Prophylactic Ligature of AV Fistula Prevents High Output Heart Failure after Kidney Transplantation

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Keywords

High-flow fistula · Fistula ligature · Heart failure · Kidney transplantation

Abstract

Background: Arteriovenous (AV) fistulas are considered the gold standard for ensuring safe and long-term vascular access in patients with haemodialysis-dependent end-stage renal disease. However, previous studies demonstrated that high-flow AV fistulas might add additional cardiovascular burden in the post-transplant setting, leading to frequent fistula closure in this population. Currently, there is no consensus regarding management of high-flow fistulas in post-transplant patients with stable kidney function. The present randomized controlled trial examines the effect of prophylactic AV fistula closure on high-output heart failure. **Methods:** Twenty-eight kidney transplant patients with stable graft function, absence of pre-existing severe cardiac failure, and brachial arterial flow rate of at least 1,500 mL/min were recruited and randomized in a 1:1 ratio to an intervention and control group, respectively. The intervention group was subject to immediate fistula ligature. Patients within the control group were referred to fistula ligature only if the

main study endpoint high-output heart failure was reached. The latter was defined by the presence of at least 1 clinical sign (i.e., worsening NYHA score) and at least 2 of the following echocardiographic parameters: diameter of right atrium (major) >53 mm, right atrium (minor) >44 mm, inferior vena cava $\geq$ 21 mm, right pulmonary artery >20 mm, TAPSE <16 mm, systolic pulmonary artery pressure >40 mm Hg, and/or left ventricular eccentricity index <1. During a 24-month follow-up period, quarterly measurements of kidney function, NT-proBNP, and lactate dehydrogenase as well as a biannual echocardiographic check-up were performed. **Results:** High-output heart failure attributable to high-flow fistula was reported in 5 of 13 control patients (38.5%), whereas no patient in the intervention group presented with clinical and echocardiographic signs of high-output heart failure during the follow-up period. Thus, prophylactic ligature of high-flow fistulas avoided high-output heart failure in our patient population ($p = 0.013$). Three patients in the control group, however, had to undergo fistula ligature due to aneurysm formation ($n = 2$) and steal phenomenon ($n = 1$). Median NT-proBNP levels decreased from 317 ng/L pre-ligature to 223 ng/L post-ligature ($p = 0.003$). Serum creatinine levels did not significantly differ before and after AV fistula ligature (1.69 vs. 1.60 mg/dL, respectively, $p = 0.059$). Improvement

of echocardiographic findings (e.g., a decrease in systolic pulmonary arterial pressure) was found in 7 of 8 ligature patients but did not reach statistical significance. **Conclusion:** Prophylactic ligature of high-flow AV fistulas after kidney transplantation can avoid high-output heart failure, and a more liberal approach to close AV fistulas might be justified.

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Introduction

Arteriovenous (AV) fistulas are considered the gold standard of long-term vascular access for haemodialysis-dependent end-stage renal disease patients based on complication and patency rate [1, 2]. While AV fistulas are associated with superior outcome compared to AV grafts and central venous catheters, they are still associated with CV burden. Dundon et al. [3] showed a significant increase in left ventricular (LV) and right ventricular end-systolic volume (21% rise in the left ventricle and 18% in the right ventricle) as well as LV mass 6 months after fistula creation. These adaptations are necessary to keep cardiac output stable while enabling an observed rise (>2,000%) in brachial artery flow. Post-transplant AV fistula management is of particular interest, though there is no consensus so far. Studying renal transplant patients with patent ($n = 39$) versus closed ($n = 22$) AV fistulas retrospectively, no significant difference in cardiac structure and function was reported between groups [4]. In contrast, Movilli et al. [5] presented favourable effects of AV fistula ligature on LV hypertrophy in a prospective trial including 61 haemodialysis patients. We previously demonstrated that the necessity of AV fistula ligation is higher than discussed in the literature [6]: In this retrospective study involving 113 patients, 29 patients (i.e., 25.7%) had to undergo ligature of AV fistula after successful renal transplantation. The predominant reason (53%, i.e., 15 patients) for fistula closure was symptomatic heart failure with echocardiographic pathology of the right heart. After AV fistula closure, clinical symptoms and capacity for daily-life activities significantly improved in all patients. Remarkably, mean fistula flow rate in patients with and without the need for AV fistula ligation was substantially different, with 2,300 and 850 mL/min, respectively. Hicks et al. [7] analyzed the incidence of fistula ligature in US transplantation centres using the USRDS database. In a total of 16,845 patients with patent AV fistula or patent AV graft, only 4.6% (i.e., 779 patients) underwent fistula closure. There was a great difference in between the 248 participating transplant cen-

tres. In >43% of hospitals, no single ligature was made; however, 11% of the clinics performed ligation in >10% of transplanted patients. Weekers et al. [8] report rapid decline of eGFR after AV fistula closure and recommend to avoid fistula closing. Other studies focused on fistula-related development of pulmonary hypertension (PAH) which is often caused by elevated pulmonary blood flow and/or increased pulmonary vascular resistance [9–11]. PAH is generally more frequent in patients on haemodialysis (31.6%) compared with patients on peritoneal dialysis (8.3%) or after kidney transplantation (5%). Remodelling of the pulmonary vascular system seems to be reversible after renal transplantation. This remodelling may be blocked or PAH may even deteriorate in patients with high-flow fistulas. In this regard, 2 case studies by Clarkson et al. [12] and Kabitz et al. [13] showed that elevated systolic pulmonary artery pressure may dissolve immediately after fistula ligature. By reviewing this controversial topic, Vanderweckene et al. [14] demonstrate an enduring need for more prospective data on long-term effects of fistula ligature on morbidity and mortality in kidney transplant patients. The aim of our study was to test whether prophylactic post-transplant ligature of AV fistulas could prevent the occurrence of adverse cardiac remodelling and consecutive heart failure related to high fistula flow in a randomized controlled intervention trial.

Material and Methods

This prospective randomized controlled trial was conducted at the Department of Internal Medicine IV, Nephrology and Hypertension, Medical University Innsbruck. Approval from the local ethics committee was obtained prior to study initiation. Written informed consent was obtained from all patients before enrolment.

Kidney transplant patients with regular post-transplant follow-up at the Department of Internal Medicine IV were eligible for study participation when meeting the following inclusion criteria:

- Kidney transplantation in the past 3–24 months at the Department of Surgery, Medical University Innsbruck.
- AV fistula with a brachial artery flow of at least 1,500 mL/min assessed with ultrasound flow measurement. Stable renal graft function (i.e., eGFR of >30 mL/min and eGFR decline <10 mL/min during months 3–6 after transplantation).

Exclusion criteria were pre-existing heart failure with ejection fraction of less than 25%, sPAP >40 mm Hg 3 months after kidney transplantation, NT-proBNP value of >1,400 pg/mL, or symptoms of congestive heart failure according to NYHA III or IV.

250 patients were screened between 2013 and 2018 in the context of their regular post-transplantation visits at the Department of Internal Medicine IV (see Fig. 1). Screening included initial echocardiography and Doppler ultrasound-based assessment of fistula flow rate. Doppler ultrasound examination was performed

Fig. 1. Screening and allocation algorithm.

by a single nephrologist with the highest experience in sonographic fistula flow examination at the Department of Internal Medicine IV using A Philips iU22 ultrasound device and a L17-5 (17 MHz) linear probe. Time-average velocity of the cross-sectional area of the brachial artery (AB) was assessed proximal of the elbow. The flow volume of the fistula is the calculated product of mean velocity $\times$ cross-sectional area. Mean flow volume rate of 3 (in case of <10% inter-measurement variation) to 5 (in case of 10–20% inter-measurement variation) consecutive measurements was used [15].

Patients were divided into 3 groups according to fistula flow: Group 1: fistula flow <1,000 mL/min. Patients assigned to group 1 were excluded because of a low likelihood of developing high-output heart failure. Group 2: fistula flow of 1,000–1,500 mL/min. Patients assigned to group 2 underwent another fistula flow assessment 3 months after the screening visit and were re-assigned to group 3 if fistula flow increased to >1,500 mL/min. Group 3: fistula flow >1,500 mL/min on first ultrasound flow assessment. These subjects were evaluated by echocardiography. Twenty-two patients (16/22 with brachiocephalic fistula) with established PAH or/and right cardiac dilatation at the first echocardiographic assessment were not eligible for randomization and referred to fistula ligation 3 months after transplantation. The remaining 28 pa-

tients allocated to group 3 fully met the inclusion criteria and were randomized in a 1:1 ratio to control and intervention groups. While the intervention group was subject to immediate AV fistula ligation at the Department of Vascular Surgery before entering a 24-month follow-up period, the control group entered follow-up without upfront surgical intervention. Both groups received the same accurate follow-up with at least biannually echocardiographic ultrasound examination and fistula flow measurement. Parameters of renal function (i.e., serum creatinine and urea level as well as eGFR according to the MDRD formula [16]) were assessed at least 3 monthly in the context of patients' routine follow-up.

The primary study endpoint was occurrence of right heart failure defined by at least 1 clinical sign and at least 2 echocardiographic parameters suggestive for right heart failure:

- Clinical signs of right heart failure: Dyspnoea on exercise (i.e., worsening in NYHA score), pleural effusions, or peripheral oedema. All patients were encouraged to exercise on a daily basis by walking after renal transplantation and to gradually increase their exercise program. If walking distance did not improve or shortness of breath occurred, patients were subject to further evaluation (i.e., echocardiography, chest X-ray, and laboratory testing).

Table 1. Patients' characteristics at baseline

Characteristics	Intervention (<i>n</i> = 14)	Control (<i>n</i> = 14)
Age, years, median (IQR) [range]	52.5 (15.5) [18–67]	52.5 (11.5) [31–69]
Sex, <i>n</i> (%)		
Male	12 (85.7)	12 (85.7)
Female	2 (14.3)	2 (14.3)
Dialysis time, months (IQR) [range]	34 (24.5) [14–90]	32.5 (32.75) [5–74]
Fistula flow, L/min per m ² body surface, median (IQR) [range]	0.98 (0.25) [0.78–1.4]	1.00 (0.58) [0.69–1.57]
Fistula flow, L/min, median (IQR) [range]	1.85 (0.48) [1.59–2.75]	1.8 (0.67) [1.5–2.8]
Proportion of upper arm fistulas, <i>n</i> (%)	3 (21.4)	6 (42.9)
eGFR, mL/min, mean (SD)	45 (13.76)	43 (10.77)
Creatinine, mg/100 mL, mean (SD)	1.64 (0.62)	1.69 (0.47)
NT-proBNP, ng/L, median (IQR)	317 (864)	281 (166)
Systolic PAP, mm Hg, median (IQR)	30.5 (16.7)	35 (11.8)
Diameter right atrium minor, mm, median (IQR)	36.5 (8.25)	38 (11)
Diameter right atrium major, mm, median (IQR)	46.5 (6.45)	48 (14)

- Echocardiographic criteria for right heart failure: Diameter of right atrium major >53 mm, diameter of right atrium minor >44 mm, inferior vena cava ≥21 mm, diameter of right pulmonary artery >20 mm, TAPSE <16 mm, systolic pulmonary artery pressure >40 mm Hg, and left ventricular eccentricity index <1.

Echocardiographic monitoring was performed at the Department of Cardiology at MUI. Echocardiographic criteria were established by our on-site cardiologist, who performed or supervised all echocardiographic exams assuring the smallest inter-operator difference for each parameter. Measurement of right atrial and ventricular diameter as well as the pulmonary artery pressure was conducted according to standard operating procedures. Measurement of systolic pulmonary artery pressure followed the principle of pulmonary outflow tract acceleration time [17].

In addition to planned biannual echocardiographic examination, patients presenting with clinical signs of heart failure were immediately referred to additional echocardiographic examination. Patients fulfilling echocardiographic and clinical criteria of right heart failure in the control group were immediately subject to fistula closure. According to state-of-the-art literature, AV fistula ligation is indicated in patients with clinical and echocardiographic signs of high-output heart failure and stable kidney graft function. Thus, remaining below echocardiographic criteria of right heart failure (see the definition earlier) was a prerequisite for entering the study. The majority of patients with upper arm fistula, especially women, had to be primarily excluded from this study due to these criteria. Pre-existing minor elevation in pulmonary artery pressure (<40 mm Hg) or pre-existing single right ventricular dilatation was no exclusion criteria since elevated PAH levels are common in patients with haemodialysis and after recent transplantation [10, 11]. However, in case of pre-existing minor PAH or single right ventricular dilatation, cautious screening for deterioration of pulmonary artery pressure or right ventricular dilatation was conducted. For patients with a single pre-existing right ventricular dilatation, a diameter increase of 50%, an ejection fraction of <25%, or an NT-proBNP of >1,600 ng/mL during follow-up prompted surgical AV fistula ligation. Focussing on right heart pathologies has been based on the available literature examining

the right heart system in nephrological context (“renal fistula toxicity”) [18–20]. In this regard, Floccari et al. [20] showed that a reduction in compliance and systolic function of right heart chambers occurs early and frequently in the course of chronic kidney disease. In addition to assessing between-group differences in the occurrence of right heart failure (i.e., primary end point), we investigated the change in NT-proBNP levels, pulmonary artery pressure, diameter of right atrium, and renal function parameters after fistula ligation. Body-surface calculation was done according to the Mosteller formula [21]. Patient follow-up was maintained for 24 months after randomization. Upon completion of follow-up, most patients continued post-transplant care at our department.

Creation and Ligation of Autogenous AV Fistulas

The following techniques are common to all autogenous vein access creations in our department of vascular surgery: The distal end of the vein is transected and ligated. After clamping the artery, a longitudinal arteriotomy of about 4-mm length is made. The AV anastomosis is performed end to side with a 6-0 or 7-0 monofilament non-absorbable continuous suture.

For ligation, the vein will be dissected, mobilized, and transected between two clamps close to the anastomosis. After ligating the proximal end, the artery will be reconstructed with a linear suture. In case of vessel elongation, the anastomosis will be resected completely and an end-to-end anastomosis of the artery will be performed. Venous aneurysm is resected close to the anastomosis, and the remaining vein is left in situ. To obtain better cosmetic results and to reduce the risk of developing thrombosis of aneurysmatic fistulas, we apply a postoperative arm compression bandage for 3 weeks.

Statistical Analysis

Clinical data collection was performed using routinely implemented computerized clinical documentation systems at our department (Powerchart and Diadem). The distribution of high-output heart failure between groups was analyzed using the chi-square test based on 2 × 2 tabulation. The comparison of laboratory

Table 2. Ligature criteria in patients (control group)

Patient 1	Systolic PAP 50 mm Hg, diameter of right atrium 40/53 mm, RPA 19 mm (borderline to 20 mm) Patient's condition: impaired performance status, dyspnoea NYHA II
Patient 2	Systolic PAP 40 mm Hg, RPA 23 mm, diameter of right atrium 49/58 mm (fulfilling both criteria for right atrium dilatation), TAPSE 13 Patient's condition: newly occurred dyspnoea NYHA III
Patient 3	Diameter of right atrium 53/45 mm (fulfilling both criteria for right atrium dilatation) Patient's condition: newly occurred dyspnoea NYHA II
Patient 4	Diameter of right atrium 45/55 mm (fulfilling both criteria for right atrium dilatation) Patient's condition: newly occurred dyspnoea NYHA II with very high shunt volume (2.8 L/min)
Patient 5	RPA 21 mm, diameter right atrium 44/49 mm, left ventricular eccentricity index 0.84, Inferior vena cava >21 mm Patient's condition: worsening leg oedema with very high shunt volume (2.8 L/min)

Table 3. Comparing patients with prophylactic ligature and patients with high-output failure directly before ligature

Characteristics	Intervention group patients, <i>n</i> = 14	High-output failure patients, <i>n</i> = 5
Time between study recruitment and ligature, months (range)	1.0 (1–8)	7.0 (4–24)
Time on dialysis (range)	34.0 (14–90)	43.0 (12–74)
Diameter of right atrium major, mm, median (range)	46.5 (36–52)	53 (53–58)
Diameter of right atrium minor, mm, median (range)	36.5 (29–42)	45 (40–49)
Median systolic PAP, mmHg, median (range)	30.5 (25–50)	35 (27–50)
NT-proBNP, ng/L, median (range)	317 (50–1907)	337 (134–2239)
Creatinine level, mg/100 mL, mean (range)	1.64 (0.96–3.11)	1.83 (1.32–2.27)
eGFR, mL/min, mean (SD)	45 (20–60)	44 (30–53)
Lactate dehydrogenase level, U/L, median (range)	282 (177–581)	189 (179–467)

and echocardiographic findings before and after fistula ligature was performed using a 2-tailed *t* test for normal distributed data or the Wilcoxon signed-rank test for non-normal distributed data. Normal distribution of data was assessed by using the Shapiro-Wilk test. Correlation between fistula flow rate and various clinical parameters was conducted by using linear regression analysis and ANOVA. The cut-off for statistical significance was set at a *p* value of <0.05. Statistical analysis was performed using Microsoft Excel and SPSS.

Results

The baseline characteristics of intervention and control group patients are shown in Table 1. In each group, 1 patient died during the follow-up period, but deaths were not related to the study procedure. In the intervention group, 1 patient died of suspected myocardial infarction 5 months after fistula ligature. In the control group,

death was confirmed as myocardial infarction related. No renal- or heart-failure-related deaths were observed. In each group, 1 patient was lost to follow-up.

The primary endpoint right heart failure, and thus indication for fistula ligature, occurred in 38.5%, i.e., in 5 of 13 control group patients (per-protocol analysis). In the intervention group, no patient presented with right heart failure according to study definitions. Prophylactic AV fistula ligature prevented right heart failure compared to the control group (*p* = 0.013). The clinical presentation of each patient meeting ligature criteria is shown in Table 2. No significant correlation was found between any laboratory parameter and the occurrence of right heart failure in the control group. The predominant criterion for reaching the echocardiographic end point right heart failure was dilatation of the right atrium with a diameter >53 mm major or >44 minor (80%). Two patients presented with increased systolic PAP, one each with TAPSE <16

mm, left ventricular eccentricity index abnormalities, or dilated inferior vena cava. Clinical characteristics of patients receiving prophylactic fistula ligation (intervention group) and patients that underwent fistula ligation due to occurrence of right heart failure (control group) are shown in Table 3. No significant between-group differences were found.

Overall, AV fistula ligation led to a decrease in NT-proBNP levels when comparing median levels directly before and after fistula closure in all patients that underwent ligation (intervention group + control group). Median NT-proBNP pre-ligation was 317 ng/L (95% CI $\pm$ 292) compared to 223 ng/L (95% CI $\pm$ 243) post-ligation (p = 0.003). Eighteen of 21 patients that underwent ligation (2 patients excluded due to missing laboratory data) presented with a fall in NT-proBNP levels (median decrease of 36%, 95% CI $\pm$ 18%). Comparing the average of last 3 NT-proBNP values before ligation with the average of first 3 values after ligation, the same trend could be observed: Median average levels before and after surgical intervention were 327 ng/L (95% CI $\pm$ 390) and 202 ng/L (95% CI $\pm$ 219), respectively (p = 0.006).

Mean creatinine levels remained stable after fistula ligation in 21 patients (2 patients with missing laboratory data), that is, 1.69 mg/dL (95% CI $\pm$ 0.27) pre-ligation versus 1.60 mg/dL (95% CI $\pm$ 0.24) post-ligation. 14 patients experienced a drop in serum creatinine levels ranging from -7 to -28% , and 7 patients presented increasing serum creatinine levels from $+1$ to $+46\%$. Overall, a non-significant mean creatinine decrease of 7% (95% CI $\pm$ 7%) from pre- to post-ligation was observed (p = 0.059). Thus, in our study cohort, the closure of AV fistula seems to have little impact on renal function with a slight tendency towards declining creatinine levels.

The following echocardiographic changes were documented after fistula ligation: The mean diameter of the right atrium (major) showed a slight reduction from 48 mm (95% CI $\pm$ 4.2) to 45 mm (95% CI $\pm$ 2.21). Ten of 15 patients with available echo data 3 months after ligation showed a mean decrease in atrium size of 11% (range 4–45%). However, observed changes in right heart diameters were not statistically significant.

No patient in the intervention group presented with symptoms of congestive heart failure during the 24-month follow-up period. As in the total cohort of patients that underwent ligation, NT-proBNP levels declined in the intervention group: 9 of 10 patients with available NT-proBNP levels directly after ligation showed falling or unchanged NT-proBNP values. The median NT-proBNP

value was 510 ng/L (95% CI $\pm$ 349) pre-OP, compared to 317 ng/L (95% CI $\pm$ 278) post-OP (p = 0.021). Likewise, the average of last 3 NT-proBNP values before and first 3 NT-proBNP values after ligation was 317 and 232.5 ng/L, respectively (p value 0.037). No significant correlation was found between fistula flow rate and NT-proBNP, atrial size, or systolic PAP.

During post-study observation, all 12 intervention group patients (1 death and 1 lost to follow-up) remained stable in cardiac and renal function (up to 88 months of routine post-transplantation follow-up). In the intervention group, 7 of 8 patients with available data (i.e., echo within 3 months post-OP) had better or constant systolic PAP levels (87.5%), 1 patient had an increase in pulmonary artery pressure (p = 0.115), and 6 of 7 patients (85.7%) showed an improved TAPSE as parameter for right heart function [22] within 3 months after ligation. Along with these echocardiographic findings, all patients reported better performance status, resolving shortness of breath and easing in daily routine activities after fistula ligation. In the control group, 1 patient (7.15%) underwent fistula ligation due to exercise-limiting acral ischaemia (“steal phenomenon”) and 2 patients (14.3%) due to progredient aneurysm with progressive risk of rupture. Another patient (7.15%) underwent fistula ligation because of impaired performance status and deteriorating dyspnoea without meeting echo criteria for right heart failure. The patient recovered quickly after fistula ligation and improved from NYHA class IV to II. AV fistula closure was an overall safe procedure; however, 1 case of bilateral pulmonary embolism was observed after removing fistula compression within 1 week after the surgical intervention. In all other patients where compression was continued for at least 3–4 weeks after fistula closure, no such complication could be observed. In addition, 1 patient developed thrombosis of post-ligation dilated radial artery (diameter 6–8 mm) within 5 days after surgical intervention. This intervention-related complication was managed conservatively because of maintained forearm perfusion via a patent and also dilated A. ulnaris (3–4 mm).

Discussion

There is substantial uncertainty regarding fistula management after successful kidney transplantation. High-flow fistulas are regularly closed when aneurysm with concomitant risk of rupture, steal syndrome with acral ischaemia, and/or congestive heart failure at NYHA stage

III or IV are present. However, both in the presence and absence of typical clinical ligature indications, there is great variety in routine clinical management [14]. With respect to own retrospective data [6] showing up to 25% occurrence of high-output heart failure with consecutive closure of fistulas, we conducted a prospective randomized controlled trial evaluating the potential benefit of prophylactic ligature of high-flow AV fistulas. Patients with fistula flow >1,500 mL/min, stable renal function, and absence of clinical and echocardiographic signs necessitating urgent fistula ligation were randomized in a 1:1 ratio to an intervention and control group. In the intervention group, patients were subject to immediate AV fistula ligation, and in the control group, patients were cautiously monitored. The occurrence of right heart failure in 5 patients in the control group as compared to no single case in the intervention group confirmed our hypothesis that prophylactic fistula closure prevents high-output heart failure. We also observed significant reduction of NT-proBNP levels in 18 of 21 patients undergoing fistula ligation – a strong indication that burden on right and left heart systems might be reduced after fistula ligation. The declining systolic PAP in the intervention group implicates a potential role of pulmonary vascular system in maintaining high cardiac output. Systolic PAP was previously found to be higher in patients on haemodialysis compared to peritoneal dialysis or kidney transplant patients and to decline after renal transplantation [10]. Based on these findings, we thus postponed fistula closure for 3 months after transplantation to include only patients without recovery of PAH following kidney transplantation.

Reversibility of heart rate (“Nicoladoni-Branham sign”) [23] and systolic PAP after (sub)total manual compression of high-flow fistulas for 1 to 2 min may deliver additional important information if high cardiac output is fixed or reversible. In this regard, a compression-induced reduction in echocardiographically assessed sPAP has been shown to be predictive for reversibility of PAH after fistula ligation in 80% of cases [24]. Reduced TAPSE has been previously demonstrated to correlate with systolic PAP and predict CV mortality risk in congestive heart failure patients with stage III chronic kidney disease, adding significant prognostic information to the NYHA stage [20]. In our control group, however, decreased TAPSE was observed in 1 patient only and thus might not be suitable as single parameter for timing high-flow fistula closure. The definition of high-flow fistula in the literature remains unclear. Following own data [6], we used a cut-off of 1,500 mL/min. A pre-

vious cross-sectional study used a cut-off of 2,000 mL/min and normalized fistula flow to body height (raise to the power of 2.7), thereby demonstrating predictive potential of fistula flow for the development of right heart failure [23]. Normalizing fistula flow to body surface area or height reflects differences in patient size more accurately but did not affect the results within our patient cohort (data not shown). A significant decrease in LV mass and improvement of cardiac diameters, output, and index as well as NT-proBNP levels have been shown after AV fistula closure in 27 post-transplant patients; however, no specific fistula flow cut-off for ligature referral was reported [25]. Some previous studies claimed little impact of fistulas on cardiac function [4, 26, 27]; however, retrospective design and short follow-up were substantial limitations of these studies. Our findings are in line with other studies demonstrating a positive impact of fistula ligation on cardiac function [28, 29]. It is important to mention that patients with overt PAH or signs of heart failure (NYHA III and IV) at screening visit were excluded from the present study and subject to fistula closure if the diagnosis was still confirmed 3 months after kidney transplantation. However, in asymptomatic patients without further options for autologous fistula creation and no progression to right heart failure or overt PAH in echocardiography, fistula flow reduction by means of PTFE tube interposition at the site of AV fistula anastomosis may be an alternative option instead of fistula ligation. AV fistula banding or reconstruction of anastomosis might reduce PAH and/or high-output heart failure while maintaining fistula patency; however, these approaches are associated with a high risk of peri-interventional thrombosis and their efficacy seems to be rather low. At least in our facility, flow reduction approaches with banding or reconstruction are regularly found to be transient and PAH and/or high-output heart failure frequently re-occurs within 12 months. Due to these facts, we decided to surgically ligate AV fistulas within the present study and generally reserve fistula banding or reconstruction of anastomosis for patients without overt heart failure but foreseeable need of dialysis within the next 2 years (e.g., in patients with eGFR <30 mL/min). The study’s strategy to primarily avoid high fistula flow complications by timely ligation – which seems to be the case according to our study findings – might indeed increase the risk of losing fistula options for subsequent treatment of transplant failure; however, during the 24-month follow-up none of the study patients developed dialysis-dependent kidney transplant dysfunction. The cardiovascular benefit of this strategy

might outweigh any potential risk that comes with a loss of fistula options. In this regard, catheter-based approaches might represent an alternative option for dialysis access. Further large-scale clinical trials are mandatory to assess the risk-benefit ratio of this strategy. Nevertheless, we found that more than half of patients undergoing forearm fistula closure had a venous branch from the dorsal side of the forearm that kept their fistula vein patent after ligation. This might allow to re-use the AV fistula as radiocephalic fistula (proximal forearm) in case of subsequent need of dialysis.

To our knowledge, this is the first prospective, randomized controlled trial showing that prophylactic AV fistula ligation can avoid high-output heart failure in kidney transplant patients with fistula flow >1,500 mL/min, stable renal function, and absence of clinical and echocardiographic signs necessitating urgent fistula ligation. Study design and clear-cut definition of the primary end-point (i.e., right heart failure based on clinical and echocardiographic parameters) are particular study strengths. However, based on its pilot trial character, this single-centre study has several limitations. In addition to a rather small sample size, echocardiographic examination and NT-proBNP levels were not available within 3 months after ligation in some of the patients. Intra- and inter-observer variability was not evaluated with respect to echocardiographic assessment. Nevertheless, despite small sample size, a statistically significant difference in the occurrence of right heart failure was observed between the intervention and control groups. Fistula ligation is generally well tolerated and considered safe with recommended post-interventional compression. Based on the fact that interventional group patients showed declining NT-proBNP and sPAP levels after fistula ligation while maintaining a stable kidney graft function, prophylactic ligation of high-flow fistulas might be justified. In addition to heart failure risk, patients with high-volume fistula flow rates are at increased risk for developing aneurysm and/or steal phenomenon, which highlights the importance of fistula flow monitoring during routine transplant follow-up.

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Conclusion

By demonstrating prevention of right heart failure with prophylactic ligation of high-flow fistulas (>1,500 mL/min) in kidney transplant patients with stable graft function, this pilot randomized controlled trial shall encourage further multicentre trial efforts to improve post-transplant fistula management and, thus, patient outcome. Until then, the present study might provide some guidance for clinical management of high-flow fistulas after renal transplantation.

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Statement of Ethics

This prospective randomized controlled trial was conducted at the Department of Internal Medicine IV, Nephrology and Hypertension, Medical University Innsbruck. Approval from the local ethics committee was obtained prior to study initiation. Written informed consent was obtained from all patients before enrolment.

Conflict of Interest Statement

All authors declare no conflict of interest.

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Author Contributions

M.T.: research idea, study design, patient recruitment, and obtaining ethics committee approval. S.M.: design of echo criteria and performing/supervising echo exams. L.P. and M.G.: surgery of study patients. M.T., S.M., and M.P.: data acquisition. P.H., M.T., and M.P.: data analysis/interpretation. P.H.: statistical analysis. P.H., M.P., M.G., and M.T.: manuscript preparation and drafting. M.T.: responsible for the integrity of data analysis.

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