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Clinical epidemiology of arteriovenous fistula in 2007

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ABSTRACT

The native arteriovenous fistula (AVF) is considered the best access for hemodialysis due to its longer survival and lower complication rates as compared with other forms of vascular access. However, broad practice variation exists in the use of AVF among different countries and even within the same country among different regions and centers. Several barriers to AVF placement have been identified in the last decade that might explain its suboptimal use among both prevalent and incident patients. The present review summarizes and discusses recent findings from epidemiological studies on practice patterns and risk factors for AVF failure. Special emphasis is devoted to drawbacks and payoffs consequent upon the choice of the AVF as access for dialysis. In fact the AVF requires major investments in the short run but far less assistance and rework thereafter. Primary AVF failure, due to early failure or lack of maturation, is currently considered a key area of investigation to improve vascular access outcomes. The main challenge for the nephrologist today is to minimize the risk of primary failure while attempting to provide most patients with a native AVF. Improving vascular access outcomes is clearly a complex and difficult task. Recent experience from the United States suggests that multidisciplinary management is the most appropriate approach to deal with all the multifaceted aspects of end-stage renal disease care and to increase the likelihood of success.

Key words: *Arteriovenous fistula, Primary failure, Vascular access outcomes, Risk factors*

INTRODUCTION

Chronic life-sustaining hemodialysis requires a durable access to the circulatory system to feed the extracorporeal circuit (1). The ideal permanent vascular access should (a) provide longevity of use with minimal complication rates from infection and thrombosis and (b) supply high blood flow rates to deliver the prescribed dialysis dose. Failure to achieve these goals has tremendous biological and economical health consequences. It has been estimated that vascular access procedures and complications account for over 20% of hospitalizations of dialysis patients and cost over $1 billion annually in the United States (2).

Currently, the native arteriovenous fistula (AVF) comes closest to satisfying these criteria because it lasts longer, needs less rework and is associated with lower rates of infections, hospitalization and death as compared to other vascular accesses (1, 2). An analysis from Canada showed that among hemodialysis patients the cost of vascular access care was more than 5-fold lower in those who began treatment with a functioning native AVF, compared with those treated with a synthetic graft or permanent catheter (3). However, in recent years, fewer new patients have received a fistula as first permanent access, and its use among those already on hemodialysis has tended to decline (2, 4).

In an effort to improve vascular access outcomes, the National Kidney Foundation published the Dialysis Outcome Quality Initiative (DOQI) guidelines in 1997, 2001 and 2006 (1). These evidence- and opinion-based guidelines have stimulated a large body of epidemiological and clinical studies so far.

Most importantly they (a) provide recommendations to optimize vascular access management, (b) urge nephrologists to increase the number of patients dialyzing with an AVF, and (c) represent a useful tool to formulate further research questions.

Based on these recommendations, a special project was launched in July 2003 in the United States, called the National Vascular Access Improvement Initiative, which has since become known as the Fistula First Breakthrough Initiative (FFBI), a coalition of a cross-section of the end-stage renal disease (ESRD) community, sponsored by the Centers for Medicare & Medicaid Services (CMS). The Coalition includes the 18 ESRD networks, the renal community (dialysis providers, primary care physicians, nephrologists, vascular access surgeons, interventional radiologists, state survey agencies, professional societies and patient advocacy groups). Initial assistance in developing the Initiative was provided by the Institute for Healthcare Improvement (IHI) (5). The purpose of the Coalition was to increase the likelihood that every suitable patient would receive the optimal form of vascular access for that patient, and that vascular access complications would be reduced through appropriate access surveillance, monitoring and intervention. Specifically, the main goal was to reach the targets of fistula use as recommended by the K/DOQI – i.e., fistula rates of at least 40% and 50% for prevalent and incident patients, respectively – by the end of June 2006. Unexpectedly, the Initiative proved to be successful 1 year in advance (5), leading to an extension of the Initiative to the year 2009, and a new prevalence goal of 66%. Of note, initial assessment of the impact of the first DOQI guidelines indicated a relatively slow growth in the use of AVF prior to 2002 (6). After introduction of the FFBI, there has been a more substantial improvement in the prevalence of AVF in hemodialysis patients (7). Whether the AVF prevalence rate can be increased to reach 66% by 2009 as desired by the CMS (8) is currently uncertain, as is the impact of this increase of AVF construction on the fraction of poorly functioning fistulae.

We believe that the improvement of vascular access outcomes is a patient care priority on both sides of the Atlantic and that the principles and strategies of the National Vascular Access Improvement Initiative deserve the attention of the worldwide renal community. For these reasons the present reviews summarize consolidated knowledge and recent findings that help us understand how to achieve this important goal, with special focus on maximization of native fistula use, prevention and management of its most common complications and the most urgent questions that need to be addressed in the near future.

The present issue of the *Journal of Nephrology* devotes two articles to the problem of vascular accesses and the AVF: (a) epidemiological notes on vascular access options and outcomes, (b) and recent advances in AVF biology and pathophysiology. Further articles will be part of the fistula project in subsequent issues of the Journal.

Vascular access options and problems

Following the wrist/mid-forearm and upper-arm arteriovenous fistula, secondary vascular access options include the arteriovenous graft and the permanent cuffed central venous catheter. However, as compared with the native fistula, these access devices present more problems with flow, increased cost and morbidity (2, 4). Furthermore, large studies have shown a graded mortality risk, from both cardiovascular and infectious diseases, dependent on access type, with the highest risk associated with catheters, followed by grafts and then native fistulae (9, 10).

Despite these findings and the most updated recommendations (1), dialysis access data from 2002–2003 recently analyzed as part of the Dialysis Outcomes and Practice Patterns Study (DOPPS II) show broad practice variations and suboptimal fistula use (7). As compared with previous DOPPS data, prevalent hemodialysis patients dialyzed via an AVF increased from 24% to only 33% in the United States, whereas use decreased from 80% to 74% in Europe (4, 11). As mentioned, however, a large number of US institutions have successfully increased the prevalence of native arteriovenous fistulae by implementing multiprofessional interdisciplinary programs, led by a nephrologist or by a renal nurse (12-14).

Yet, the increasing use of catheters for dialysis is a matter of concern all over the world, but particularly in Europe, where the proportion of prevalent patients with permanent catheters has been estimated to be as high as 25% (15). Recent surveys in Italy, reported a decline in the use of both fistulae and grafts over the last 5 years (from 90% to less than 80% and from 10% to less that 5%, respectively) accompanied by an increased number of prevalent patients using permanent catheters, from 5% to over 15% (16). Although several justifiable reasons exist for protracted dialysis catheter use – e.g., as bridge angioaccess device while the patient is awaiting living-related kidney

donor transplantation or maturation of an autologous fistula or graft – vascular anatomy unsuitability or exhaustion of all possible options is an increasingly advocated indication (15). Underestimation of the opportunities to succeed even in the most difficult cases, along with an easy attitude to surrender, may be responsible for the alarming increase in the use of catheters in Europe.

It has been shown that the above-mentioned variations in fistula prevalence by country or large geographic region persist even after adjustment for multiple demographic factors and comorbid conditions (17). In addition, variations exist in single dialysis units within a metropolitan area, probably reflecting the individual preferences or skill level of the surgeons, nephrologists and dialysis unit staff (4). Furthermore, there are studies documenting that grafts are often and explicitly preferred over fistulae (18). Understanding how practice patterns and patient characteristics may impact on the prevalence of patients dialyzing with a fistula and identifying barriers to optimal vascular access choice are of paramount importance to increase the rate of fistula placement in United States and to interrupt the decline of fistula use in Europe.

Barriers to fistula placement

A recent analysis of Veterans Affairs Administration data in the United States reported that the likelihood of fistula placement was a direct function of the volume of center procedures and suggested the existence of a clustering effect at the level of the surgeon, indicating an association with surgeon practice patterns (19). It is possible that superior processes of care in larger centers may reflect not only the development of greater levels of skill resulting from the greater number of procedures performed but also better dissemination of guidelines within the surgical community and more communication between surgeons and nephrologists. Additional factors may well be local policies, degrees of access to tertiary care, reimbursement practices and other financial issues penalizing fistula construction.

In addition to clinical policies, 3 further factors may have impacted on fistula utilization. First, patients entering dialysis programs today tend to be older and more commonly have diabetes. As a result of a more liberal access to dialysis, an aging population and the diabetes epidemic, such patients have multiple comorbid conditions (20, 21). Older age, diabetes and cardiovascular diseases are usually associated with poor quality of the arteries and veins which make the construction of distal fistulae more challenging. In spite of the exceptional skills and dedication called upon, fistula placement tends to be less successful in these patients when measured as maturation, short- and long-term patency rates, ease of cannulation and need for further assistance/intervention to prevent and treat complications. Indeed the choice of the fistula has been shown to be strongly related to younger age, male gender, nondiabetic status, lower body mass index, no history of angina, absence of peripheral vascular disease and European countries versus United States (2, 4).

Second, there has been a concurrent increased emphasis on dialysis adequacy in the last several decades that has led to higher blood flow requirements to deliver higher dialysis doses without increasing dialysis times. As a result the average blood flow has increased from less than 250 ml/min to values often greater than 300 ml/min. In the United States, the last clinical performance report from the CMS indicated average blood flows >400 ml/min in both fistulae and grafts (22). These considerations have probably led to an increased utilization of grafts or larger gauge catheters (23).

Third, it may be that both surgeons and nephrologists caring for patients with apparent or established poor prognosis actually practice therapeutic nihilism. Indeed, the choice of the fistula implies a considerable initial effort in terms of care planning and access assistance, whereas in the short run early failure or lack of maturation might be problematic (24). This may also explain why fistulae remain underutilized among patients referred late to the nephrologist. These patients tend to be older and are often seen by other specialists for multiple comorbid conditions, which may engender hesitation or even reluctance to consider additional care plans. It has been reported that patients referred late to the nephrologist are highly likely to use catheters not only at initiation of dialysis but also in the subsequent months and are also less likely to receive a fistula as permanent access (2, 4).

The existence of these multiple associations between clinical characteristics, suboptimal care before/around dialysis initiation and type of vascular access in use raises the issue of indication bias that must be taken into account when interpreting the results of patient survival data (10). In other words, unmeasured or unmeasurable factors (such as the degree of disease severity, of vessel availability or sclerosis or even other, unknown factors) may mask residual confounding predisposing patients to both use of suboptimal vascular access and death. On the other hand, multiple studies have also shown that grafts have

poorer outcomes than fistulae even in facilities in which grafts are preferred over fistulae (20) and that there are reasons to prefer the native fistula over other accesses. The growing use of grafts in the United States observed in the 1980s triggered important waves of investigations showing that (a) grafts are at very high risk of thrombosis (usually secondary to progressive stenosis at the level of the venous anastomosis or draining vein), (b) prophylactic angioplasty of these lesions is necessary to improve access patency and (c) monitoring methods for detection of hemodynamically significant graft stenosis are required to trigger these prophylactic procedures (1). Most importantly, graft stenosis is not only a frequent event, but it tends to recur, making monitoring and intervention assistance protocols labor intensive and costly (2).

The choice of the native fistula: drawbacks and payoffs

A major problem with the arteriovenous fistula is the high frequency of primary failure, either due to early thrombosis or lack of maturation. Placing fistulae in more patients as is recommended by the FFBI (5) is expected to increase the risk of primary failure. Indeed this risk was around 10%-20% in former studies (2, 25), whereas in more recent series it has been reported to be from 2 to 5 times higher (2). Programs that adopt the CMS FFBI may find an increasing fraction of such fistulae not maturing to a point permitting successful cannulation and hemodialysis (26-28).

This variation in AVF maturation may result from both variability in the risk factor distribution in different study populations and differences in the outcome definition adopted which includes 2 interrelated events. In fact insufficient maturation may predispose to early thrombosis and vice versa, problematic vessels at risk of early complications may slow or hinder the arterialization process of the vein making the fistula conduit unusable for dialysis. Objective and accurate criteria for primary failure cannot be adopted easily in clinical research, and some variation exists in the published literature regarding the definition of what an "unsuccessful" as opposed to a "successful" fistula is. From a practical view point, some clinical characteristics may appear unequivocal and easily applicable such as the presence of a thrill or bruit, the ability to cannulate and use the fistula reproducibly for a minimum period of time with a prespecified dialysis blood flow. However, detailed information cannot be easily collected in large studies. The use of the fistula for at least 2 or 4 weeks of consecutive dialysis sessions after the first cannulation has been recently advocated (2) and adopted in some investigations (29, 30). This time criterion appears to be reliable since it is based on reproducible measurements of time and is acceptably valid, although extrinsic factors rather than intrinsic properties of the conduit (e.g., underestimation of the dry body weight with hypovolemia) may be responsible for unsuccessful utilization.

Few investigations have made an attempt to estimate the incidence of primary failure based on the above criteria. In 1 recent multicenter study, 513 out of 535 consecutive incident hemodialysis patients (96%) received a native fistula (24). Primary failure (defined as unsuccessful fistula utilization for at least 6 consecutive dialysis sessions – 2 weeks) occurred in 119 of them (23%). Of these, a salvage procedure was successful in 35 patients, while 84 subjects (16%) underwent a second fistula construction. In this series, primary and secondary thrombotic events within 1 month of fistula placement occurred with a frequency of 11.8% and 8.3%, respectively. In series including lower proportions of patients receiving a native fistula as first access, Feldman et al (using the same operational criteria) reported a primary failure of 44.5% (29), whereas Lok et al found a primary failure rate of 41% (30). These earlier events demand subsequent interventions for repair and salvage or to promote fistula maturation, or alternatively, for the construction of another vascular access. If the patient is already on dialysis, these problems entail prolonged hemodialysis with a temporary dialysis catheter with all its attendant complications, including poor blood flows, frequent thrombosis or malfunction, and life-threatening bacteriemia.

Primary failure impacts also on the overall survival probability of the access. One-year primary (intervention-free or unassisted) and secondary (assisted) fistula survival probabilities have been found to be higher than those of grafts after exclusion of early events but not when early events were included in the analyses (31, 32). Clearly, the risk of complications and the frequency of rescue procedures are much lower once fistulae have matured enough to be used. It has been shown that the risk of infection is higher in grafts and that maintaining long-term patency requires a 2.4- to 7-fold higher number of salvage interventions in grafts than in fistulae (2). Therefore, the fistula requires a greater investment in the short run but far less assistance and rework thereafter. The main challenge for the nephrologist is to minimize the risk of primary failure while attempting to provide most patients with a native fistula.

RISK FACTORS OF PRIMARY FISTULA FAILURE

The identification of risk factors for early thrombosis or lack of maturation has been attempted with the purpose of enhancing the likelihood of a successful fistula placement and advice decision making in the access type selection process (24, 29, 30). Unfortunately, at present no easily accessible, valid and reliable diagnostic test is available to provide clinicians with meaningful prognostic information. Indeed primary failure occurs with similar frequency in centers where preoperative vascular mapping is routinely used to guide the choice of access type and location (32) as well as in programs where routine mapping is not in place (33).

Unplanned surgery and late referral to the nephrologist, quality/diameter of the vessels, presence of cardiovascular diseases (peripheral and coronary artery diseases and heart failure), normal or low blood pressure, older age and race have all been found to predict primary failure (24, 29, 30). The experience of the surgeon may also be an important factor affecting primary failure in general, but especially early complications and thrombosis (3). Lok et al recently tried to differentiate between early surgical failure (e.g., as a result of thrombosis or technical complications) and failure to mature (30). Failure to mature was defined as a fistula that was used for hemodialysis and was unable to provide the prescribed dialysis dose via 2-needle cannulation consistently (i.e., 2-needle cannulation for two thirds or more of all dialysis runs) for 1 month within 6 months of its creation, despite interventions to facilitate maturation. They defined 4 risk categories for failure to mature (low, moderate, high and very high) derived from a logistic model including age, coronary artery disease, peripheral vascular disease and race as predictors and validated a simple and easily reproducible preoperative, clinical prediction rule to determine fistulae that are likely to fail maturation. These categories predicted a risk of failure to mature estimated at 24%, 34%, 50% and 69% among four quartiles (30). Despite such efforts, it is unclear whether the best option for the patient at high risk for primary failure is to receive an arteriovenous graft or to receive a fistula anyway once optimal strategies to treat modifiable risk factors for early thrombosis and lack of maturation (hypovolemia and cardiac diseases) have been addressed. Indeed a substantial proportion of patients with marginal fistulae may still undergo successful salvage procedures or receive successful placement of a new fistula after a former fistula has failed (33). Alternatively, some advocate the placement of a forearm loop graft when the artery or veins in the forearm are unsuitable for primary AVF construction in order to mature the vein in the upper arm followed by a strategy of conversion to an elbow-level AVF rather than attempts to salvage a graft with repeated interventions. Unfortunately, the benefits of possible other interventions and maneuvers such as a treatment course based on antiplatelet agents or regular hand exercise to promote maturation of a primary new fistula are still unproven (2).

FACTORS IMPACTING LONGER TERM OUTCOMES

The natural development of the fistula suggests which factors may interfere with the process of arterialization of the vein once the arteriovenous anastomosis is made and which may favor stenosis and thrombosis of the conduit. It has been shown that the blood flow rate within the radial artery increases from 20-30 ml/min before surgery to 200-300 ml/min immediately after surgery and to 600-1,200 ml/min in a few weeks, provided that the vessel is healthy and the blood pressure is normal (34). Data reported by Lomonte et al (35) document that the most rapid increases in flow occur within the first week, with progressively smaller increases. In their series, in 17 of 18 primary radiocephalic fistulae, brachial artery flow feeding the fistula was >480 ml/min at day 28 postconstruction. Final flow at 4-12 months averaged almost a liter. Since the blood flow at rest to the arm averages less than 80 ml/min (36), the above studies suggest that a clinical assessment of maturation can be made at 1 month. Indeed, some programs do make the evaluation as early as 1 month (37).

Flow increases as a result of both vasodilatation and eccentric hypertrophy of the venous limb and vascular remodeling without hypertrophy of the arterial vessel, the amount of which is mostly influenced by the quality of the artery. Intuitively, fistula failure can be expected to occur when the vessel wall is either not ready for use (insufficient maturation), is damaged (unskilled cannulation practice) or becomes abnormal (atherosclerosis, calcifications and/or fibrosis); when rheological factors slow the speed of the blood within the conduit (hypovolemia and underestimation of the dry body weight, hypotension and/or cardiac disease); and when the blood itself and/or the vessel walls contain factors favoring fibrin formation and platelet aggregation (coagulation

factors, platelet dysfunction and genetic and nontraditional cardiovascular risk factors). The idea of the Virchow's triad gives priority to thrombosis as the major complication of the arteriovenous fistula, although it is usually preceded by vessel stenosis. As a matter of fact, thrombosis is also the final mechanism through which the fistula fails, whereas other complications such as edema, hyper-flow and heart failure, acute or chronic ischemia, hematoma, infections, aneurysms and pseudo-aneurysms occur with relatively low frequency (33).

Numerous clinicopathological risk factors for failure have emerged from observational studies and can be incorporated into this pathophysiological model. Despite biological plausibility, for some (gender, age, diabetes and cancer, for example), available data are inconsistent (2, 38). Conversely cardiovascular diseases, late referral and use of catheters were consistently found to predict shorter fistula survival even accounting for concomitant comorbidities and other prognostic factors (3, 24, 39, 40).

Interestingly, in 1 of the above-mentioned series, an interaction was found between insufficient predialysis care and heart failure, with lack of independent effects of cardiac diseases in presence of timely patient referral to the nephrologist (24). This sheds light on the importance of treatment of cardiovascular diseases and preparation for dialysis, including timely vascular access placement (5, 39). To allow the fistula to be ready for use prior to the need for maintenance dialysis and considering an average maturation time of 2-4 months, access placement should be planned in a timely fashion in predialysis patients, possibly when their creatinine clearance is less than 25 ml/min, and depending on the rate of disease progression (1). Indeed, 2 recent studies showed that a maturation time of at least 2 month and 2 weeks, respectively, predicts longer primary and secondary fistula survival from the first cannulation date (39, 40). The issue of the optimal waiting time between placement and first fistula use has recently been debated after a second publication from the DOPPS failed to show an association between maturation time policy of the center and fistula survival (41). The authors raised doubts regarding the importance of allowing a minimum period of time since creation and suggested that clinical examination rather than the time elapsed since its creation should form the basis of the decision to cannulate (41). The use of the facility-level practice pattern rather the measured maturation time of the fistula was criticized given that physicians' opinions and experiences as well as the actual maturation allowed may vary widely within facilities independent of their policy (42). A consensus was finally reached to consider at least 1 month of maturation time safer even when the fistula appears clinically ready for use sooner (42, 43). Indeed, because time is only 1 component of the maturation process of the fistula, early cannulation may not only increase the risk of failure through subclinical microhemorrhages, fibrosis and vessel wall damage, even in the absence of overt hematomas, but also interfere with the access maturation process itself (44, 45).

Cannulation techniques, through tissue displacement and repair, may also impact the enlargement of the fistula, as well as induce the formation of aneurisms and scars that in turn may favor the development of stenotic lesions and have an impact on fistula survival. The puncture of the arteriovenous conduit causes a wall defect, initially filled by thrombi and subsequently repaired by healing. There are 3 options for cannulation: (a) the rope ladder pattern, with punctures regularly distributed along the entire length of the arterialized vein; (b) the area puncture pattern with needling restricted to small areas and (c) the buttonhole pattern, where punctures are always performed through exactly identical spots using dull needles. Of the 3 methods, the buttonhole has the theoretical advantage of limiting the process of dilatation and fibrosis because the thrombus is displaced while it is undergoing organization, favoring the formation of a cylindrical scar from the subcutaneous and vessel wall tissues. The rope ladder technique may have the initial advantage of favoring progressive dilation along the entire length of the fistula. The area puncture technique is probably associated with the worst consequences – i.e., circumscribed dilation, disruption of wall texture and aneurysm formation. However, these hypotheses have not been tested in experimental studies to date.

Finally, few but interesting data have been reported on measures of venous distensibility and their potential to predict conduit maturation and longevity (46); on the negative impact of preexisting intimal hyperplasia (47); on the role of markers of inflammation (48); and on cytomegalovirus serology, hyperparathyroidism and use of high doses of recombinant human erythropoietin (49); hyperhomocysteinemia (50); thrombophilic disorders (51); and platelet activation (52). These epidemiological findings need to be integrated with emerging cellular and molecular data on neointimal hyperplasia and stenotic lesions of the arteriovenous fistula.

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