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Controversies in the management of the haemodialysis-related arteriovenous fistula following kidney transplantation

Pauline Vanderweckene[1], Laurent Weekers[1], Patrizio Lancellotti[1,2] and François Jouret[1,2]

[1]Divisions of Nephrology and Cardiology, Department of Internal Medicine, University of Liège Hospital (ULg CHU), Liège, Belgium and [2]Groupe Interdisciplinaire de Génoprotéomique Appliquée (GIGA), Cardiovascular Sciences, University of Liège, Liège, Belgium

Correspondence and offprint requests to: François Jouret; E-mail: francois.jouret@chu.ulg.ac.be

Abstract

Arteriovenous fistula (AVF) is regarded as the best vascular access for chronic haemodialysis (HD). Still, AVF inherently causes significant haemodynamic changes. Although the necessity for vascular access despite its putative cardiovascular complications favours AVF creation in patients under chronic HD, one may question whether sustaining a functional AVF after successful kidney transplantation extends the haemodynamic threat. Small prospective series suggest that AVF ligation causes rapid and sustained reduction in left ventricular hypertrophy. Still, the benefits of such a cardiac remodelling in long-terms of cardiovascular morbi-mortality still need to be proven. Furthermore, the elevation of diastolic blood pressure and arterial stiffness caused by AVF ligation may blunt the expected cardio-protection. Finally, the closure of a functioning AVF may accelerate the decline of kidney graft function. As a whole, the current management of a functioning AVF in kidney transplant recipients remains controversial and does not rely on strong evidence-based data. The individual risk of graft dysfunction and a return to chronic HD also needs to be balanced. Careful pre-operative functional assessments, including cardio-pulmonary testing and estimated glomerular filtration rate slope estimation, may help better selection of who might benefit the most from AVF closure. Large-scale prospective, ideally multi-centric, trials are essentially needed.

Key words: arterial stiffness, arteriovenous fistula, blood pressure, eGFR, kidney transplant recipients, left ventricular, total peripheral resistance

Introduction

Arteriovenous fistula (AVF) is regarded as the best vascular access for chronic haemodialysis (HD) in patients with end-stage renal disease (ESRD) [1, 2]. AVF provides better patient access and survival in comparison to arteriovenous grafts and central venous catheters, because with fewer access-related infections and endovascular interventions [3–5]. Efficient HD requires a flow rate of 400–600 mL/min. Since the brachial flow only reaches 60–120 mL/min in physiological conditions, a

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permanent vascular access needs to be surgically created on the basis of vessel mapping studies. A distal-to-proximal approach starting from the non-dominant arm is preferred to preserve patients' quality of life, as suggested in K/DOQI guidelines. AVF referral within ∼12 months of the estimated time to dialysis performed best among time frame strategies, although the timing of referral is classically guided by the patient's age and by his/her individual likelihood and rate of progression to ESRD [6, 7]. The AVF flows in the forearm usually reach 500–900 mL/min, whereas those in the upper arm are 900–1500 mL/min [2, 8]. Inherently, AVF causes significant haemodynamic changes in patients under chronic HD, which may lead to serious complications, including arterial steal, pulmonary hypertension (PH) and high-output cardiac failure [9]. As a reminder, high-flow accesses have been defined as flows between 1 and 1.5 L/min and/or >20% of the cardiac output (CO) [10].

Although the necessity for vascular access despite its putative increased risk of cardiovascular complications favours AVF creation in patients under chronic HD, one may question whether sustaining a functional AVF after kidney transplantation (KTx) extends such a haemodynamic threat [11–13]. *A contrario*, the AVF-associated hyperdynamic circulation has been suggested to reduce blood pressure (BP) and arterial stiffness, as well as to preserve kidney function in patients with advanced chronic kidney disease (CKD) [14–16]. Nowadays, there is no consensus concerning the strategy between surgical ligation versus watchful preservation of a functioning AVF in kidney transplant recipients (KTRs) with a well-functioning graft [17]. The present review aims at summarizing the scientific evidence concerning AVF impacts on renal and cardiovascular functions at the successive stages of kidney disease, i.e. pre-terminal CKD, chronic HD and post-KTx.

Global haemodynamic impacts of AVF

In the non-transplant population with CKD, the creation of an AVF for the purpose of HD initiation has been reported to slow down CKD progression [15, 16]. Golper *et al.* [15] retrospectively observed in a series of 123 CKD patients that AVF surgery was associated with a significant deceleration of estimated glomerular filtration rate (eGFR) slope decline from 5.9 to 0.5 mL/min/year. These intriguing observations were confirmed in a nationwide cohort of 3026 CKD US veterans: a significant reduction of eGFR loss was observed following AVF creation (from −5.6 to −4.1 mL/min/1.73 m^2/year) [16]. These clinical findings may be partly explained by the pathophysiological cascades of remote ischaemic preconditioning [18]. AVF causes brief, but repeated, periods of local ischaemia, thereby inducing systemic protection against tissue hypoperfusion. AVF also adds a low-resistance, high-compliance venous compartment to the arterial system, which may attenuate both arterial stiffness and pressure load [14]. In animals, experimental AVF acutely decreases BP and increases pulse pressure, whereas fistula closure restores BP to normal levels by modulating sodium excretion [19–21]. Similar observations were made in humans [22]. Within 14 days following AVF creation, the secretion of the atrial natriuretic peptide is induced by volume loading, whereas the release of brain natriuretic peptide is stimulated by progressive left ventricle (LV) diastolic dysfunction [23]. In an open-label, multicentre, prospective, randomized, controlled trial, Lobo *et al.* [22, 24] demonstrated that implanting a central iliac arteriovenous coupler in patients with uncontrolled hypertension produced a marked reduction in average 24-h ambulatory BP at 6 months and significantly reduced hypertensive complications.

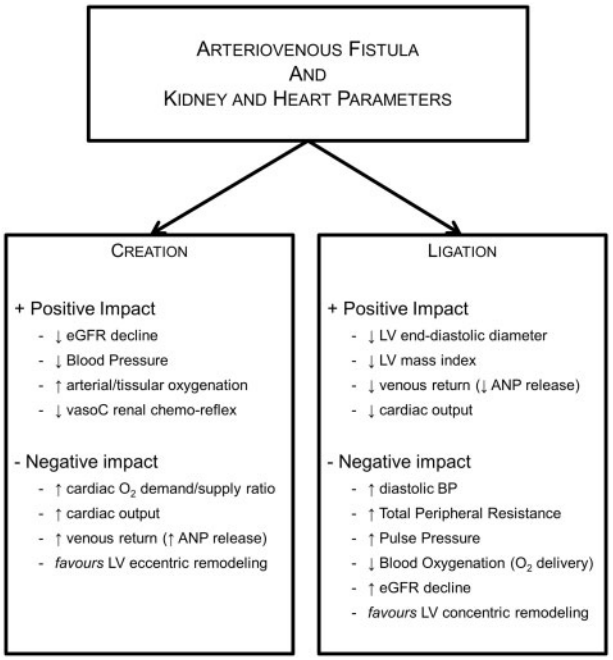

Fig. 1. Schematic summary of haemodynamic changes caused by the creation vs. ligation of an arteriovenous fistula. ANP, atrial natriuretic peptide; BP, blood pressure; LV, left ventricle; vasoC, vasoconstrictive.

This clinical trial included 83 patients randomly allocated in a 1:1 ratio to undergo implantation of an arteriovenous anastomosis plus current pharmaceutical treatment or to maintain current treatment alone (controls). Mean systolic 24-h ambulatory BP reduced by 13.5 mmHg ($P<0.0001$ versus baseline) in arteriovenous coupler recipients and by 0.5 mmHg ($P=0.86$ versus baseline) in controls. Physiologically, the addition of a low-resistance, high-compliance venous segment in parallel to the systemic arterial circulation reduces overall systemic vascular resistance (SVR), similar to Ohm's law of electrical resistance [25]. Cardiac afterload is further reduced by the reduction of effective arterial volume and arterial stress, and the slowing of reflected pressure waves [25]. Reduction of distending BP in the aorta may also improve arterial compliance, thereby generating a feed-forward loop based on reduced SVR, improved compliance and reduced BP and the long-term beneficial cardiac and aortic remodelling. Finally, AVF-mediated venous return necessarily favours pulmonary flow, which may in turn recruit larger lung areas and increase arterial oxygen content [26]. One may thus advocate that AVF favourably influence CKD progression by improving oxygen delivery to the kidney, thereby attenuating the vasoconstrictive renal chemo-reflex [18, 27] (Figure 1).

These encouraging data may be challenged by the adverse impact of AVF on the balance between poorer subendocardial oxygen supply and increased oxygen demand consequent to a greater CO [28, 29] (Figure 1).

Haemodynamic impacts of high-flow AVF in patients under chronic HD

AVF has been associated with various haemodynamic complications in patients under chronic HD, including arterial steal, PH and high-output cardiac failure. The first clinical manifestation of arterial 'steal' was reported in 1969 [30, 31]. Patients with steal progressively develop mild paraesthesia, persistent

pain, motor dysfunction and ulcerations, which correspond to ischaemic neuropathy [32]. Risk factors for the development of arterial steal include diabetes mellitus, tobacco use, female gender, advanced age, prior ipsilateral arteriovenous access placement and peripheral arterial disease [33]. HD-related steal seems to occur more frequently with brachial AVF than with radial or ulnar fistulas. In a systematic review of the Medline literature (from 2000 to 2014, including 43 English-written reports of prospective trials), Al-Jaishi *et al.* [34] concluded that the median complication rate of steal events per 1000 patient days was 0.05. The authors acknowledged that the risk of bias was high and event rates were highly variable, partly due to poor quality studies, significant heterogeneity of study populations and inconsistent definitions of 'steal syndrome'.

PH secondary to high-flow AVF has been reported [35]. PH is defined as a mean pulmonary artery pressure $\geq$25 mmHg at rest and concerns 40–48% of the population receiving long-term HD via surgical AVF [35–37]. Both ESRD and AVF are thought to participate in PH development [38]. Hormonal and metabolic perturbations caused by ESRD induce pulmonary arterial vasoconstriction and elevated pulmonary vascular resistance. Pulmonary arterial pressure may be further increased by the AVF-associated high CO, anaemia and fluid overload. Mortality among PH patients is three times higher compared with those without PH [37].

High-output cardiac failure is characterized by signs and symptoms (i.e. dyspnoea, orthopnoea, paroxysmal dyspnoea and pulmonary and/or peripheral oedema) of systemic congestion in combination with a CO >8.0 L/min and/or a cardiac index >4.0 L/min/m^2 [39, 40]. LV ejection fraction is usually preserved. In such a typical case of chronic volume overload, normal systolic function and low mass-to-volume ratio, the clinical outcome appears more dependent on LV dilatation than LV hypertrophy [41]. Still, LV hypertrophy is highly prevalent among patients with ESRD, and is an independent predictor of morbi-mortality in patients under chronic HD [42, 43]. LV hypertrophy results from combined effects of chronic haemodynamic overload, including increased flow and pressure, and non-haemodynamic biochemical and neurohumoral factors, including anaemia, chronically elevated fibroblast growth factor 23, hypoalbuminaemia and uraemic toxins [43, 44]. Age and diabetes also participate in LV hypertrophy. The HD-associated LV hypertrophy is mostly eccentric, with increased LV mass and relatively normal wall thickness. Early observations estimated that when >20% of the CO is shunted through the AVF, it predisposes to cardiac failure [31]. Reddy *et al.* [9] retrospectively characterized the long-term changes in cardiac structure and function in 137 patients undergoing AVF creation for chronic HD. Of important note, the monocentric observational design of this study, with no control group, does not allow separation of the beneficial effects of chronic HD (including volume removal) from the deleterious haemodynamic effects of the AVF. Still, after a median follow-up of 2.6 years post-AVF and HD initiation, Reddy *et al.* observed reductions in BP, body weight and estimated plasma volume coupled with modest reverse LV remodelling, which may reflect decreased LV pressure load from efficient renal replacement therapy. In contrast, AVF creation was associated with significant right ventricle (RV) dilatation and deterioration in RV function. Similar observations were reported in a longitudinal series including 24 ESRD patients [45]. Sequential cardiac magnetic resonance imaging (MRI) showed significant increases in LV and RV end-systolic volumes, left and right atrial area and LV mass following AVF creation. No significant change in aortic distensibility was identified. Note that such AVF-induced RV dilation has been independently associated with increased risk of death [9]. Buchanan *et al.* [46] recently performed a comprehensive study of the cardiovascular impact of HD sessions using intradialytic cardiac MRI in 12 stable patients. Cardiac MRI measurements included cardiac index, stroke volume index, global and regional contractile function (myocardial strain), coronary artery flow and myocardial perfusion. All measures of systolic contractile function dropped during HD, with partial recovery after dialysis. All patients experienced some degree of segmental LV dysfunction, with severity proportional to ultrafiltration rate and BP reduction. Myocardial perfusion decreased significantly during HD session [46]. In a single centre between 2003 and 2006, Movilli *et al.* [47] enrolled 25 consecutive HD patients who underwent AVF ligation and conversion to a tunnelled central venous catheter, and compared them with 36 controls with a well-functioning AVF. Outcomes were changes in echocardiographic parameters obtained before and 6 months after AVF closure for patients in the AVF-closure group, and at baseline and 6 months later for controls. Closure of the AVF caused a significant decrease in LV internal diastolic diameter, interventricular septum thickness and diastolic posterior wall thickness. This was associated with a significant decrease in LV mass and a more favourable shift of cardiac geometry towards normality.

To date, there is no consensus as to the threshold flow values in the management of steal syndrome, PH and cardiac failure in patients under chronic HD [48, 49]. The causal link between access flow and increased morbi-mortality probably exists, but still needs to be directly proven [8, 50].

Haemodynamic impacts of AVF in patients following KTx

The impact of patent AVF after successful KTx on cardiac morphology and function remains largely controversial. On one hand, the persistence of large high-flow AVF for prolonged periods of time has been reported to have little influence on heart parameters in 61 stable KTRs with adequate renal function (i.e. serum creatinine level <2 mg/dL) [12]. On the other hand, the maintenance of long-lasting AVF has been independently associated with LV hypertrophy in a monocentric cohort of 162 KTRs [11]. LV hypertrophy, with uncontrolled hypertension and persistent anaemia, contributes to the increased cardiac mortality observed among KTRs [51, 52]. Furthermore, high-output cardiac failure secondary to high-flow AVF might be a frequent condition in the KTR population. In a retrospective study including 113 KTRs with a functioning AVF, 25.7% required AVF ligation for clinical suspicion of cardiac failure. The mean shunt flow in the intervention group was 2197.2 mL/min, whereas the mean shunt flow in the non-intervention group was only 850.9 mL/min [53].

The impact of surgical ligation of the AVF on cardiovascular parameters has been studied in both observational cohorts and prospective studies including a limited number of transplant patients [12, 19, 47, 54–58] (Figure 1). In a retrospective monocentric cohort, Soleimani *et al.* [57] showed that spontaneous AVF thrombosis in 17 KTRs does not cause significant LV structural modifications compared with 23 control KTRs with a functioning AVF. Similarly, Glowinski *et al.* [58] reported in a prospective series of nine KTRs with normal-flow AVF that AVF ligation ($n=5$) or thrombosis ($n=4$) does not significantly impact cardiac function after a 3-month follow-up, in comparison with nine age- and gender-matched controls with a functioning AVF. By strong contrast, Unger *et al.* [55] demonstrated that AVF

surgical ligation reduced LV end-diastolic diameter and mass indexes within 10 weeks post-surgery, in a prospective series of 17 stable KTRs. Note that the interventricular septum thickness remained unchanged, and a slight but significant increase in posterior wall thickness was observed. Diastolic and mean arterial BP slightly, but significantly, increased following AVF ligation [55]. These observations were confirmed after a long-term follow-up of 21 months [56]. Interestingly enough, post-operative reductions in LV hypertrophy could be predicted by the dynamic increase in total peripheral resistance (TPR) and BP observed during an acute occlusion of the AVF by pneumatic compression. Hence, an increase in TPR of more than a third of baseline value predicted a ≥5% reduction in LV end-diastolic diameter index with positive predictive value of 80%. Similarly, an increase in BP during pneumatic compression of >10% of baseline predicted a ≥5% reduction in LV end-diastolic diameter index with a positive predictive value of 88% [55]. van Duijnhoven *et al.* [54] found a correlation between pre-operative LV mass and LV end-diastolic diameter and the reduction in LV mass as determined 4–5 months following AVF ligation.

Such a beneficial flow-dependent impact of AVF ligation on LV mass reduction may be partly blunted by the concurrent increase of arterial BP and TPR, as well as by the persisting abnormalities in LV geometry [29]. In a well-designed prospective study including 16 KTRs, the 24-h ambulatory blood pressure monitoring (ABPM) showed a significant increase of diastolic BP, with no systolic changes, at 1 month after surgical AVF closure [19]. BP remained unchanged within a similar time frame in 14 KTRs with a functioning fistula. It is important to remember that 24-h ABPM better assesses BP load, better correlates with target organ lesions and has superior prognostic significance compared with single BP measurement [59]. Since hypertension negatively influences long-term outcomes after KTx, the clinical benefits of LV mass reduction after AVF ligation may be unbalanced by BP increase [29]. Moreover, in hypertensive CKD patients, the concentric pattern of LV hypertrophy, which corresponds to the predominant geometry after AVF ligation, represents an independent prognostic factor of cardiovascular events [60, 61]. Finally, Ferro *et al.* [62] reported in 250 stable KTRs that the presence of a functioning AVF independently correlated with an increased aortic augmentation index (calculated by non-invasive pulse wave exploration) on the basis of a multivariate analysis (Table 1).

Concerning the evolution of renal graft function, Vajdic *et al.* retrospectively showed in a historical cohort including 311 KTRs that patients with a functioning AVF at 1 year post-KTx (69 ± 21 mL/min/1.73 m^2, $n = 239$) had significantly lower Modification of Diet in Renal Disease (MDRD) eGFR values than those with spontaneously closed AVF (74 ± 19 mL/min/1.73 m^2, $n = 72$). Adjusted analyses suggested that AVF persistence was

Table 1. Summary of the main observations post ligation of functioning AVF in KTRs

Study	Year	KTRs (*n*)	Techniques	Main findings
Retrospective				
De Lima *et al.* [12]	1999	61	Echocardiography	AVF patency • Little impact on cardiac morphology and function
Soleimani *et al.* [57]	2012	40	Echocardiography	AVF thrombosis • No impact on LV morphology
Schier *et al.* [53]	2013	113		AVF ligation in 25.7% of KTRs for suspected cardiac failure
Kolonko *et al.* [11]	2014	162	Echocardiography	AVF patency • LV hypertrophy
Weekers *et al.* [13]	2017	99	eGFR slope	AVF ligation • Accelerated eGFR decline
Prospective				
van Duijnhoven *et al.* [54]	2001	20	Echocardiography (12–16 weeks)	AVF ligation • Improvement in LV hypertrophy • Reduction in LV end-diastolic diameter
Unger *et al.* [55]	2002	17	Echocardiography (10 weeks)	AVF ligation • Reduction in LV end-diastolic diameter • Reduction in LV mass index • Increase of diastolic arterial BP
Unger *et al.* [56]	2004	17	Echocardiography (21 weeks)	AVF ligation • Reduction in LV end-diastolic diameter • Reduction in LV mass index • Increase of diastolic arterial BP
Unger *et al.* [19]	2008	16	24 h ABPM (4 weeks)	AVF ligation • Increase of diastolic arterial BP
Movilli *et al.* [47]	2010	61	Echocardiography (24 weeks)	AVF ligation • LV normal or concentric remodelling
Glowinski *et al.* [58]	2012	18	Echocardiography (12 weeks)	AVF ligation • No impact on cardiac function
Transversal				
Ferro *et al.* [62]	2002	250	Pulse wave	AVF patency • Increased arterial stiffness
Vajdic *et al.* [63]	2010	311	eGFR	AVF ligation • Better renal function at 1-year AVF patency • Increased risk of graft loss

associated with an increased risk allograft loss [63]. Note that this retrospective cohort only considered patients with AVF at the time of KTx, and excluded 91 KTRs because of early graft loss, non-functioning kidneys, technical failures or deaths during the first year post-KTx. Kidney graft function was transversally compared at 1 year post-KTx, with no consideration for eGFR slopes. Consequently, the main limitation of this observational retrospective cohort concerns the complete identification of inequities between groups. Ultimately, the physicians in charge may biasedly decide not to close the functioning AVF in patients at higher risk for CKD progression and ESRD. In a retrospective monocentric study including 285 KTRs, we investigated whether the closure of a functioning AVF significantly influenced eGFR slope (calculated using linear mixed models based on MDRD equation) post-KTx. AVF closure occurred at 653 ± 441 days post-KTx, with a thrombosis/ligation ratio of 19/95. In order to limit the unavoidable influence of transplantation vintage on eGFR slope, we first matched the follow-up periods before versus after AVF closure for every single patient. Hence, we found that the closure of a functioning AVF significantly accelerates eGFR decline over the consecutive 12-month period [13].

Conclusions and perspectives

The present review highlights that the current management of functioning AVF following KTx remains largely controversial (Figure 1). Surgical ligation is usually performed in patients with specific indications, like high-flow fistula with arterial steal, LV dilation, high-risk cardiovascular status or cosmetic reasons. The possible threat of graft dysfunction and a return to chronic HD also need to be discussed with the patient. The creation of a novel efficient AVF in case of ESRD may be extremely difficult in KTRs and not always feasible when peripheral veins are exhausted.

Small prospective series suggest that AVF ligation causes rapid and sustained reduction in LV hypertrophy [55, 56]. Still, the benefits of such a cardiac remodelling in long terms of cardiovascular morbi-mortality still need to be proven. Furthermore, as emphasized by Unger and Wissing [29], the subsequent elevation of diastolic BP and evolution toward LV concentric geometry (with increased wall thickness) may blunt the cardio-protection expected from AVF closure [19]. Furthermore, the closure of a functioning AVF may accelerate the decline of kidney graft function [13]. Therefore, careful pre-operative functional assessments, including the dynamic response of TPR and BP to a transient pneumatic occlusion of the AVF [55] and the calculation of MDRD-eGFR slope [64], may help better selection of KTRs who might benefit the most from AVF closure. Additionally, BP levels should be systematically monitored following AVF surgery, *a fortiori* when pre-operative diastolic BP is >90 mmHg. These assumptions do not rely on strong evidence-based data, and definitely need to be tested in large-scale prospective, ideally multi-centric, populations.

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Conflict of interest statement

None declared.

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