Clin Transplant 2013: 27: 858–865 DOI: 10.1111/ctr.12248

Clinical Transplantation

Incidence of arteriovenous fistula closure due to high-output cardiac failure in kidney-transplanted patients

Schier T, Göbel G, Bösmüller C, Gruber I, Tiefenthaler M. Incidence of arteriovenous fistula closure due to high-output cardiac failure in kidney-transplanted patients.

Abstract: Background: Some hemodialysis patients develop arteriovenous (AV) fistulas with high flows. This volume overload can result in high-output cardiac failure. To date, predisposing access flow rates are unknown.
Methods: A retrospective study of all kidney-transplant recipients at the Medical University of Innsbruck (MUI) from 2005 to 2010 included 797 patients with the following criteria: previous hemodialysis with a native AV fistula or a graft, sufficient function of the kidney transplant up to the time of the data analysis, and follow-up care at the MUI.
Results: Twenty-nine of the 113 patients (25.7%) needed an AV fistula closure, mostly because of symptoms 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. Shunt closures were most frequently made in patients with upper-arm shunts (41.7%).
Conclusion: The necessity of shunt closure is not a rarity. Patients who underwent an AV fistula ligature had high access flows with about 2200 mL/min. As the symptoms of cardiac failure greatly improved after shunt closure, patients with high access flow may benefit from such an intervention.

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Key words: arteriovenous fistula – high-output cardiac failure – kidney transplantation – shunt flow – shunt ligature

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Conflict of interest: None.

Accepted for publication 19 August 2013

Vascular access for hemodialysis is one of the most important clinical problems in patients with end-stage renal disease (1). There are several possibilities for hemodialysis access, such as the native arteriovenous (AV) fistula, an AV graft, or venous catheters. The AV fistula is the method of choice for hemodialysis patients and is created by short-circuiting an artery with a vein, mostly located on the upper extremity (cephalic vein or brachial vein). Because of a blood flow of about 400 mL/min needed for high-quality dialysis, superior patency, and low incidence of infection, the AV fistula is the better choice compared with an AV graft or catheter (2, 3). For this reason, the majority of the hemodialysis patients have native AV fistulas; in the year 2010, the fraction of the AV fistula was 65.4% in Austria in incident patients (4). The most common complications of an AV fistula are infections, aneurysms, and high-output cardiac failure (3). Cardiovascular disease is the principal cause of morbidity in dialysis patients and patients having a sufficient kidney transplant (1, 4). In case of a kidney transplantation, the AV fistula is left open as it is not predictable how long the transplant provides a sufficient renal function. Only in a few exceptions, it is indicated to close an AV fistula surgically, such as heart failure, high-flow fistula, vascular access complications, and important esthetic reasons, but there are no evidence-based guidelines when to intervene (1). The closure results usually in the loss of the fistula, which cannot be reconstructed in case of a recurrent requirement for hemodialysis. Some patients develop an AV fistula with a very high blood flow. The access blood flow of AV shunts depends on many different factors such as systemic hemodynamics, the presence of significant vascular stenosis, and the size and endothelial function of the shunt artery and the shunt vein (5). The high blood flow results in cardiac stress because a high blood flow increases the cardiac output per minute, and the high diameter of the fistula decreases the peripheral resistance. This results in symptoms of heart failure (2).

There is no consensus in expert opinions from what shunt flow on an AV fistula is called a high-flow fistula. In several case reports, however, high-flow fistulas are defined with access blood flows (Qa) more than 2000 mL/min and Qa/Co ratios greater than 30–35% (2). Several reports describe that large AV fistulas can cause high-output cardiac failure, ventricular hypertrophy, left ventricular (LV) dilatation, elevated LV diastolic filling pressure, structural and functional cardiac changes, secondary pulmonary hypertension, cardiomegaly, arterial stiffness augmentation, distal ischemia, and aneurysm formation (1–3, 6–10). Presently, it is not proven whether these changes only occur in patients with underlying cardiac disease or whether all patients with native AV fistulas are at risk (11). Furthermore, it has to be mentioned that patients with chronic kidney disease generally have multiple cardiac risk factors and a high prevalence of cardiovascular disease (2). Generally, there are two different positions in the literature: Some studies (for example, De Lima et al. [6], Meeus et al. [9], etc.) conclude that symptomatic cardiac failure as a complication of AV fistulas is uncommon and usually occurs in patients with underlying cardiac disease and that the persistence of high-flow AV fistulas for a long period has little impact on cardiac morphology and function. In contrast, prospective studies of Unger (12) and Van Dujnhover (13) show a positive effect of AV fistula ligature on the myocardium. In these studies, the left ventricle mass and the left ventricle diameter decrease after surgical shunt closure. Although there are several reports of shunt closure after transplantation (1, 6, 12, 13), none has reported systematically access flows before closure so far. Here, we present the largest series to date with documented shunt flows in native AV fistulas consisting of 113 patients after successful kidney transplantation. We have 29 patients with ligature of the AV fistula after kidney transplantation mostly because of high-output cardiac failure or dyspnea on physical examination. This study shows that the necessity of shunt closure in kidney-transplanted patients is not a rarity (25.7%).

Methods

Description of the cohort

All patients who received a kidney transplant at the Medical University of Innsbruck (MUI) in the years 2005–2010 represent the base of this study (797 patients). Patients using a catheter for dialysis access or peritoneal dialysis before transplantation or pre-emptive transplantation are excluded. Criteria for inclusion are the sufficient function of the kidney transplant up to the time of the data analysis and follow-up care after transplantation at the MUI. One hundred and thirteen patients achieve these criteria and are analyzed for this retrospective study. The underlying kidney disease of every patient was classified into 11 categories. The categories are diabetes, hypertension, glomerulonephritis, hereditary nephropathy, interstitial nephropathy, participation in vasculitis, autoimmune disease/systemic lupus erythematosus, myeloma, Goodpasture's syndrome, and other diseases which cannot be assigned to one of these categories (Table 1). The duration of hemodialysis was calculated in months, and the dialysis access is classified in five categories with regard to the localization and the shunt vein: upper-arm cephalic shunt, forearm cephalic shunt, upper-arm basilica shunt, forearm basilica shunt, and AV fistulas with a Gore-Tex interponate. With regard to the cardiac complications, the N-terminal pro-brain natriuretic peptide (NT-proBNP) laboratory values were compared. We selected the last measured value and the value before and after closure in patients with AV fistula ligature. In addition to that abnormalities of the right ventricle and pulmonary hypertension seen in echocardiography, the number of heart-failure pharmaceuticals were also documented. As heart-failure pharmaceuticals, we implicated ACE inhibitors, AT1 antagonists, beta blocker, diuretics, aldosterone antagonists, and heart glycosides. Kidney function was estimated by creatinine clearance calculated by the MDRD formula. We chose the creatinine value two months after transplantation so that the values from each patient are comparable. We documented shunt bandings and shunt closures, the date of this event, and the shunt flow after banding.

The 113 patients in the study consist of 42 women and 71 men. All patients undergo routine echocardiography after kidney transplantation annually. Patients with patent fistulas reporting shortness of breath during exercise are additionally evaluated for the access flow and are subjected to shunt closure if signs of right heart failure or pulmonary hypertension are present in echocardiography. Most frequent signs are pulmonary hypertension (mean pulmonary arterial pressure >25 mm Hg) and dilation of the pulmonary artery. However, right ventricular geometry was not measured on a regular basis in this retrospective study. Patients are separated in a "shunt intervention group" (29 patients; 28 shunt

Table 1. Patient characteristics

	Overall n = 113 (100%)	Shunt intervention n = 29 (25.7%)	No shunt intervention n = 84 (74.3%)
Gender			
Female	42 (37.2%)	12 (28.6%)	30 (71.4%)
Male	71 (62.8%)	17 (23.9%)	54 (76.1%)
Age at kidney transplantation, mean (SD), yr	55.1 (12.8)	51.64 (13.7)	56.3 (12.3)
Time on dialysis, mean (SD), months	42.9 (29.7)	43.4 (27.6)	42.7 (30.5)
Number of kidney transplantations, n (%)			
1	88 (100%)	20 (22.7%)	68 (77.3%)
2	17 (100%)	7 (41.2%)	10 (58.8%)
3/4	7 (100%)	2 (28.6%)	5 (71.4%)
Creatinine (mg/dL), mean (SD)	1.5 (0.7)	1.3 (0.6)	1.5 (0.8)
Glomerular filtration rate (mL/min), mean (SD)	55.0 (20.0)	61.9 (21.3)	52.6 (18.8)
Time between NTX and ligature, median (VAR), yr		2.5 (3.1)	
Underlying kidney disease			
Diabetes	14 (100%)	1 (7.1%)	13 (92.9%)
Hypertony	11 (100%)	2 (18.2%)	9 (81.8%)
Glomerulonephritis	23 (100%)	6 (26.1%)	17 (73.9%)
Hereditary nephropathy	19 (100%)	5 (26.3%)	14 (73.7%)
Interstitial nephropathy	9 (100%)	2 (22.2%)	7 (77.8%)
Participation in vasculitis	3 (100%)	1 (33.3%)	2 (66.7%)
Autoimmune disease/ systemic lupus erythematosus	6 (100%)	2 (33.3%)	4 (66.7%)
Myeloma	2 (100%)	1 (50%)	1 (50%)
Goodpasture's syndrome	1 (100%)	0 (0.0%)	1 (100.0%)
Others	8 (100%)	2 (25.0%)	6 (75.0%)
Not known	17 (100%)	7 (41.2%)	10 (58.8%)

The creatinine values are documented two months after kidney transplantation. The glomerular filtration rate is calculated with the Modification of Diet in Renal Disease (MDRD) formula. Values in brackets are standard deviation or if indicated percentage.

ligatures and one shunt banding; three of them with grafts) and a "non-intervention group" (84 patients; eleven of them with grafts). Twenty-nine of 113 or 25.7% of patients (12 of 42 or 28.6% of women, and 17 of 71 or 23.9% of men) had an AV fistula intervention. All but one patient underwent complete shunt closure. One of the women had a shunt banding because of borderline kidney graft function (eGFR 18 mL/min). After completion of this study, she also underwent a complete shunt closure because of symptoms of high-output cardiac failure, and her shunt flow had risen from 800 mL/min after the banding to 2200 mL/min within 18 months. After this intervention, the symptoms improved again within two wk.

Shunt flow measurement

Shunt flow in milliliter per minute was documented choosing either the last measurement before AV fistula closure or the last documented shunt flow measurement.

Shunt flow is measured with duplex sonography of the brachial artery above the elbow. This part is straight, usually without changes in

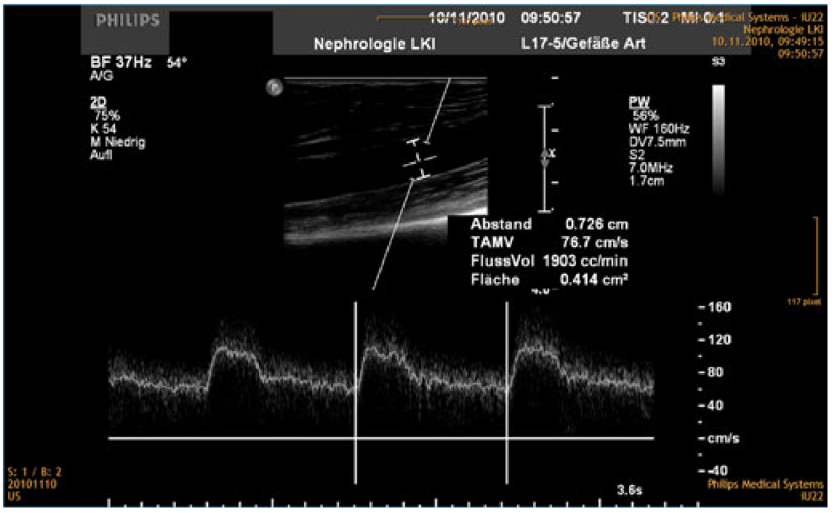

Fig. 1. Typical flow measurement of brachial artery feeding a high-flow arteriovenous (AV) fistula: The sample volume encloses the whole vascular diameter of the most straight part of the brachial artery in the medial bicipital sulcus.

diameter of the artery and in the medial bicipital sulcus easily accessible. By color mode, the laminar flow is detected, because media sclerosis of long-term dialysis patients may absorb 2.5 MHz ultrasound waves and thereby result in incorrect readings. The whole diameter of the artery is measured to avoid overestimation of brachial artery flow. As brachial artery flow of resting arms without shunts is usually between 40–50 mL/min, brachial artery flow in patients with dialysis shunts is assumed to be the access flow. Measurements of flows are repeated at least three times. When measurements differ for more than 20%, additional measurements are performed. Due to the turbulent flow in AV fistulas, we do not measure flows in the venous part of the fistulas (Fig. 1).

Ligation of hemodialysis vascular access – description of technical process

The procedure is usually performed under local anesthesia. Exceptions to that are patients′ requests for general anesthesia or the presence of large aneurysmatic veins. In these cases, the procedures are performed in regional or in general anesthesia.

The cutaneous incision is the same as if a new AV fistula was constructed. First, the anastomosis of the AV fistula is dissected in such a way as to enable the artery proximal and distal of the AV junction and the connected vein to be clamped. If there is an aneurysm at the anastomosis, the part of the aneurysm which can be reached by the incision must be dissected. Then the patient receives 2500 IU of heparin. Under clamping the formerly dissected vessels, the vein is disconnected from the artery, and the proximal part of the shunt vein, especially in cases of aneurysm, is removed after ligation. The arterial leakage is closed by a linear, usually double-layered, non-absorbable suture. Under the control of hemostasis, the cutaneous incision is sewed by single sutures of the subcutis and continuous suture of the skin. After the procedure, the arm must be bandaged in double layer completely for at least 2–3 wk to avoid phlebothrombosis or phlebitis in the remainder of the venous part of the vascular access. Usually, patients developed a thrombosis of the first few centimeter of the ligated vessel. We observed no clinical pulmonary embolism or deep venous thrombosis of the upper limb.

Statistics and ethical considerations

Categorical variables are reported using absolute and relative frequencies. Quantitative parameters are reported using the mean and standard deviation or – in case of non-normality – using the median and interquartile range. Differences between means were determined using *t*-test and (in case of more factors) factorial analysis of variance (ANOVA) after log-transformation of quantitative variables. All statistical analyses were conducted using SPSS 18 (IBM, Chicago, IL, USA). The present study was approved by the ethical review committee of the MUI.

Authors had access to all clinical data and were fully involved in formulating the analyses and questions of interest.

Results

High fistula flow is associated with shunt ligation

The mean shunt flow in the intervention group is 2197.2 (1691.2–2703.3) mL/min, whereas the mean shunt flow in the non-intervention group is 850.9 (725.2–976.6) mL/min ($p < 0.001$, Fig. 2).

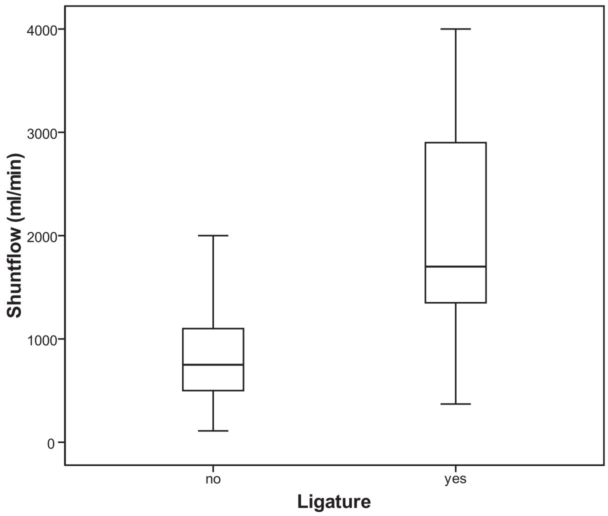

Fig. 2. Illustration of the shunt flow depending on the non-intervention group (ligature: no) and in the shunt intervention group (ligature: yes).

Twenty-six of 28 shunt closures were performed due to flow-related fistula problems. The most common reason for shunt closure is the existence of dyspnea or other symptoms of cardiac failure likely due to high-output cardiac failure (15 of the 28 patients; 53.0%). The vascular surgeons refuse to close AV fistulas without pathology in echocardiography in these patients. Therefore, dilation of right ventricular outflow, right heart distension, or pulmonary hypertension is verified by echocardiography in all patients who undergo shunt closure due to shortness of breath. The most frequent findings in echocardiography are pulmonary hypertension and right ventricular dilation. Dilated pulmonary outlet is also recorded. All patients with shortness of breath reported improvement of their symptoms and regain of exercise capacity. Other reasons for ligations are high access flows (6 of 28; 21.4%) and aneurysm formation (5 out of 28; 17.8%). Only two shunt ligations were not flow related, one because of esthetic reasons and one due to infection. No serious adverse events of shunt intervention occurred.

Fistula flow but not fistula position determines ligation

In the intervention group consisting of both, ligature of upper-arm and forearm AV fistulas, there is a significant difference in flow as compared to the non-intervention group. According to the fact that upper-arm fistulas have higher flows than forearm fistulas (14), we assumed that the position of the fistula might have an impact on ligation rates as well. Although in our cohort patients with upper-arm shunts undergo AV fistula ligation more frequently than patients with forearm shunts (10 of 24 patients, 41.7% vs. 16 of 56 patients, 30%, Table 2), flow rates in upper arm and forearm do not differ significantly in both the intervention group (2624 vs. 2151 mL/min *t*-test, n.s). and the non-intervention group (860 vs. 853 mL/min *t*-test, n.s).

The small group of patients with upper-arm basilica shunts (n = 4) have a ligature rate of 50%.

NT-proBNP values may be reduced by shunt closure

In this retrospective study, NT-proBNP values prior and after shunt ligature were recorded for only seven patients. The median interquartile range (IQR) of the NT-proBNP values in the shunt intervention group before AV fistula closure is 3709.4 (659.9–6758.9) ng/L, and after AV fistula closure, it decreases to 1290.9 (416.9–2164.9) ng/L, and dyspnea and other symptoms of cardiac failure improved after shunt closure (Fig. 3). Patients in the non-intervention group have a median (IQR) NT-proBNP of 5791 (3374.9–8207.2) ng/L (n = 66). Although the NT-proBNP values

Table 2. Shunt localization and shunt flow

	Forearm shunt cephalic vein	Basilic vein	Upper arm shunt cephalic vein	Basilic vein	Others (Gore-Tex, thigh)
Shunt intervention					
n	16	0	8	2	3
Shunt flow, mean (95% CI)	2151.3 (1369.7–2932.8)	not valid	2625.0 (1515.9–3734.1)	2200.0 (0.0–11094.3)	1300.0 (803.2–1796.8)
No shunt intervention					
n	33	4	9	2	9
Shunt flow, mean (95% CI)	853.0 (679.4–1026.6)	985.0 (429.3–1540.7)	860.0 (443.9–1276.1)	435.0 (0.0–1260.9)	916.3 (518.6–1313.9)
Overall					
n	49	4	17	4	12
Shunt flow, mean (95% CI)	1276.9 (960.9–1593.0)	985.0 (429.3–1540.7)	1690.6 (1012.2–2369.0)	1317.5 (0.0–3178.6)	975.0 (686.8–1263.2)

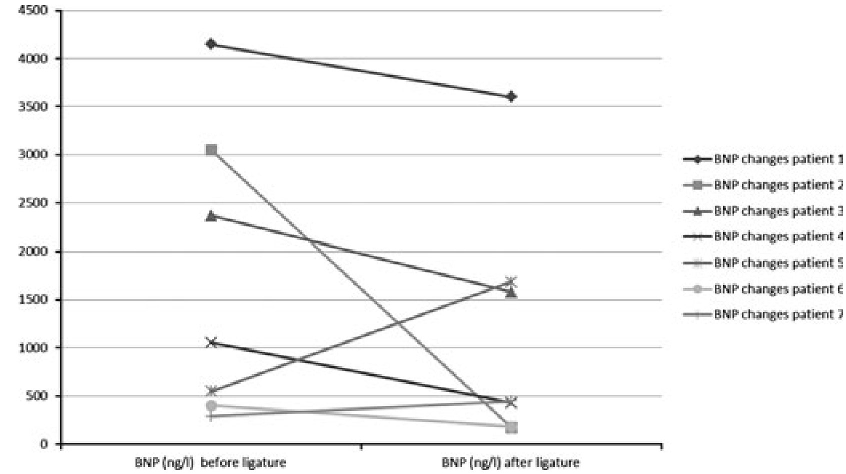

Fig. 3. N-terminal pro-brain natriuretic peptide (NT-proBNP) values in seven patients before and after arteriovenous (AV) fistula intervention (last measured value before and last documented value after shunt intervention).

dropped in five of seven patients after shunt ligature, the difference is not statistically significant.

The underlying kidney disease does not have an influence on the incidence of shunt ligature

For every patient, the underlying kidney disease is classified in several categories. The categories are diabetes, hypertension, glomerulonephritis, hereditary nephropathy, interstitial nephropathy, participation in vasculitis, autoimmune disease/ systemic lupus erythematosus, myeloma, Goodpasture's syndrome, and other diseases which cannot be assigned to one of the previous categories (Table 1). The underlying kidney disease does not have an influence on ligature rate, and consequently, there is no coherency between a certain disease and shunt ligature in this study.

No correlation is found between the number of kidney transplantations of a patient and AV fistula ligature and no coherency between the time on hemodialysis and the need for AV fistula closure.

Discussion

The study presented here is to our knowledge the largest so far on AV fistulas after renal transplantation and clearly shows that a high fistula flow is associated with the necessity of fistula ligature to avoid high-output heart failure (Fig. 2). Earlier studies on fistula ligature are case reports or studies based on smaller collectives or not considering flow rates in fistulas. The study performed by Manca et al. (1) evaluated the history of AV fistulas in 365 patients with functioning kidney transplants. Forty-two of the 365 patients (11.5%) underwent a surgical shunt closure because of aneurysm formation, ischemic syndrome, infections, edema, and esthetic reasons. In this study, there was no surgical shunt closure because of dyspnea or other symptoms of high-output cardiac failure and does not contain any shunt flow measurements. The authors concluded that routine shunt closure is not indicated. The first two cases of cardiomegaly with high-output cardiac failure as a complication of high-flow AV fistulas were already reported in 1972 (1). In agreement with this, the present study also shows that cardiac abnormalities in patients with AV fistulas occur frequently (33 of 81 or 41%, of echocardiographically evaluated patients). In contrast, Meeus et al. (9) state that symptomatic cardiac failure as a complication of shunts is uncommon and usually occurs in patients with underlying cardiac disease. There are different reports which support either the theory of increased cardiovascular risk (15) or the opinion of Meeus et al. (9). De Lima et al. (6) come to the conclusion that the persistence of high-flow AV fistulas for a long period has little impact on cardiac morphology and function. But it has to be mentioned that their study was based on relatively young patients (33.4 ± 12.5 yr) with good general clinical and cardiac conditions and therefore does not represent the usual population who undergo kidney transplantation, whereas the mean age at the time of kidney transplantation in our study was 55 yr (Table 1), thus representing a more usual population of kidney-transplant recipients. Unger et al. (12) state that LV hypertrophy and dilatation is a usual problem in kidney-transplanted patients which can be explained partially by the volume overload of AV fistulas. In a study with 17 kidney-transplanted patients, they show that volume overload is associated with the development of heart failure and high mortality. Clarkson (3) describes a single case where an AV fistula was the major reason for high pulmonary arterial pressure and early right ventricular decompensation. De Lima et al. (6) compare echocardiographic parameters of 39 renal-transplanted patients with functioning fistulas with 21 patients who had a closed fistula. Their results also support the theory that AV fistulas can produce cardiac dilatation. Because the clinical presentation of cardiac failure may be obscured by other factors like anemia and hypertension, noninvasive methods for evaluation of the hemodynamic burden of an AV fistula may help to establish the diagnosis of high-output cardiac failure (12, 16).

Patients at the MUI are routinely scheduled for annual echocardiography. Only patients with exercise-induced dyspnea are subjected to additional unscheduled echocardiography for right ventricular hypertrophy and pulmonary hypertension. In the study presented here, 41% of the evaluated patients show cardiac abnormalities of the right ventricle or pulmonary hypertension. These results agree with the assumption that high-flow AV fistulas (2200 mL/min) can cause adverse cardiac changes. To date, we assume that low flow shunts with 300–800 mL/min may not cause pulmonary hypertension and, therefore, closure will be unlikely to elevate exercise-induced dyspnea. However, taking into account that almost 40% of the patients in the non-intervention group show pulmonary hypertension or right heart pathology in echocardiographic examination, this assumption may not be right. We therefore started a prospective national multicenter randomized controlled trial of patients three months after successful kidney transplantation. Inclusion criteria are stable kidney function and access flow above 1500 mL/min. Patients with dilated pulmonary artery, overt pulmonary hypertension, or left heart failure with ejection fraction below 25% are subjected to immediate shunt closure, because watchful waiting seems inappropriate due to the severe cardiac pathology. We also extended routine echocardiographic examination to measure TAPSE, pulmonary artery diameter, and right ventricular dimensions on a regular basis in all new kidney-transplant recipients.

It has been previously reported that AV fistulas on the upper arm have higher flows than forearm fistulas (14). We therefore assumed that we may find higher ligature rates in upper-arm fistulas. In this retrospective study, we describe a slightly higher frequency of ligation of fistulas in the upper arm, however, this difference is statistically not significant (Table 2). This fact may be attributed to the low numbers of upper-arm shunt ligatures and to the minimal differences in flow in the ligation groups of patients with upper arm as compared to forearm AV fistulas.

Previous studies state that the effects of AV shunts on the myocardium are at least partially reversible (13). In our study, although not significant, the NT-proBNP values decrease in five of seven patients after shunt closure (Fig. 2). As the number of patients with recorded NT-proBNP before and after the ligature is too low for a reliable statistical analysis, it would be worthwhile to further persecute this aspect.

LV failure associated with elevated NT-proBNP values is very frequent in patients with chronic renal failure (17). The high levels of NT-proBNP in the non-intervention group of our study may, thus, be explained at least in part with underlying left heart failure as indicated by pulmonary hypertension in 23 of 58 or 40% of echocardiographically evaluated patients.

It remains unclear why some patients develop heart failure while other patients do not. Specific characteristics of either the patients or the shunts, or both, may play a role in the development of heart failure (11). Ponsin et al. (18) describe an association between signs of cardiac insufficiency and the product of fistula blood flow and fistula duration. This could explain why also AV fistula with normal to slightly increased flows can cause heart failure. The present study shows no correlation between the fistula duration (time on hemodialysis) and the need for AV fistula closure due to heart failure. But there is a tendency for a correlation between the shunt flow and the urgency of AV fistula ligature because of signs of cardiac failure, as fistulas with very high shunt flows needed to be closed earlier than fistulas with lower (but also high) shunt flows (data not shown).

Taken together, our study indicates that the necessity of shunt closure in kidney-transplanted patients is not a rarity and averages 25.7%. Patients mostly underwent AV fistula ligature because of dyspnea or other symptoms of high-output cardiac failure and had high access flows with a median of 2200 mL/min. As the NT-proBNP values decreased and the symptoms of cardiac failure greatly improved after shunt closure, patients with high access flows may benefit from an intervention. Due to the retrospective nature of this study, we cannot exclude that the high percentage of shunt ligature results from a referral of symptomatic patients from other centers of post-transplant care to the MUI. Absence of avert heart failure is a prerequisite for transplant listing; therefore, hard endpoints indicative for decompensated heart failure are sparse in this cohort. On the other hand, to date, there are no data available to sharpen the awareness for heart failure due to the high access flow.

Until prospective randomized trials like our upcoming study can demonstrate a benefit of the surgical shunt closure to avoid the development of high-output cardiac failure in patients with high access flows, the individual decision whether to close an AV fistula or not must include all relevant factors, especially with regard to kidney transplant function and the possibility for the creation of a new shunt in case of transplant failure. As the clinical presentation of cardiac failure may be obscured by other factors like anemia and hypertension, the echocardiographic monitoring or other noninvasive methods for evaluation of the hemodynamic burden of the AV fistula may be useful to intervene in time.

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