Arteriovenous fistula after renal transplantation: utility, futility or threat?

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Keywords: arteriovenous fistulas; left ventricular morphology; renal transplantation

Introduction

Creation of an arteriovenous (AV) fistula for haemodialysis therapy provides convenient access to the circulation in patients with end-stage renal disease. However, the chronic volume overload induced by the AV fistula induces structural and functional cardiac changes, including left ventricular remodelling, which may be deleterious. The balance between the need for vascular access and the deleterious effects of a patent AV fistula on cardiac function and morphology obviously favours the former in patients requiring long-term haemodialysis. After renal transplantation, however, the value of keeping an AV fistula patent is more uncertain and whether it should be closed after successful renal transplantation remains a matter of debate. Since recent studies have provided more insight into the cardiac and haemodynamic changes induced by the procedure, this review aims to summarize the pros and cons of AV fistula closure.

Determinants of left ventricular morphology after renal transplantation

Left ventricular hypertrophy is highly prevalent among patients with end-stage renal disease [1]. Hypertension and chronic anaemia appear to be the main stimuli for the development of left ventricular hypertrophy in dialysis patients, although age, diabetes and metabolic factors may also play a role. Left ventricular dilatation is also frequent and is associated with anaemia, hypertension, hypoalbuminaemia, ischaemic heart disease and plasma volume expansion [2]. In addition, left ventricular adaptation to the chronic volume overload induced by AV fistulas is characterized by increased stroke volume and cardiac output and by left ventricular enlargement; the resulting left ventricular hypertrophy is predominantly eccentric (i.e. characterized by increased left ventricular mass with normal relative wall thickness) [2,3]. Renal transplantation improves left ventricular volume, paralleling the correction of uraemia and volume status, the normalization of the haemoglobin level and the rise in serum albumin and may reduce left ventricular hypertrophy [4,5]. However, the prevalence of left ventricular hypertrophy remains high, with uncontrolled hypertension and anaemia as main contributing factors. Strict blood pressure control contributes to the regression of left ventricular hypertrophy [6]. The effect of a patent AV fistula on left ventricular morphology after renal transplantation had received little attention until recent data suggested a significant contribution to residual hypertrophy [7–11].

Deleterious effects of AV fistulas

Complications of AV fistulas are not uncommon and include steal syndrome, arm oedema, thrombosis and, rarely, traumatic bleeding. Furthermore, patients frequently consider the presence of a dilated and
pulsatile fistula as non-aesthetic. In addition to local complications, a haemodynamically significant role of the fistula is supported by numerous case reports showing high output cardiac failure subsiding after AV fistula closure. Obviously, these reports involved patients with large AV fistulas and it is difficult to extrapolate the detrimental effects of AV fistulas to larger samples of patients with smaller AV access. Even when heart failure is not evident, the creation of an AV fistula stimulates brain natriuretic peptide (BNP) release in response to myocardial tension and increased intravascular volume [12], an interesting observation in light of the fact that raised BNP may predict survival even in patients with asymptomatic heart failure [13]. In addition, AV fistula creation may adversely affect the balance between cardiac oxygen supply and demand [14] and may predispose to a risk of myocardial ischaemia by reducing subendocardial perfusion [15].

Creation of an AV fistula increases left ventricular volume [12,16] and left ventricular mass is higher in transplanted patients when there is a patent AV fistula [11]. As in patients with hypertension, left ventricular mass is an independent risk factor for adverse outcomes in patients with chronic kidney disease [17] and after renal transplantation [18,19]. In uraemic patients with left ventricular dilatation, normal systolic function and a low mass-to-volume ratio, a condition that is a hallmark of volume overload and the presence of an AV fistula, the clinical outcome may be more dependent on the degree of LV dilatation than the degree of hypertrophy [5].

**Rationale for AV fistula closure**

Several prospective studies have shown an early decrease in left ventricular volume and mass after AV fistula closure [7,9], although these studies involved a rather limited number of selected patients with large and mainly symptomatic fistulas. A 6.4–8.6% decrease in left ventricular mass was found 1 month after AV fistula closure [9,10], reaching 11.1% and 15.8% at 3–4 and 21 months, respectively [7,10]. Not all patients responded to surgical closure to a similar degree and the increase in total peripheral resistance and in blood pressure during an acute compression best predicted left ventricular diameter and mass reduction [9].

Left ventricular mass reduction of a similar magnitude during antihypertensive treatment is associated with a marked reduction in risk for subsequent cardiovascular disease in hypertensive patients [20]. But will the reduced left ventricular hypertrophy associated with fistula closure translate into a similar cardiovascular risk reduction? There are currently no data allowing this extrapolation, as this would require a large population sample. Moreover, after adjustment for left ventricular mass, hypertensive patients with the eccentric left ventricular hypertrophy pattern, which is frequently found in patients with large AV fistulas (Figure 1), have been shown to experience a lower incidence of cardiovascular events compared with those patients with concentric hypertrophy (that is, increased left ventricular mass and relative wall thickness) [21]. Furthermore, in hypertensive patients, the concentric pattern, which is also the predominant geometry after AV fistula closure (Figure 1) [10], has been shown to confer a risk significantly higher than that conferred by normal left ventricular geometry [21]. Thus, beyond the net reduction in left ventricular mass, the expected beneficial effects of AV fistula closure may be hampered by the lack of normalization of left ventricular morphology. In addition to the effects on left ventricular morphology, patients often report exercise tolerance improvement (unpublished data), but this should be investigated further.

**Which patients should be considered for surgical closure?**

Should the renal graft deteriorate and graft loss occur, a return to haemodialysis therapy would require creation of a new vascular access, and ligation of an AV fistula carries the obvious disadvantage of destroying a functioning vascular access. The ideal patient for fistula closure should, therefore, have a minimal risk of graft failure that would ultimately require a new functional AV fistula and should expect significant long-term benefits from fistula closure. Hence, fistula closure should be restricted to patients with good graft function and without significant proteinuria, no history of severe or multiple acute rejection episodes and no signs of recurrence of the primary kidney disease in the graft. In our centre, 41 renal transplant patients (20 male and 21 female) underwent surgical closure of a patent AV fistula between September 1999 and April 2004. The fistula
was closed a median of 2.1 years (range: 0.7–16.5 years) after transplantation and the mean age at fistula closure was 50.2 ± 13.9 years. During a median follow-up of 45.8 months (range: 4.6–73 months), three patients returned to dialysis because of chronic allograft nephropathy and one patient died of heart failure. The overall actuarial graft survival was 84% and the death-censored graft survival was 87.9% (Figure 2). A new AV fistula could be created in all three patients who needed to resume haemodialysis. Our experience suggests that medium-term graft loss is low in carefully selected renal transplant patients and that surgical closure of an AV fistula does not seem to preclude the creation of a new vascular access should the patient need to restart dialysis. However, this low incidence of renal graft loss is likely to increase with a longer follow-up period. Furthermore, peripheral vascular status should be included in the decision analysis, to avoid closure of a vascular access in patients who have few suitable veins remaining.

Conclusions

AV fistula closure reduces left ventricular volume and mass in renal transplant patients. Whether fistula closure will reduce the associated high cardiac morbidity and mortality is unknown. There are clearly insufficient data yet to promote systematic closure of AV fistulas in kidney transplant patients with stable renal function, unless symptoms are present. The balance might favour closure in selected asymptomatic patients, with a large AV fistula, a dilated left ventricle, a low probability of graft loss and a high risk of cardiac events. Randomized large-scale prospective studies are clearly needed and, potentially, will better define the protective role of fistula closure.

Acknowledgements. P.U. has received a grant from the Fonds pour la Chirurgie Cardiaque.

Conflict of interest statement. None declared.

References

Genetic factors in progressive renal disease: the good ones, the bad ones and the ugly ducklings

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**Keywords:** animal models; gene expression profiling; genetic predisposition; kidney diseases; polymorphisms; repair capacity

**Introduction**

Worldwide, >1 million people have developed end-stage renal disease (ESRD) and need renal replacement therapy. ESRD is secondary to a broad range of diseases that include diabetic nephropathy and focal and segmental glomerulosclerosis. The rate of progression to ESRD varies among patients suffering from kidney diseases, and is to a large extent determined by genetic factors. We will discuss studies that have provided evidence for a genetic component underlying susceptibility to progressive renal disease. On the one hand, gene mutations may result in a disturbed function of the corresponding protein, which will lead directly to kidney disease. On the other hand, genetic factors may become manifest only in the presence of systemic diseases, such as hypertension and diabetes mellitus, and thus modify the outcome of the kidney disease. For instance, polymorphisms in genes encoding proteins that are able to protect the renal tissue against permanent damage may be the basis of differences in susceptibility to disease progression among patients. Identification of novel genetic factors determining renal disease susceptibility may increase the understanding of the pathogenesis of ESRD. The regenerative effects of endogenous molecules in the kidney may be exploited to counteract the growing incidence of ESRD efficiently.

**Genetic factors in kidney diseases**

In some cases, the relationship between genetics and renal disease development is evident. Examples are familial forms of focal and segmental glomerulosclerosis that are caused by mutations in the podocyte molecules podocin, CD2-associated protein, α-actinin-4 or the canonical transient receptor potential 6 [1–4]. Screening for mutations in the above-mentioned genes in sporadic cases of nephrotic syndrome has provided new insights and is increasingly being integrated in paediatric nephrology [5].

Genetic factors frequently have a less direct influence on renal disease development and become manifest only in the presence of ‘permissive conditions’ such as diabetes mellitus and hypertension. Conversely, not all patients suffering from these conditions develop renal disease or progress to ESRD, and it is likely that genetic factors determine the time of onset and the rate of progression of the kidney disease. Several studies of genetic linkage analyses in diabetic nephropathy have shown a susceptibility locus on chromosome 18q [6,7]. A polymorphism in the DNA sequence of the CNDP1 gene, which encodes the enzyme carnosinase-1, on chromosome 18q in diabetic patients determines susceptibility to develop diabetic nephropathy [8].