4 weeks) and the multiple potential access sites. Their overwhelming disadvantage is their propensity for venous outflow stenosis caused by endothelial and fibromuscular hyperplasia [7, 9, 10, 14–16].

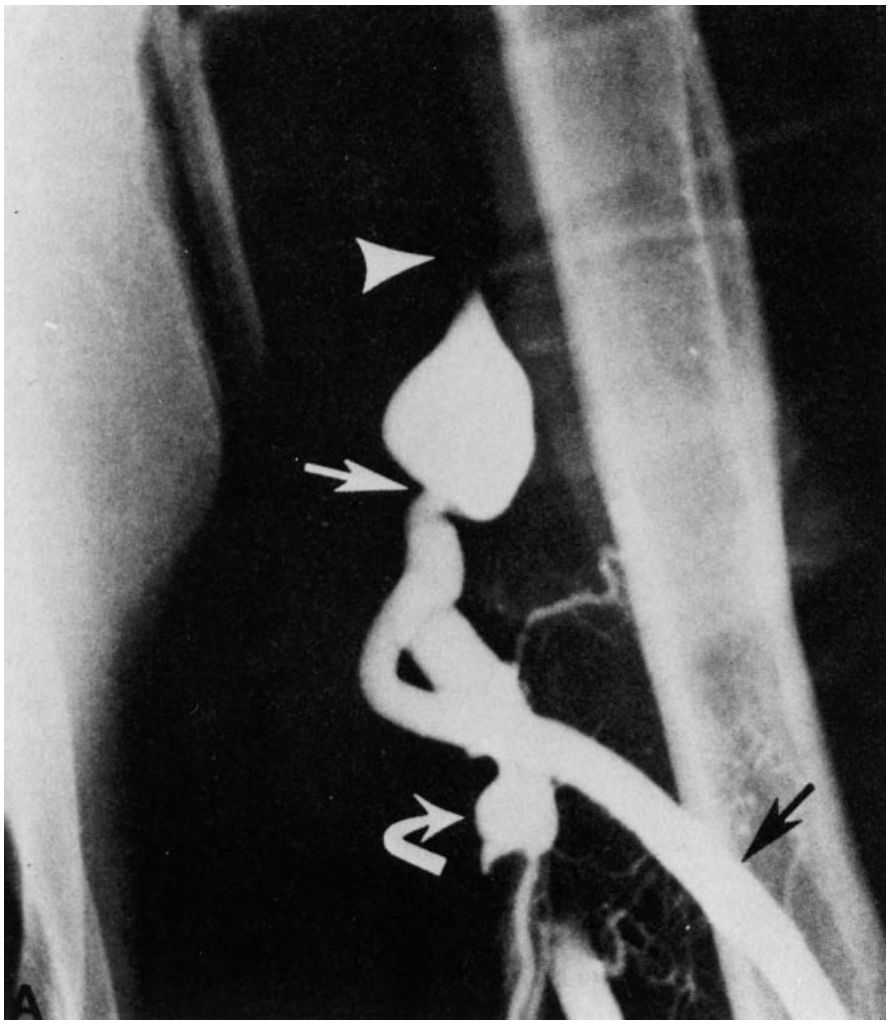

Fig. 2. Radiograph of outflow stenosis at vein graft anastomosis in an AV graft before (*A*) and after (*B*), opposite page, correction with angioplasty. A. *White arrowhead* represents location of occluding blood pressure cuff. *White arrow* shows stenosis at vein graft anastomosis. *Black arrow* represents AV graft. *Curved white* arrow indicates proximal native vein.

The third type of permanent vascular access, developed in the late 1980s, is the cuffed, tunneled, internal jugular dialysis catheter [17–25]. Although capable of providing permanent vascular access, its overall performance is inferior to the AV approach in all aspects [7, 9, 10, 20–25]. Its principal role is as a "bridge" creating immediate access to the circulation and allowing a smooth clinical transition to the creation of a permanent vascular access.

Access failure

Failure of permanent vascular access in hemodialysis patients occurs for two reasons. Failure ensues in more than 80% of cases because a thrombotic episode cannot be resolved [7, 9, 10, 14–16, 26–39]. Failure secondary to infection or other complications occurs in approximately 15% to 20% of cases. Two large series of studies by different investigating groups (Duke University and Austin Clinic), as collated by the Dialysis Outcome Quality Initiative (DOQI) for vascular access, found strikingly similar results. At Duke, thrombosis accounted for 84% of all AV access loss, at the Austin Clinic, 85%. Similarly, the DOQI-derived conclusion from several large investigative efforts into the causes of thrombosis from Duke University, Austin Clinic, and University of California, San Diego, indicate that more than 80% of access failures were caused by outflow stenoses in the venous circulation, 84%, 86%, and 92% at these institutions, respectively [7, 14–16, 26–39]. These areas of stenosis generally occurred at or near the vein/graft anastomosis, at areas of vein bifurcation, at areas of calcified venous valves, or at the site of a central venous cannulation [26–38]. Fewer than 2% of the total access failures resulted from arterial stenosis. Fewer than 15% occurred without a clearly defined anatomic cause. Histologic evaluation revealed that endothelial and fibromuscular hyperplasia was the leading cause of these venous outflow stenoses, and that 50% to 70% of these stenoses occurred at or within 3 cm of the vein/graft anastomosis (Figs. 1 and 2) [14–16, 26–38]. Native AV fistulas lacking a vein/graft

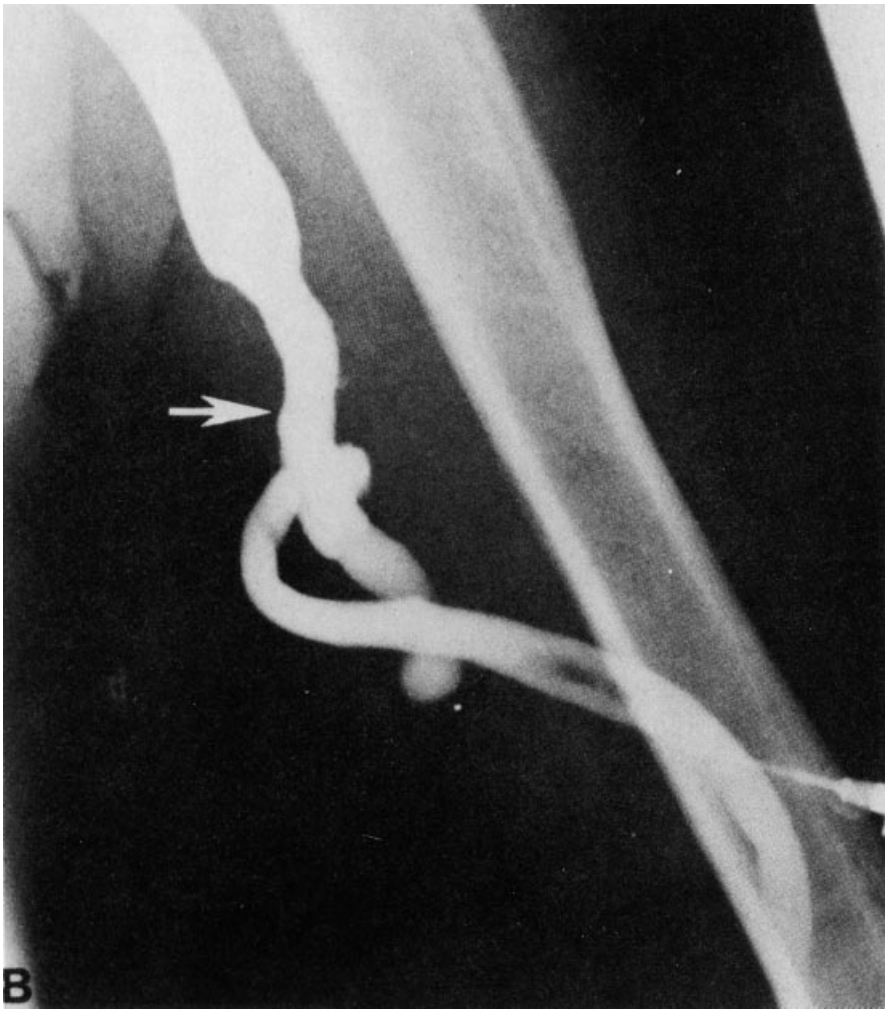

Fig. 2. B. *White arrow* shows stenosis post angioplasty demonstrating restored venous flow. (From Schwab SJ, Saeed M, Sussman SK, McCann RL, Stickel DL: Transluminal angioplasty of venous stenoses in polytetrafluoroethylene vascular access grafts. *Kidney Int* 32:395–398, 1987.)

anastomosis had a lower rate of stenosis. Thus, access failure both in AV fistulas and AV grafts was secondary to fibromuscular and intimal hyperplasia in the venous circulation. The potential causes of the endothelial and fibromuscular hyperplasia will be discussed later in this Forum.

How accurate is our information about the natural history of vascular access in hemodialysis patients? The National Kidney Foundation developed evidence-based practice guidelines on vascular access, the Dialysis Outcome Quality Initiative, and formed the largest data base available on hemodialysis vascular access [7]. The guideline development team reviewed more than 3500 manuscripts in the course of its work. The working group that constructed the guidelines comprised representatives from all professional disciplines involved in the formation, maintenance, and care of vascular access [7]. Several key conclusions were reached. Native AV fistulas (excluding fistulas that fail to mature in the first 60 days for successful initial cannulation) have a much longer patency rate than do AV grafts (Fig. 3). Primary patency reflects patency to the "initial intervention" on the access; initial intervention could be thrombolysis or elective angioplasty or surgery. Cumulative patency (defined as patency of the access regardless of the number of interventions) revealed improved performance in AV graft patency compared to AV fistulas (Fig. 4); however, this improvement in AV graft patency was obtained by an increased number of access interventions. The procedures required to maintain AV graft patency were three- to sixfold higher than that needed to maintain patency of primary AV fistulas. When center analysis was used (selecting data only from centers with an active prospective monitoring and preventive therapy plan) AV fistulas and AV grafts had nearly equal cumulative patency rates but at the expense of many more corrective procedures for AV grafts (Fig. 5). The 3-year cumulative patency for AV grafts is generally 50%, even at the reporting centers with the best outcomes [7]. Thus, even at superior centers, only 50% of AV grafts generally survive longer

than 3 years. Similar evaluation of studies examining cuffed, tunneled catheters found a much shorter lifespan (on average, 12 months) and a much higher complication rate than with AV access; thus, the DOQI discouraged the use of these catheters for permanent access [7].

Access salvage

Prospective monitoring. Multiple investigators have shown that thrombosis rates and AV graft patency improve significantly when prospective screening techniques are used to detect early outflow stenosis (abstract; Depner et al, *J Am Soc Nephrol* 7:1405, 1996) [9, 10, 26–48]. European investigators have shown significant benefit in prospective monitoring and ensuing early correction of incipient outflow stenoses of AV fistulas [36, 39]. The theoretical benefits of graft and fistula monitoring are that early fibromuscular hyperplasia can be successfully treated by percutaneous techniques, thereby preventing thrombosis and extending the life of the access. Although not a cure, utilization of monitoring techniques holds the promise of significantly increasing AV patency (Figs. 4 and 5).

The utility and validity of monitoring techniques for detecting venous outflow stenoses in AV grafts and fistulas have gradually improved over the last decade (Table 1). The earliest technique used sequential measurements of dynamic venous dialysis pressure [26]. The approach had the advantage of being inexpensive and readily available, but it required slowing blood flows to obtain repetitive measurements, and use of the venous drip-pressure monitor of the hemodialysis machine resulted in measurements that were quite variable. Thus, the confounding variables introduced by differences in blood flow, length and type of tubing, and type of monitor all needed to be taken into account in using this technique [26, 28]. This technique identified stenoses after a significant stenosis already had occurred, and was most accurate for vein/graft stenoses, but it missed stenoses farther up the extremity, where collateral circulation could allow dissipation of the venous pressure. Nonetheless, most studies indicated that, despite its shortcomings, the technique significantly improved access patency (Table 2) [7, 26, 28].

These techniques were supplanted by specialized devices for measuring static venous pressure or venous pressure at blood flows of 0 ml/min [27]. Because these devices avoided the variables induced by blood flow and the dependency on needle size, and because they used a single standard-pressure transducer, they increased the accuracy of access monitoring [27]. Measuring static venous dialysis pressure was dramatically simplified recently; it can now be performed without separate devices [40].

Direct intra-access measures of blood flow are currently the most accurate method for detecting access stenosis. Access flow has been carefully validated by using ultrasound dilution (abstract; Depner et al, ibid) [41–45]. Conductance dilution and duplex colorflow Doppler techniques also are available [43, 46, 47]. Colorflow Doppler has a confounding variable, however: flow measurements are operator- and machine-dependent and have significant variability [48]. Data obtained by ultrasound dilution suggest that access flow of less than 600 ml/min in PTFE grafts is likely to lead rapidly to access thrombosis. In addition, if the flow is less than 1000 ml/min, decrements in access flow of >15% are equally likely to predict thrombosis and hemodynamically significant stenosis (abstract; Depner et al, ibid) [41–45]. Monthly access flow monitoring seems to be an adequate standard. Access flow should be measured at standard times in the hemodialysis treatment to obtain reproducible data and to avoid the variability induced by decreases in cardiac output that are associated with ultrafiltration. In a study not yet published, we evaluated ultrasound-dilution-determined access flow before and after angioplasty in a one-year prospective trial (Table 3). The mean percentage increase in flow following percutaneous transluminal angioplasty (PTA) was 33% in AV fistulas and 41% in AV grafts. Failure to increase blood flow greater than 10% by PTA was associated with a high likelihood of further fall in flow and thrombosis. Corrective angioplasty, although beneficial, failed to restore flow to peak levels. Regardless of the mode of monitoring, with a single exception [49], investigators have found significant improvements (40%–80%) in cumulative access patency when prospective monitoring techniques are combined with early correction of outflow stenosis using either angioplasty or surgical revision [26–40].

Treatment of outflow stenoses. As I have said, hemodynamically significant venous outflow stenoses must be treated to avoid access thrombosis. If not successfully treated, when a critical reduction in venous diameter occurs, thrombosis ensues and flow ceases. Hemodynamic significance has been defined by access flow as well as by venous dialysis pressure, as I have just discussed [26–40]. To date, no data have convincingly demonstrated that correcting mild stenoses, that is, venous narrowings without hemodynamic significance, is of any value. Stenoses of 50% to 70% of lumen diameter respond reasonably well to transluminal angioplasty [7, 26–37, 39]. Mean duration of patency following the first angioplasty of a stenosis of 50% to 70% of lumen diameter is approximately 6 months [7]. Thus, repetitive angioplasties frequently are necessary. Because intervention that does not improve hemodynamic parameters is of little value, successful intervention requires return of the hemodynamic monitoring parameter, such as access blood flow, to normal. Despite one favorable study [39], the DOQI consensus is that the use of metallic stents

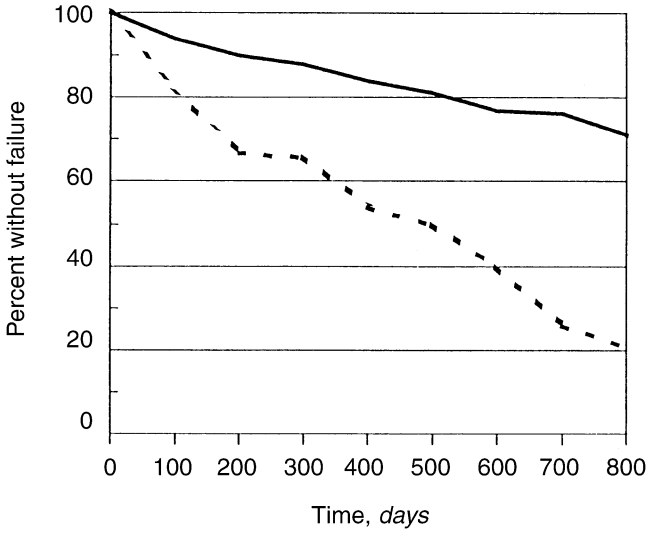

Fig. 3. Primary unassisted patency of AV fistulas and AV grafts. *Solid line* represents AV fistula patency. *Dashed line* represents AV graft patency. AV fistula patency excludes fistulas that did not mature sufficiently to allow initial cannulation. Graph derived from summed data analysis from the Vascular Access DOQI [7]. Primary patency reflects patency from initial cannulation to first intervention. First intervention could reflect thrombosis, removal, angioplasty, or surgical revision.

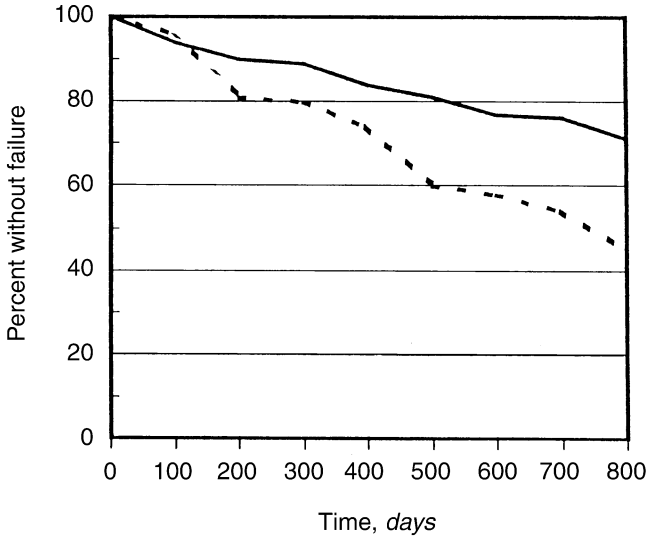

Fig. 4. Cumulative patency of AV fistulas and AV grafts. *Solid line* represents AV fistula patency. *Dashed line* represents AV graft patency. AV fistula patency excludes AV fistulas that did not mature sufficiently to allow initial cannulation. Graph derived from summed data analysis from the Vascular Access DOQI [7]. Cumulative patency reflects patency from initial cannulation to abandonment or removal of access. AV graft intervention (procedure) rate $> 3 \times$ AV fistula intervention rate.

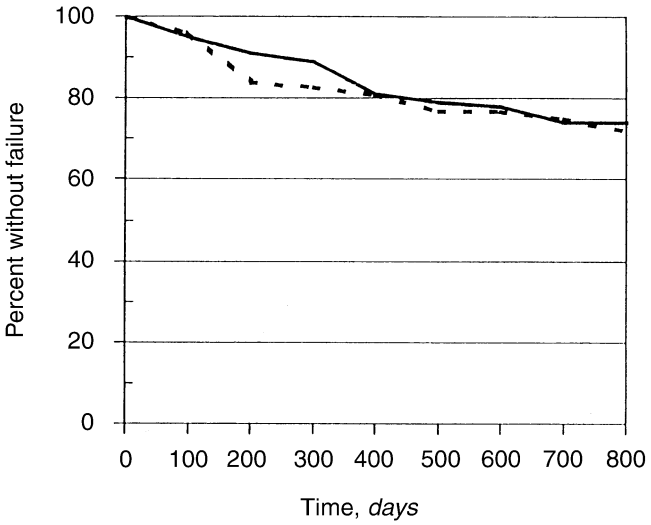

Fig. 5. Cumulative patency of AV fistulas and AV grafts with prospective monitoring and intervention. *Solid line* represents AV fistula patency. *Dashed line* represents AV graft patency. AV fistula patency excludes AV fistulas that did not mature sufficiently to allow initial cannulation. Cumulative patency reflects patency from initial cannulation to abandonment or removal of access. AV graft intervention (procedure) rate $> 6 \times$ AV fistula intervention rate.

Table 1. Prospective monitoring of AV access: The progress of technology

Dynamic venous pressure [26][a]
Static venous pressure [27]
Intra-access blood flow [43, 44]

[a] Numbers in brackets refer to references

generally has been of little value in improving access patency after angioplasty. Stents prevent surgical revision of the involved area; thus their value is minimal in peripheral stenoses, where surgical revision is an excellent option. Theoretically, the placement of a stent in an abnormal vascular bed could serve as a powerful mitogen for further hyperplasia and dysplasia. This does appear to be the case in most studies, which show diminished rather than increased patency when stents are employed in nonelastic lesions [50, 51]. Stents, however, do improve patency rates in elastic stenoses. By definition, elastic stenosis returns after angioplasty to the originial lumen diameter. Thus elastic stenoses do not respond to angioplasty alone. Elastic stenoses make up 20% to 25% of all venous stenoses (Fig. 6). The ideal locations for such stent use are central veins, where surgical revision options are limited. Recurrent stenosis of central vein elastic lesions occurs even after stenting, so ongoing monitoring is required.

Not surprisingly, severe outflow stenoses (>90% of the lumen diameter) generally are more likely to thrombose, and they also are more resistant to percutaneous angioplasty than are less severe stenoses detected prospectively (abstract; Middleton et al, *J Am Soc Nephrol* 79:A0838, 1414, 1996) [49, 52]. Typically, only a 40% 3-month patency is achieved when angioplasty is em-

Table 2. Thrombosis and fistula replacement[a]

	Patient years of dialysis	Episodes of thrombosis	Thromboses per patient/year	Fistulas replaced	Replacement per patient/year
1985–1986[b]					
12 months	85.3	52	0.61	22	0.26
1987–1988[c]					
32 months	265.0	52	0.20	19	0.07

[a] From Ref. 26. This prospective study used dynamic venous dialysis pressure and preventive angioplasty and surgical access revision
[b] Pre-study retrospective control data
[c] Study data

Table 3. Access flow before and after angioplasty[a]

AV fistula Peak flow postplacement	AV graft Peak flow postplacement
940 ml/min (N = 3)	1320 ml/min (N = 14)
Pre-angioplasty 670 ml/min (N = 3)	Pre-angioplasty 760 ml/min (N = 14)
Post-angioplasty 890 ml/min (N = 3)	Post-angioplasty 1070 ml/min (N = 14)

[a] Mean access flow was determined by ultrasound dilution

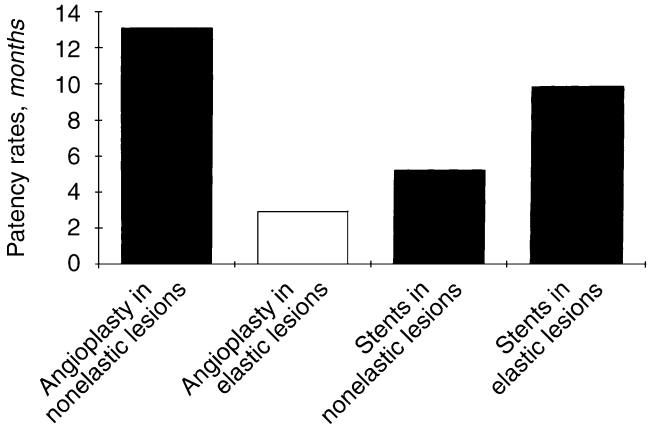

Fig. 6. Central vein stenosis recurrence rate following angioplasty or angioplasty and use of a wall stent. (From Ref. 52.)

ployed for these lesions [7]. The surgical data are less clear, but preliminary observations suggest that surgical revision holds much greater promise, with 6- to 12-month patency rates of 60% to 70% reported in patients with these severe stenoses (abstract; Middleton et al, ibid) [49, 52].

Access thrombosis in AV grafts can be successfully treated with either surgical embolectomy or with pharmacologic or mechanical thrombolysis. Thrombectomy entails incising the graft and inserting an embolectomy balloon to clear the clot from the thrombosed access. "Pulse spray" thrombolysis uses pulsed injections of urokinase via crossed catheters in the clotted access graft until the clot is dissolved (Fig. 7). Mechanical thrombolysis uses either pulsed saline in a technique similar to pulse-spray thrombolysis or a specific clot-macerating device [32, 33, 53, 54]. In experienced centers, 85% to 90% of AV graft thrombosis episodes are resolvable with any of these techniques [7, 11, 32, 33, 53, 54]. The more important issue is treatment of the underlying stenosis following resolution of the thrombus. Failure to correct the underlying stenosis results in rapid re-thrombosis within days to weeks [7].

In short, salvage techniques and strategies currently allow us to extend the life of 70% of AV grafts for as long as 3 years (Fig. 5) [7, 36–39]. These salvage procedures also can be used with AV fistulas, although with less success. The long-term key to access viability, however, is not treating progressive venous stenosis (although that is required today) but preventing the endothelial and fibromuscular hyperplasia that leads to the vast majority of access failures. I will now turn to a discussion of the cellular and subcellular events that lead to venous stenosis, and the possibility of preventing fibromuscular hyperplasia.

The prevailing consensus is that venous stenosis is caused by endothelial injury and vascular smooth muscle hyperplasia in areas where flow turbulence, vessel stretch, and shear stress occur. Many instances of outflow stenosis occur at such locations, but little stenosis develops at the equally turbulent artery/graft anastomosis or at the site of the artery/vein anastomosis in the AV fistula [7, 14–16, 26–39]. Thus, additional factors must be present for hyperplasia to occur. Each venipuncture of the hemodialysis access forms a localized platelet plug, with resultant exposure of the downstream vessel to a host of platelet-derived cytokines such as platelet-derived growth factor (PDGF). Windus has shown that platelets do not deposit directly at the vein/graft anastomosis [55]. In a series of elegant studies, Himmelfarb and Couper have elucidated the potential cause of this phenomenon [56]. Previously, Sreedhara and associates had reported that high-dose dipyridamole decreased access thrombosis at new, but not at previously established, AV grafts [57]; the reasons for this observation are unclear. The observations by Himmelfarb and Couper suggest that the mechanism for this effect might not be related to the effect of dipyridamole on coagulation, but

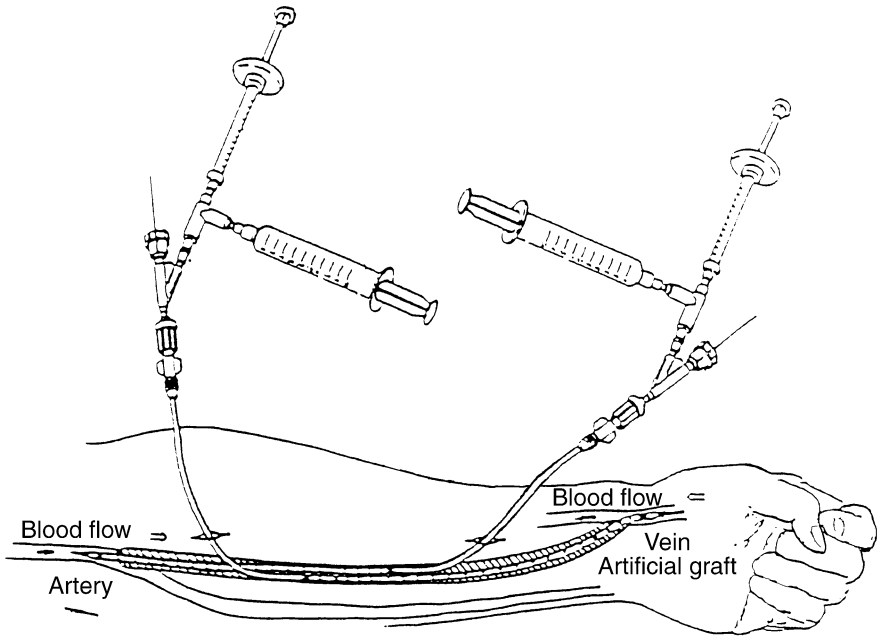

Fig. 7. Schematic drawing of pulse spray thrombolysis of an AV graft. (Reprinted with permission from AngioDynamics, Inc., Glens Falls, New York.)

Table 4. Maintaining access patency

Prospective monitoring for stenoses (see Table 1)
Therapy of stenoses
Percutaneous angioplasty
Use of stents for elastic stenoses
Surgical revision
Prevention
Radiation
Grafts designed to minimize turbulence
Gene therapy
Pharmacologic therapy
Cytokine inhibitors

rather to an inhibitory effect of dipyridamole on platelet-derived cytokines, which stimulate endothelial and fibromuscular hyperplasia in the vessel wall in response to turbulence injury. The theory that vascular smooth muscle hyperplasia reflects a response to injury in which PDGF is prominent suggests that vein stenosis is preventable. Regardless of the mechanism, these theories open the possibility that fibromuscular hyperplasia could be inhibited by pharmacologic therapy that will inhibit the development and progression of outflow stenosis.

Another approach to the elimination of fibromuscular hyperplasia is the use of radiation at areas of turbulence to minimize vein/graft stenosis (Table 4). Prospective clinical studies using these novel therapies represent a major step forward in our thinking and hold great promise for our patients and for the ESRD system. Equally exciting is the promise of gene therapy, as proposed by Sukatme in a recent Nephrology Forum [58]. Yet another possibility is that the AV access itself can be modified to minimize turbulence and reduce vessel wall injury. A recently developed "venous flare" AV graft holds promise and is currently in clinical trials [59]. That we could prevent this injury, rather than merely react to it, appears a very real possibility for the future.

Summary

Access to large blood vessels capable of providing rapid extracorporeal blood flow is essential for maintenance hemodialysis. Access to the circulation is still best provided by native AV fistulas, but AV grafts offer an acceptable alternative. Efforts at encouraging earlier referrals to nephrologists likely will facilitate preservation of vascular access sites and will allow AV fistulas to be placed in a higher percentage of cases; the latter goal was one of the primary recommendations of the DOQI [7]. Recent data from the DOPPS study confirm these predictions [6]. Patients referred early to a nephrologist are 4 times more likely to have a permanent access placed prior to starting dialysis and are 9 times more likely to have an AV fistula [6]. Increasing the percentage of native AV fistulas among dialysis patients in the US is an enormous step forward in decreasing patient morbidity and cost to the ESRD system. A goal of 40% AV fistulas in the US hemodialysis population is attainable over the next 3 years if patients are referred to nephrologists early. I would argue (as did DOQI) that such referral should occur when the serum creatinine concentration reaches 3–4 mg/dl. In addition, strategies for prospective detection of hemodynamically significant outflow stenoses, when combined with pro-active correc-

tion of this offending lesion, significantly improve access patency and should be universally adopted.

The morbidity and costs associated with maintenance of vascular access constitute an enormous burden both for our patients and for the end-stage renal disease system. Significant advances have occurred in our understanding of AV access failure, and our therapeutic techniques have improved significantly. The ideal approach, however, is prevention of the endothelial and fibromuscular hyperplasia that leads to the vast majority of access failures. Vigorous basic science investigation of vascular biology and active clinical investigation of medical and surgical therapy are required to eliminate this bane of our patients' existence.

QUESTIONS AND ANSWERS

Dr. John T. Harrington (*Dean, Tufts University School of Medicine, Boston, Massachusetts*): The access devices that we use have been around a long time. The 1960 external Scribner shunt has come and gone; the AV fistula dates from 1966; and the Gore-Tex graft has been with us for more than 20 years. Why don't we have anything new in the access realm? Is anything likely to come down the pike in the next 5 years that will prevent us from having to deal with all of the issues that you talked about?

Dr. Schwab: I think it is unlikely. The latest device that has come on the market that is widely used is the Silastic/silicone cuffed-tunneled cathether. These catheters serve best as an access bridge to permanent access. Comparative trials of new AV graft materials have been ongoing. To date none has emerged as superior to PTFE. The only new improvement that appears promising is modifying the vein graft anastomosis, by so-called flares or inserts, which may minimize turbulence. In addition, several companies are starting clinical trials with a totally subcutaneous hemodialysis catheter port. Nonetheless, the Cimino fistula is still by far the most trouble-free long-term access device available.

Dr. Harrington: You commented on the difference between 50% and 80% stenosis. Fifty percent stenosis of the access marks the time when you would like intervention to begin; 75% to 80% stenosis is where disasters are likely to take place fairly soon. Do we know enough about the rate of progression from 50% to 80% stenosis so that if you find someone with 50% stenosis, you can state that within 3, 6, or 9 months that stenosis will become 80%, or is the time course unpredictable?

Dr. Schwab: It should be predictable. Unfortunately, we currently do not have the information at hand to make a rational prediction about either the rate of progression of stenosis or what level of stenosis is associated with a thrombosis. We do know that AV grafts clot readily at blood flows of less than 600 ml/min. We also know that venous segments shown radiographically to be 50% blocked are often, but not always, associated with decreased access flow. We also know that when these 50% venous stenoses are corrected, access flow improves significantly and access patency improves.

Dr. Andrew J. King (*Division of Nephrology, New England Medical Center*): If you go to any dialysis unit in the United States, you likely will find a subgroup of patients who are receiving long-term systemic anticoagulation therapy with warfarin (Coumadin). Do you think there is an appropriate role for these agents in patients with access dysfunction? Do data support the long-term use of Coumadin?

Dr. Schwab: The data on systemic anticoagulation for improving access patency are very limited. The DOQI panel wanted to make statements dealing with anticoagulation, but the published literature was inconclusive. Thus the DOQI panel lacked evidence to guide them in making an evidence-based statement. In addition, a consensus could not be reached. It is our practice to anticoagulate only patients who develop repetitive thrombosis without an anatomic stenosis.

Dr. Ajay Singh (*Division of Nephrology, New England Medical Center*): I have two questions. There seems to be a tremendous variability among centers in the United States, and also between centers in the US and abroad, on fistula creation rates. One reason you mentioned is early referral. Could you elaborate on some of the other reasons why such variability exists?

Dr. Schwab: We believe that there are multiple reasons why the United States lags in AV fistula formation. One reason is that we tend to have a much higher incidence of diabetes as a cause of ESRD and a much higher acceptance rate for dialysis than do most other countries. Fistulas develop less well in an aging diabetic population. A second reason is that in the US, patients are referred to nephrologists late in the course of their disease. This late referral has prompted the use of rapidly maturing rather than slowly maturing accesses. A third reason is that brachial AV fistulas, which can be formed in older diabetics whereas Cimino fistulas cannot, are not widely used in the United States.

The DOQI panel thought the quickest way to increase the percentage of patients receiving AV fistulas would be to institute a change in referral patterns. I believe that nephrologists should, at the very latest, see patients by the time they develop a serum creatinine of 4 mg/dl. A goal of 40% AV fistulas in the prevalent hemodialysis population (compared with 17% currently) is a reasonable goal for 3 years from now if early referral can be accomplished.

Dr. Singh: Can you update us on anti-endothelial antibodies or protein S deficiency and their association with graft thrombosis?

Dr. Schwab: A series of hypercoagulable states (anti-

phospholopid antibody, etc.) lead to an increase in thrombosis in the absence of outflow stenosis in a small subset of patients. I say a "small" subset of patients because when the DOQI panel tried to determine from the published literature how often thrombosis occurs without significant stenoses, they concluded that this event occurred in fewer than 10% of patients with thrombosis. The working group felt that the principal problem wasn't hypercoagulability but rather failure to deal with the outflow stenosis that caused the thrombosis.

Dr. Andrew S. Levey (*Division of Nephrology, New England Medical Center*): You have come to a very logical set of conclusions. I would like to focus on your recommendations for prospective monitoring and early interventions on PTFE grafts. We all agree that randomized trials yield the best kind of evidence. You're making recommendations on the basis of non-randomized trials. Clearly, some of the results are striking but, as you point out, there is a sevenfold increase in the number of procedures required to maintain graft access patency. Have you done a cost-effectiveness analysis to compare the strategy of monitoring and early intervention versus access de-clotting and revision only after graft thrombosis?

Dr. Schwab: Anatole Besarab and colleagues conducted a well-constructed cost analysis of the use of static venous dialysis pressure monitoring [27]. They found that cumulative costs were substantially less with prospective intervention than with a conservative approach because aggressive intervention minimized unscheduled thrombotic events and minimized hospital days. That is the only study that has specifically addressed cost. The question you are asking is, are we merely substituting one procedure for another? We might be. I would also argue that even if that were the case, we are substituting an elective procedure for an urgent and unscheduled procedure.

Dr. Richard Roher (*Chief, Division of Surgical Transplants, New England Medical Center*): I congratulate you on a thorough review of the AV access field. From my perspective I have no major argument with your conclusions. I might add as well that dialysis patients all should have their access planning integrated with their transplant plans, because many could even avoid dialysis access. Also, my view is that we should view catheters in the great veins as completely unnecessary even though we know that in the real world they are needed from time to time. But we should view every one of them as indicative of our failure to make timely provisions for appropriate dialysis access.

I have a couple of observations and a couple of questions. The causes of intimal and fibromuscular hyperplasia that lead to loss of various conduits in other areas of surgery are fascinating. We see it all the time in our liver patients, whom we transplant with their TIPS, which always stenose at the outflow end even though they're veno-venous. Similarly, in patients with arterial-arterial bypass, again it is the outflow end that always has the problem, even in the absence of the needle sticks that bedevil AV fistulas. I always have been amused over some of the statistics, while not doubting for a second that AV fistulas are superior to grafts. Patients who tend to have the better veins are also younger, more robust patients and thus likely to be transplant patients. On the basis of Kaplan-Meiers' statistics, younger transplant patients are recorded at the time they get their transplant as having patent fistulas. By definition, the fistulas never fail because of the transplant. There are additional biases when access policies differ. If you have an older patient with poor veins, and you have an active peritoneal dialysis program, sometimes you don't try as hard to keep a graft or a fistula patent.

In addition to age and diabetes, what are your thoughts about the import of obesity as American beefs up and body mass index soars? I would have thought that at some point, body mass index, perhaps over 30, would become a factor. Finally, is it ever too early to create an AV fistula? Why not put it in whenever the serum creatinine is elevated?

Dr. Schwab: The relationship between patient size and access outcome has not, to my knowledge, been studied. Everyone thinks that there's an inverse relationship, in that as patients become larger, access outcomes are worse. Unfortunately, there's little in the literature to prove the point. Question two is, "when do you place an AV fistula?" The DOQI workgroup concluded that, unlike an AV graft, there was little evidence that placing an AV fistula early caused premature access failure. There was also very little evidence that placing an AV fistula early led to significant cardiovascular abnormalities. The working group concluded that by placing a primary AV fistula in a patient with a serum creatinine of 4 mg/dl, one optimizes the chance of maintaining a functioning AV fistula when the need for dialysis arises. Preliminary observations from the DOPPS study suggest that early referral to a nephrologist dramatically increases the likelihood of an AV fistula being present when dialysis is started [6].

Dr. Harrington: DOQI recommends referral to a nephrologist when the serum creatinine is 4 mg/dl. The recommendations don't explicitly suggest placing a fistula around the time the patient first sees a nephrologist. Am I wrong about that?

Dr. Schwab: No. You are correct. The reason behind that is as follows: If a patient has a creatinine of 4 mg/dl and has potential living-related donors, we think it is unnecessary to form an AV fistula.

Dr. Saad Al Shohaib (*Consultant Nephrologist, National Guard King Khalid Hospital, Jeddah, Saudi Arabia*): I have a comment and a question. In Saudi Arabia the situation is somewhat different. Patients are referred

quite late to the nephrologist. It is not unusual to see a patient for the first time whose serum creatinine level exceeds 10 mg/dl. In a situation like this, central lines are often left longer than usual, thus causing more complications, including infections, venous stenosis, and thrombosis.

My question is this: do diabetics tend to have a higher rate of access problems and complications, particularly re-stenosis?

Dr. Schwab: A study by Windus and associates suggests that type-I and type-II diabetics have more access morbidity than do nondiabetics [60]. The other factor associated with adverse outcomes was age.

Dr. Klemens Meyer (*Division of Nephrology, New England Medical Center*): We know that people whose veins have been damaged by venipuncture can have trouble forming an AV fistula, but what about the patients who have not had repeated venipunctures? What does it mean to have "bad veins?" Why do elderly diabetics not form usable fistulas?

Dr. Schwab: I think the answer is that we don't know. We do know that as you age, arterial flow diminishes and arteries become less distensible. Whether diabetics don't form AV access as well as nondiabetics because of either arterial or venous problems or both is unclear to me. Perhaps Dr. Rohrer has an opinion.

Dr. Rohrer: I think there is a metabolic defect in these patients, and also in lupus patients, that affects their vessels. But I cannot define it well. There is something about their vessels, too fragile or too small in a predictable sort of way time after time, that makes them simply fail to mature.

Dr. Meyer: What's your approach to the patient whose fistula doesn't develop? Do you work that patient up? Do you do an ultrasound? Do you do a venogram? Or do you just wait a few weeks to months and then go higher in the arm or go to a graft?

Dr. Schwab: The literature suggests that primary AV fistulas can be salvaged by identifying and tying off collateral vessels so that the blood flow is forced to flow along a single vein. Our practice is, if a radiocephalic fistula does not develop in 3 months, we either revise it as I outlined earlier or form a brachiocephalic fistula on the same side.

Dr. Ronald D. Perrone (*Division of Nephrology, New England Medical Center*): Could you comment on how you deliver bioactive agents into a graft? What sort of technology has been developed to do this? Are they systemically administered, or are they administered locally, continuously infused, impregnated, or how?

Dr. Schwab: The agents that are coming to trial now all are substances that are taken orally, once or twice per day. Gene constructs, assuming that they come into use, presumably will be delivered directly to vein anastomoses by ultrasound-directed puncture or by impregnation into the graft prior to placement. With radiation therapy, there are two options. One is the technique used in the coronary circulation, in which external beam therapy is not an option; radioactive capsules are floated to the area of angioplasty for controlled periods after the angioplasty. That certainly is possible for vein graft anastomoses, but the second option, external beam radiation, is easier and is possible in hemodialysis AV access.

Dr. Singh: I recall that that there seems to be some association between the dose of erythropoietin given intravenously and the potential for stenosis. Are there some data to support that? If there are, and given the fact that there is evidence suggesting that you get higher hematocrits if you use lower doses of Epo subcutaneously, shouldn't we all use subcutaneous Epo in outpatients?

Dr. Schwab: Let me deal with your question in two parts. First, what is the potential of erythropoietin as a mitogen for fibromuscular hyperplasia? The evidence is indirect. No prospective clinical trials have shown a difference in thrombosis rates as a function of Epo dose or of how Epo is administered. No convincing studies have suggested that increasing the hematocrit as high as 36% has any significant effect on the thrombosis rate. The Normal Hematocrit Cardiac Trial showed that patients randomized to a hematocrit of 42% $\pm$ 3% had a statistically greater likelihood of access thrombosis than did those randomized to the lower hematocrit target [61]. The reason for the greater thrombosis rate, be it more intravenous iron, much higher Epo doses, or a higher hematocrit, is unknown. Second, the DOQI panel for anemia suggested that we should convert to subcutaneous Epo dosing, primarily because we will save substantial sums of money while arriving at the same hematocrit target.

Dr. King: You alluded to the data from Jonathan Himmelfarb on endothelial hyperplasia [56], but of course the pathologic lesion is primarily vascular smooth muscle hyperplasia. In your discussion, you suggested that the hyperplasia is mediated by growth factors, including PDGF. Could you elaborate on that hypothesis and the purported cytokines involved?

Dr. Schwab: Himmelfarb demonstrated recently in *Kidney International* that PDGF stimulated smooth muscle proliferation in cell culture [56]. He then showed that you could inhibit this hyperplasia almost completely by the use of pharmacologic doses of dipyridamole.

Dr. Al Shohaib: When you say that patients should have access established when the creatinine is around 4 mg/dl, shouldn't one take into consideration the rate of progression of the renal disease? One patient with a serum creatinine of 4 mg/dl might require dialysis within a few months, whereas another might remain stable for a few years.

My second question is about patients with polycystic

kidney disease. As you know, these patients tend to have a higher hematocrit compared with other patients with end-stage disease. Do these patients have more access problems, or a higher rate of stenosis or thrombosis, than do other patients with end-stage disease?

Dr. Schwab: First, yes, rate of progression should be taken into consideration. However, by the time the patient's serum creatinine reaches 4 mg/dl, you must begin considering access placement, understanding that AV fistula maturation can take a year or more. Second, to my knowledge, there is no evidence that polycystic kidney disease per se is associated with reduced vascular access longevity.

Dr. Meyer: Is there any evidence that chronic trauma, such as excessive compression of the access with clamps or repeated puncture at one site, predisposes to stenosis?

Dr. Schwab: Evidence from our own program indicates that excessive pressure, mediated either by digital pressure or by a hemostasis clamp, will lead to thrombosis in the absence of stenosis. Indeed, studies from our center over the last 5 or 6 years have shown repeatedly that the percentage of nonanatomic or nonstenosis thrombosis is higher when a new unit opens, and diminishes over a period of 6 months to one year as the nurses gain experience; this finding squares with that from other centers.

Dr. Debbie Beasley (*Division of Nephrology, New England Medical Center*): Can you comment on which cytokine inhibitors are in clinical trials?

Dr. Schwab: To my knowledge, no companies are bringing cytokine inhibitors to trials in the area of hemodialysis access patency. Most of the agents that are suitable for an access patency trial are being tested to treat post-angioplasty injury in the coronary circulation. A prospective trial of dipyridamole, based on the previous pilot trial [57], is being actively considered. The NIH is now considering a request for applications (RFA) in the area of hemodialysis vascular access.

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