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Abstract:

Background. Kidney transplantation (KTx) is considered as the best kidney replacement therapy and arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis. The systematic ligation of a functioning AVF in stable kidney transplant recipients remains debatable.

Methods. In this prospective study, we investigated the hemodynamic impact of the surgical closure of AVF in KTRs. Forty-three KTRs underwent an ambulatory blood pressure monitoring (24h-ABPM) before surgical closure of AVF (T0) and 12 months later (M12), as well as measurement of serum cardiac biomarkers (i.e., soluble suppression of tumorigenicity 2 (ST2), N-terminal pro b-type natriuretic peptide (NT-proBNP) and Galectin-3). Serum tests were also performed 6 months after AVF closure (M6). An echocardiographic exam was done at each time-point. All serum creatinine values were collected to compare the individual eGFR slopes before versus after AVF closure. The latest measure of the AVF flow (QAVF) prior to KTx was recorded.

Results. Diastolic blood pressure (DBP) significantly raised from T0 to M12: + 4.4±7.3 mmHg (p=0.0003) for 24h, + 3.8±7.4 mmHg (p=0.0018) during the day, and + 6.3±9.9 mmHg (p=0.0002) during the night, leading to an increased proportion of KTRs with ESH-defined arterial hypertension after AVF ligation. No change was observed for systolic BP. NT-proBNP significantly dropped between T0 and M6 (345 [190; 553] to 230 [118; 458] pg/mL, p=0.0001) and then remained stable from M6 to M12, while ST2 and Galectin-3 levels did not change from T0 to M12. We observed a significant decrease of left ventricular (LV) end-diastolic volume, LV end-systolic volume, LV mass, interventricular septum diameter, left atrial (LA) volume, and tricuspid annular plane systolic excursion from T0 to M6, and then a stability from M6 to M12. LV ejection fraction and eGFR slope remained stable during the whole study. These observations remained unchanged after adjustment for QAVF.

Conclusion The closure of a patent AVF in KTRs is associated with elevation of DBP, drop of serum NT-proBNP levels, reduction of LV/LA dimensions, and stable eGFR slope.

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The Impact of Elective Ligation of the Arteriovenous Fistula on Cardiac and Renal Functions in Kidney Transplant Recipients

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Abbreviations

24h-ABPM	Ambulatory blood pressure monitoring
AVF	Arteriovenous fistula
BP	Blood pressure
BSA	Body surface area

CI	Cardiac index
CO	Cardiac output
CMIA	Chemiluminescent microparticle
cMRI	Cardiac magnetic resonance imaging
DBP	Diastolic blood pressure
dDFG	Delayed graft function requiring dialysis
ECDs	Expanded criteria donors
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ESRD	End-stage renal disease
GEE	General estimating equations
GLM	General linear mixed (model)
HF	Heart failure
IVS	Interventricular septum
K/DOQI	Kidney Dialysis Outcome Quality Initiative
KDIGO	Kidney Disease: Improving Global Outcomes
KTRs	Kidney transplant recipients
KTx	Kidney transplantation
LA	Left atrial
LAV	Left atrial volume
LV	Left ventricle

LVEDD	Left ventricular end-diastolic diameter
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
LVESV	Left ventricular end-systolic volume
MDRD	Modification of Diet in Renal Disease
NT-proBNP	N-terminal pro b-type natriuretic peptide
PW	Posterior wall
QAVF	Arteriovenous fistula flow
Q1	First quartile
Q3	Third quartile
RV	Right ventricle
RWT	Relative wall thickness
SBP	Systolic blood pressure
SCr	Serum creatinine
SD	Standard deviation
ST2	Suppression of tumorigenicity 2 marker
SV	Stroke volume
TAPSE	Tricuspid annular plane systolic excursion

Keywords

Arteriovenous fistula; Kidney transplantation; Echocardiography; Left ventricular hypertrophy; Blood pressure; eGFR

Key Points

- Surgical AVF ligation in KTRs is associated with a significant increase of diastolic BP, while systolic BP remains stable.
- AVF closure in KTRs leads to an improvement of LV and LA morphology and a decrease of serum NT-proBNP levels.
- There is no significant effect of AVF ligation on kidney allograft function: the eGFR remains stable over time.

Abstract

Background. Kidney transplantation (KTx) is considered as the best kidney replacement therapy and arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis. The systematic ligation of a functioning AVF in stable kidney transplant recipients remains debatable.

Methods. In this prospective study, we investigated the hemodynamic impact of the surgical closure of AVF in KTRs. Forty-three KTRs underwent an ambulatory blood pressure monitoring (24h-ABPM) before surgical closure of AVF (T0) and 12 months later (M12), as well as measurement of serum cardiac biomarkers (i.e., soluble suppression of tumorigenicity 2 (ST2), N-terminal pro b-type natriuretic peptide (NT-proBNP) and Galectin-3). Serum tests were also performed 6 months after AVF closure (M6). An echocardiographic

exam was done at each time-point. All serum creatinine values were collected to compare the individual eGFR slopes before *versus* after AVF closure. The latest measure of the AVF flow (QAVF) prior to KTx was recorded.

Results. Diastolic blood pressure (DBP) significantly raised from T0 to M12: + 4.4±7.3 mmHg (p=0.0003) for 24h, + 3.8±7.4 mmHg (p=0.0018) during the day, and + 6.3±9.9 mmHg (p=0.0002) during the night, leading to an increased proportion of KTRs with ESH-defined arterial hypertension after AVF ligation. No change was observed for systolic BP. NT-proBNP significantly dropped between T0 and M6 (345 [190; 553] to 230 [118; 458] pg/mL, p=0.0001) and then remained stable from M6 to M12, while ST2 and Galectin-3 levels did not change from T0 to M12. We observed a significant decrease of left ventricular (LV) end-diastolic volume, LV end-systolic volume, LV mass, interventricular septum diameter, left atrial (LA) volume, and tricuspid annular plane systolic excursion from T0 to M6, and then a stability from M6 to M12. LV ejection fraction and eGFR slope remained stable during the whole study. These observations remained unchanged after adjustment for QAVF.

Conclusion The closure of a patent AVF in KTRs is associated with elevation of DBP, drop of serum NT-proBNP levels, reduction of LV/LA dimensions, and stable eGFR slope.

Introduction

Since its first description by Brescia and Cimino in 1966(1), arteriovenous fistula (AVF) has been rapidly regarded as the best vascular access for patients with end-stage renal disease (ESRD) undergoing hemodialysis, as stated by the Kidney Dialysis Outcome Quality Initiative (K/DOQI) of the National Kidney Foundation(2), by the Kidney Disease: Improving Global Outcomes (KDIGO)(3) and by the European Society for Vascular Surgery(4). AVF carries a lower risk of infection and thrombosis in comparison to catheters. Although the indications and the surgical techniques of AVF creation are rather consensual, limited literature exists regarding the management of a functioning AVF in kidney transplant recipients (KTRs) with a stable and sufficient renal function. Kidney transplantation (KTx) represents the best option for patients with ESRD, with significant improvement of survival and quality of life compared to dialysis. However, the global survival of a kidney graft at 5 years remains ~70%(5). The main reasons for graft loss are acute rejection and chronic graft dysfunction. The pathophysiology of the latter is poorly understood and includes infectious, immunological, and hemodynamic causes. Among the hemodynamic causes, the impact of AVF ligation on renal graft function remains controversial. In most cases, AVF remains functional after a successful KTx. The persistence of a functional AVF at 1-year *post* KTx has been retrospectively associated with a lower estimated glomerular filtration rate (eGFR) and an increased risk for graft loss(6). Whereas in another publication, a significant acceleration of eGFR decline over the 12 months following the closure of a functioning AVF in KTRs(7) has been reported in a retrospective monocentric cohort. By contrast, AVF closure has been associated with cardioprotective effects in prospective studies with a rather limited number of KTRs(8–11). These observations were not confirmed in other trials in which AVF persistence for prolonged periods of time *post* KTx had minor consequences on cardiac morphology and function(12–14). Thus, based on this highly controversial literature, the systematic ligation of a functioning AVF remains debatable in stable KTRs.

The protocol in our center is to surgically ligate AVFs 1-year post KTx with the patient's approval if the eGFR is stable and higher than 45 ml/min/1.73m2 or if there are symptoms or signs of overt heart failure (HF). We conducted a prospective single-center trial to monitor the variations in renal graft function, cardiac hemodynamics, and blood pressure (BP) up to 4 years after AVF surgical ligation *post* KTx.

Patients and Methods

Patients. From January 2017 to January 2022, 43 patients were recruited and followed-up a signed informed consent at the University of Liège Hospital (ULiège CHU) in Liège, Belgium. This observational study was approved by the institutional review board (IRB) of ULiège CHU (Reference number: B707201630146), in adherence to the Declaration of Helsinki. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism". Between 2017 and 2019, we recruited up to 15 KTRs per year but Coronavirus disease 2019 pandemic interrupted this enrollment from 2020 to 2021. In subset populations, the follow-up was extended to 24 months (M24) after AVF ligation in 15 patients, to 36 months (M36) in 8 patients, and to 48 months (M48) in 10 patients.

Design of the prospective study. Before the surgical ligation of AVF (T0) and 12 months after the surgery (M12), all patients had a 24-hour ambulatory blood pressure monitoring (24h-ABPM). The 24h-ABPM was performed via Mobil-O-Graph 24h PWA Monitor (IEM GmbH, Aachen, Germany). BP was measured every 20 minutes during the day and every 30 minutes during the night. Mean day-time and night-time systolic (SBP), diastolic (DBP) BP levels were calculated on the basis of self-declared awake and asleep periods. A patient was categorized as dipper when his night–day SBP ratio ≤ 0.9 or non-dipper when his night–day SBP ratio was > 0.9. A measurement of serum cardiac biomarkers (i.e., soluble suppression

of tumorigenicity 2 (ST2), N-terminal pro b-type natriuretic peptide (NT-proBNP) and Galectin-3) was performed at T0, at 6 months after AVF closure (M6) and at M12. ST2 was measured by enzyme-linked immunosorbent assay (ELISA), NT-proBNP by chemiluminescent microparticle (CMIA) method on Alinity I (Abbott, Abbott Park, IL, USA), and Galectin-3 levels by Alinity C (Abbott, Abbott Park, IL, USA). We prospectively collected all serum creatinine (SCr) values regularly measured during the conventional follow-up of KTRs. SCr was measured by enzymatic method (Alinity C, Abbott, Abbott Park, IL, USA). The eGFR was determined using the Modification of Diet in Renal Disease (MDRD) equation(15). The MDRD equation is currently regarded as the most accurate estimation of GFR in KTRs(16). Transthoracic echocardiograms were performed by Vivid S70 (GE Healthcare, Chicago, IL, USA) at T0, M6, M12. We measured left ventricular (LV) end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV mass, interventricular septum (IVS) diameter, posterior wall (PW) diameter, relative wall thickness (RWT), stroke volume (SV), cardiac output (CO), cardiac index (CI), LV ejection fraction (LVEF), left atrial volume (LAV), E/A ratio and tricuspid annular plane systolic excursion (TAPSE). LVEDD, LVESD, LVEDV, LVESV, LV mass, SV and LAV were indexed to body surface area (BSA). Data on AVF flow (QAVF) prior to access ligation were not available as baseline (T0) parameter, but the latest QAVF that was measured prior to KTx was recorded.

Statistical analyses. Descriptive statistics were expressed as mean and standard deviation (SD) or as medians and quartiles (Q1-Q3) or continuous variables, and as frequency tables for qualitative variables. The paired Student t-test and Wilcoxon signed-rank test were used to compare the means of continuous variables, and the medians between T0 and M12, respectively. The McNemar test was used to compare the proportions of qualitative variables between T0 and M12. The evolution of the parameters along time was analyzed by the general linear mixed model (GLMM). In case of dissymmetric distribution, a logarithm transformation was applied. For binary, we used a GEE (general estimating equations)

regression model, also considering repeated measures for KTRs. Concerning the renal function, we excluded SCr values during the first 3 months *post* KTx to avoid the usual fluctuations of renal function in the immediate post-KTx period. After this period, all available SCr values were included in our analyses. Linear splines for MDRD versus time were used with one knot at the time of AVF closure, allowing separate regressions of MDRD for each time period (before and after AVF closure). Time was balanced before and after AVF closure with at least 10 observations per patient. Slopes and intercepts before and after AVF closure were compared using paired t-tests. Results were considered significant at the 5% significance level ($p<0.05$). All analyses were done with SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Our cohort study involved 43 KTRs (**Table 1**) with a female/male ratio of 15/28. Mean age was 51.3±15.4 years. The mean cold ischemia time reached 754 [532.5; 901] minutes, with a global rate of delayed graft function requiring dialysis (dDGF) of 2.9%. Expanded criteria donors (ECDs) concerned 16.7% of all KTx. AVF were in most cases located on the left (72.1%) forearm (88.4%). 83.3% of our KTRs had an eGFR ≥45mL/min/1.73m² before AVF surgical ligation. The other indications were cosmetic, and only one ligation was performed for cardiologic cause. AVF closure took place after a median time of 560 [447; 789] days post-KTx. QAVF was measured prior to KTx in 30 patients (69.8%): 750 [750; 1320] mL/min. More than 80% of KTRs had antihypertensive treatment at baseline, with a median of two drugs per patient. Five patients had more than 4 drugs.

Evolution of blood pressure levels after AVF ligation in KTRs

DBP significantly raised from T0 to M12: +4.4±7.3 mmHg (p=0.0003) for 24h-DBP, +3.8±7.4 mmHg (p=0.0018) for day-time DBP, and +6.3±9.9 mmHg (p=0.0002) for night-time

DBP (**Table 2**). SBP and heart rate remained stable over time. These results were similar with or without adjustment for QAVF (**Table 2**). The percentage of KTRs who fulfilled the hypertension criteria of the European Society of Hypertension (i.e., Mean 24h-DBP ≥80mmHg) increased from 39.5 to 65.1% (p=0.0045). The proportion of patients with a physiological dipping, decreased from 12.6% at T0 to 8.7% at M12 (p=0.041). These observations persisted until M24, M36 and M48 in the subgroups with extended follow-up. More particularly, the 24h-DBP levels increased from 78.8±8.7 mmHg (at T0) to 78.1±7.9 mmHg (at M24), 86.1±13.9 mmHg (at M36) and 83.3±6.2 mmHg (at M48), respectively (p=0.007). The percentage of KTRs treated with antihypertensive treatment remains stable during the whole study (81.4% at T0, 76.74% at M12, 86.67% at M24, 75% at M36 and 90% at M48). The median number of anti-hypertensive drugs was also constant around 2 (p=0.93).

Evolution of serum levels of cardiac biomarkers after AVF ligation in KTRs

NT-proBNP significantly dropped between T0 (345 [190; 553] pg/mL) to M6 (230 [118; 458] pg/mL; p<0.05 with or without adjustment for QAVF), and then remained stable from M6 to M12 (**Table 2**). No significant change was observed beyond M12: 251 [91; 326] pg/mL at M24; 272 [165; 740] pg/mL at M36; 203 [131; 276] pg/mL at M48. ST2 and Galectin-3 remained globally stable during the whole study, with a significant trend to decreased levels of ST2 at long term (17.7 ng/mL at M48, p=0.0023).

Evolution of the renal function after AVF ligation in KTRs

Two patients were excluded from the analysis because of a lack of a sufficient number of SCr values. Among 41 patients, there were 63.4% with a negative MDRD-eGFR slope before AVF closure, and 46.3% with a negative MDRD-eGFR slope after AVF closure. The MDRD-eGFR slope was -0.0278 mL/min/1.73m² per year [-0.339; 0.326] before AVF closure and -1.053 mL/min/1.73m² per year [-4.5656; 2.313] after AVF closure. Median time was 439 [360; 539] days before AVF closure, and 370 [336; 497] days after AVF closure.

There was no significant difference between slopes before and after AVF closure in the whole cohort (p=0.25). Mean of the paired differences between slopes in one given patient was -0.001 mL/min/1.73m² per year with 95%CI [-0.094; +0.072]. **Figure 2** depicts the eGFR slopes according to MDRD equation.

Evolution of echocardiographic parameters after AVF ligation in KTRs

Following AVF closure, we observed a significant decrease of LVEDD, LVEDV, IVS diameter, SV, LAV, CO, CI, and E/A ratio from T0 to M6. LV mass and LV mass index decreased of 32 g [45; 34] and 16.5g/m² [18.2; 13.6] from T0 to M12 (p<0.0001), respectively. There was no significant change on LVEF. Right heart parameters such basal RV end-diastolic diameter, pulmonary arterial systolic pressure and TAPSE dropped from T0 to T12. All of these data are summarized in **Table 3**. The long-term follow-up showed the persistence of the echocardiographic changes described above. The GLM model demonstrated that LAV index correlated with the concentration of serum NT-proBNP (p=0.0004). LAV index and LVEDD increased as a function of ST2 (p=0.036 and p=0.0003, respectively) and Galectin-3 (p<0.0001 and p=0.017, respectively).

Discussion

In the present prospective and systematic study, the surgical ligation of a functioning AVF causes the isolated elevation of DBP during both day- and night- times, with no significant influence on SBP. From a clinical point of view, such an increased DBP leads to the diagnosis of hypertension in a significantly higher proportion of initially normotensive patients according to European Society of Hypertension criteria(17). Still, serum levels of NT-proBNP drop concomitantly with long-term improvements of the US-based cardiac parameters. No significant impact on kidney function was noted in our prospective cohort.

A survey realized in a Polish KTx center mentioned that only one fourth of KTRs have ever considered AVF closure, mainly for cosmetic reasons(18). In an American retrospective study, more than 16.000 medical files were reviewed: only 4.6% of KTRs had AVF surgical closure, with a high variability between centers, and the systemic benefits of AVF ligation, including graft failure and all-cause mortality, were minimal(19). In our center, we propose a surgical AVF ligation to KTRs one year after KTx if eGFR >45mL/min/1.73m²; if the risk of recurrence of initial nephropathy is low or zero; if there is no history of rejection or graft loss; if the donor-specific antibodies are absent; and finally if the adherence to medication is optimal. Due to a lack of standardization or guidelines, eGFR >45mL/min/1.73m² was chosen arbitrarily. Of important note, the motivation of the patient regarding AVF ligation also influences the final surgical decision. Magnetti, et al. showed that AVF closure in 22 KTRs significantly improved kidney graft resistivity index (from 0.71 [0.66–0.74] before AVF closure to 0.66 [0.61–0.69] six months later, p<0.001), possibly via a better graft perfusion(20). Indeed, one may speculate that the AVF-associated low-resistance attenuates the arterial stiffness and wall pressure(21), thereby improving organ perfusion. Central arteriovenous anastomosis has been proposed to treat uncontrolled hypertension following this physiological hypothesis of reduced vascular resistances(22).

Management of isolated diastolic hypertension (IDH) is debated. First, IDH was regarded as part of the physiological ageing phenomenon due to arterial stiffness. However, a Finnish prospective study and two Asian meta-analysis finally demonstrated that IDH was associated with a higher cardiovascular mortality in the general population(23–25). As stated by ESH/ESC 2018 guidelines(17), lifestyle changes and antihypertensive drugs should lower office DBP to less than 90mmHg (recommendation IA), and maybe towards 80mmHg (recommendation IIaB). No specific management is proposed for KTRs. The isolated rise of DBP after AVF ligation could be related to a healthier vascular system due to the rather young age of KTRs. Unfortunately, no data were available concerning arterial stiffness or renal resistive index in our cohort.

AVF ligation induces cardiac morphological changes by suppressing the hemodynamically significant high-flow state. A prophylactic surgical high-flow AVF ligation (> 1500mL/min) has been previously shown to prevent high-output HF (0% *versus* 38.3% in the control group, p=0.013)(26,27). In our present series, 7/30 patients (23.3%) had a QAVF higher than 1500 ml/min. In a single-center randomized controlled trial (AVF ligation *versus* no ligation), the reduction of LV mass index, as well as LV and LA volumes, CO, CI, but not LVEF, after 6-months from AVF closure was reported using cardiac magnetic resonance imaging (cMRI)(28). Of important note, no change in cardiac parameters was observed in control patients with no AVF ligation, which emphasizes the statistical robustness of comparing each patient to him/herself at T0. Salehi, et al. have shown that the regression of cMRI-measured LV mass and LV mass index persists five years after AVF ligation(11). However, the cardiac parameters did not fully return to normal values since a residual concentric remodeling of LV geometry remained(8). Our results are consistent with these findings and confirm the LV and LA reverse remodeling after 6-months *post* AVF closure. We also demonstrate the stability of this condition after 12-months. Regression of LV hypertrophy in KTRs has been associated with a better survival rates and less cardiovascular events in a prospective *post hoc* analysis of two randomized control trials where changes in LV mass were observed after either starting angiotensin converting enzyme inhibitors *versus* no therapy, or add on therapy with everolimus over cyclosporine(29). LVEF was stable across the duration of the study. It is the most practical and frequently used parameter to assess LV systolic function despite the limitation of its pre- and after-load dependence. KTRs with functioning AVFs at T0 have an increased pre-load (high-flow state), which probably leads to an "over-estimation" of LV systolic function compared with after AVF closure. Therefore, the systolic function factually increases, but this effect is masked by the high-flow state *pre*-AVF ligation. Moreover, the DBP elevation post-AVF ligation probably increases the after-load, thereby reducing LVEF. The QAVF was routinely measured prior to KTx in 30 cases of our cohort. The changes in BP levels and biomarker serum concentrations after

AVF ligation were not significantly impacted after statistical adjustment for QAVF. Note that AVF flow rate does not fully respond to Poiseuille flow theory. First, the flow is pulsatile. Secondly, the modified vascular anatomy induces complex flow patterns. Furthermore, Doppler ultrasound may overestimate the blood flow in tortuous segments of the AVF(30,31).

A reduction of right ventricular longitudinal systolic function, assessed by TAPSE, after AVF closure was demonstrated. This is probably related to the fact that TAPSE is a pre-load-dependent parameter. Pulmonary hypertension is defined by a mean pulmonary arterial pressure ≥ 25 mmHg and is often seen in patients with ESRD especially those with (high-flow) AVF. Volume overload, increased vascular tone and underlying heart failure can contribute to or exacerbate pulmonary hypertension. As seen in our study, pulmonary arterial systolic pressure seems to be improved after AVF ligation, which may lead to improved cardiac outcomes.

The natriuretic peptides NT-proBNP and BNP are synthetized by atrial and ventricular myocardium, but the main stimulus is the stretch of ventricular cardiomyocytes. Pre-AVF ligation NT-proBNP is determined by the myocardial stretch (wall stress) induced by the chronic high-flow state. The normalization of the flow *post* AVF ligation causes the drop of NT-proBNP together with the reductions of LVEDV and LAV(32,33). The natriuretic peptides are used in routine clinical practice as initial screening tests to rule out HF in symptomatic patients. However, these biomarkers are not recommended to guide titration of therapy given the conflicting results of various trials(34). Our findings are in agreement with other reports that show that serum levels of NT-proBNP decrease after AVF ligation, in parallel with modifications of cardiac morphology and function(35). ST2 a biomarker of fibrosis and inflammation and is a novel biomarker to diagnose and risk stratify HF and various cardiac disease(36). A Spanish team demonstrated that a decrease of serum ST2 levels during the 2-week monitoring period was associated with less HF episodes independent of serum NT-

proBNP levels(37). Galectin-3 is a β-galactoside-binding lectin leading to apoptosis, angiogenesis, inflammation, and finally to myocardial fibrogenesis and HF. Galectin-3 is considered as a biomarker of the severity of heart fibrosis(38). Acute and chronic renal failure can increase serum Galectin-3 levels(39). Furthermore, heart transplantation does not seem to change serum levels of Galectin-3 of HF patients(40). Both biomarkers are now approved by Food and Drug Administration as complementary biomarkers to assess the global risk of HF. As mentioned above, AVF ligation was followed by cardiac functional and morphological changes, but no significant change was observed in terms of serum Galectin-3 and ST2 levels in KTRs. It is of interest to see a downward trend for serum levels of ST2 after 36 months in our cohort. These findings could be explained by persistent cardiac morphological abnormalities after AVF closure(8). To our knowledge, this is the first time serum ST2 and Galectin-3 are measured in KTRs after AVF closure. Of theoretical note, the renal clearance may also influence serum ST2 and Galectin-3 levels. We postulate that very small changes in cardiac morphology remaining *post*-AVF closure can be sufficient to stimulate ST2 and Galectin-3 production but further investigations are needed.

The impact of AVF ligation on eGFR decline in KTRs remains highly debated. A meta-analysis showed that KTRs with ligated AVF had lower SCr values with a pooled mean difference of 0.10 (95% CI, 0.04 to 0.17, p=0.003) compared to patients with left-open AVF(41). A bias of indication may partly explain these findings since higher SCr values increase the probability of ESRD in KTRs with a soon-to-come need for a vascular access and the subsequent decision to not ligate a functioning AVF in these patients. In a retrospective study individually comparing 114 KTRs with ligated AVF to themselves, the eGFR slopes were significantly different before (0.038 mL/min/month) *versus* after (-0.159 mL/min/month) AVF closure. One may extrapolate that the decline of kidney function after AVF ligation may be caused by lower pulmonary flow and decreased arterial oxygen content(7). Modifications in the body composition, including the edema-free weight and the

surface, may also interfere with eGFR assessment(42). In the present prospective study of a limited number of patients, no significant difference was found when comparing the eGFR slopes before *versus* after AVF ligation. Large inter- and intra-individual variabilities of SCr values were observed. Comparative measured GFR before and after surgery in large multicenter prospective studies may help to resolve this debated question about the impact of AVF closure on kidney function decline.

In conclusion, AVF closure in KTRs is associated with improved LV and LA morphology and decreased serum NT-proBNP levels, but these positive cardiologic impacts could be mitigated by an increase in DBP. No significant change in eGFR slopes and LVEF was observed after AVF ligation. Although our cohort is the largest one studied so far, the absence of a control group is the main limitation of our work. Note that Rao et al. have demonstrated that the absence of AVF ligation in KTRs does not change any clinical, biological, or radiological parameters at 6 months(28). Scoring scales and standardizations are needed to better assess the indications for AVF closure, including the global cardiovascular risk. The surgical ligation of a patent AVF should only be considered in patients with stable and preserved renal function or in patients at risk for HF, and careful monitoring of DBP is recommended.

Disclosure

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Tables and figures

Table 1. Characteristics of the population	
	All patients (n=43)
Recipients	
Age (years)	51.3 ± 15.4
Gender (F/M)	15/28
BMI at KTx (kg/m²)	25.9 ± 4.5
Duration of dialysis (days)	562 [298; 841]
QAVF before KTx (mL/min)	750 [750; 1320]
AVF ligation post KTx (days)	560 [447; 789]
Donor	
Age (years)	44.4 ± 11.7
Gender (F/M)	18/25
BMI (kg/m²)	25.7 ± 4.4
DBD/DCD/LD (%)	74/19/7
ECD (%)	16.7
Transplant	
CIT (min)	754 [532.5; 901]
dDGF (%)	2.9

Plus-minus values are means ± SD.

F, female; M, male; BMI, body mass index; KTx, kidney transplantation; QAVF, arteriovenous fistula flow; DBD, donor after brain death; DCD, donor after circulatory death; LD, living donor; ECD, expanded criteria donor; CIT, cold ischemic time; dDGF, dialysis-based definition delayed graft function.

Table 2. 24h Ambulatory Blood Pressure Monitoring and Cardiac biomarkers					
	T0		M12	p value	p value *QAVF
24h SBP (mmHg)	131 ± 12.6		129.5 ± 12.4	0.61	0.52
24h DBP (mmHg)	78.8 ± 8.7		83.2 ± 9.0	0.0003	0.004
Daytime SPB (mmHg)	133 ± 12.3		132 ± 12.1	0.47	0.53
Daytime DBP (mmHg)	81.4 ± 8.9		85.2 ± 9.2	0.0018	0.005
Nighttime SBP (mmHg)	123 ± 14.2		124 ± 15.9	0.55	0.98
Nighttime DBP (mmHg)	71.2 ± 9.8		77.5 ± 10.7	0.0002	0.007
24h heart rate (bpm)	72 ± 11.1		72 ± 10.5	0.85	0.57
	T0	M6	M12		
NT-proBNP (pg/mL)	345 [190; 553]	230 [118; 458]	191 [129; 344]	0.0001	0.022
ST2 (ng/mL)	23.8 [19.9; 29.8]	22.8 [19.8; 27.8]	23.5 [19.2; 32.7]	0.92	0.63
Galectin-3 (ng/mL)	19.5 [13.9; 23.6]	17.4 [13.4 ;21.2]	18.7 [13.6; 24.1]	0.30	0.21

*24h ambulatory blood pressure monitoring values are means ± standard deviation (SD). Cardiac biomarkers are medians [first quartile; third quartile]. SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro b-type natriuretic peptide; ST2, suppression of tumorigenicity 2 marker; T0, before the surgical ligation of the AVF; M6, M12: 6, 12 months after the surgery; QAVF, arteriovenous fistula flow; *QAVF, p value after adjustment for QAVF (n=30 cases)*

Table 3. Summary of changes in Echocardiograms				
	T0	M6	M12	p value
LV end-diastolic diameter (mm)	50 ± 5.07	47.4 ± 4.92	47 ± 5.94	<0.0001
LV end-diastolic diameter index (mm/m²)	26.6 ± 3.20	25.3 ± 3.11	25.1 ± 3.39	<0.0001
LV end-systolic diameter (mm)	33.4 ± 5.54	31.2 ± 4.80	33.0 ± 5.63	0.087
LV end-systolic diameter index (mm/m²)	17.8 ± 3.32	16.6 ± 3.10	17.8 ± 3.29	0.10
LV end-diastolic volume (mL)	125 ± 30.9	106 ± 24.9	105 ± 21.7	<0.0001
LV end-diastolic volume index (mL/m²)	65.8 ± 14.5	56.1 ± 11.1	55.2 ± 10.1	<0.0001
LV end-systolic volume (mL)	49 ± 16.9	42.0 ± 13.0	44.0 ± 13.2	0.012
LV end-systolic volume index (mL/m²)	25.7 ± 8.36	22.1 ± 6.28	23.0 ± 6.14	0.012
LV mass (g)	187 ± 55.6	154 ± 42.3	155 ± 50.7	<0.0001
LV mass index (g/m²)	97.9 ± 24.7	81.1 ± 17.3	81.4 ± 22.1	<0.0001
Inter ventricular septum diameter (mm)	11.6 ± 2.06	10.8 ± 2.06	10.9 ± 1.78	0.0003
Posterior wall diameter (mm)	8.45 ± 1.95	7.80 ± 1.67	7.90 ± 1.55	0.12
Relative wall thickness	0.34 ± 0.08	0.33 ± 0.081	0.34 ± 0.063	0.86
Stroke volume (mL)	97.1 ± 18.9	89.4 ± 29.9	86.5 ± 22.1	0.0061
Stroke volume index (mL/m²)	51.9 ± 9.39	46.7 ± 12.4	45.5 ± 10.4	0.0034
Cardiac output (L/min)	6.49 ± 1.15	5.61 ± 2.12	5.98 ± 1.95	0.0054
Cardiac index (L/min/m²)	3.48 ± 0.66	3.00 ± 0.94	3.15 ± 0.89	0.0079
Ejection fraction (%)	61.5 ± 6.51	60.5 ± 8.11	58.2 ± 8.74	0.078
Left atrial volume (mL)	72 ± 28.1	55.5 ± 16.1	60.2 ± 22.4	<0.0001
Left atrial volume index (mL/m²)	37.5 ± 12.6	29.3 ± 6.65	31.3 ± 9.97	<0.0001
E/A ratio	1.13 ± 0.34	0.94 ± 0.30	0.94 ± 0.34	<0.0001
TAPSE (mm)	23.4 ± 4.77	21.4 ± 3.84	21.2 ± 4.24	0.011
Basal RV end-diastolic diameter (mm)	38.5 ± 4.55	36.7 ± 3.90	36 ± 4.12	0.015
Pulmonary arterial systolic pressure (mmHg)	26.9 ± 7.17	24.4 ± 6.11	21.9 ± 6.42	0.0037

Plus-minus values are means ± SD.

LV, left ventricle; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; T0, before the surgical ligation of the AVF; M6, M12: 6, 12 months after the surgery

Figure legends

Figure 1. Evolution of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels

Changes in NT-proBNP serum levels, in the whole cohort (n=43) from baseline (T0) to 12 months (M12) post-KTx (panel A); in patients (n=15) who had follow-up to 24 months (M24) post-KTx (panel B); in patients (n=8) who had follow-up to 36 months (M36) post-KTx (panel C); and in patients (n=10) who had follow-up to 48 months (M48) post-KTx (panel D). Change in means and the 95% CI showed a significant decrease of NT-proBNP from T0 to M12 ($p<0.0001$) with the general linear mixed model (GLMM). NT-proBNP serum levels are expressed in pg/mL.

Figure 2. Evolution of estimated glomerular filtration rate (eGFR) according to Modification of Diet in Renal Disease (MDRD)

MDRD eGFR slopes (in mL/min/1.73m²) of kidney transplant recipients (KTRs) before *versus* after closure of the arteriovenous fistula (AVF). The slopes do not differ from each other through time (p=0.248).

Figure 1.

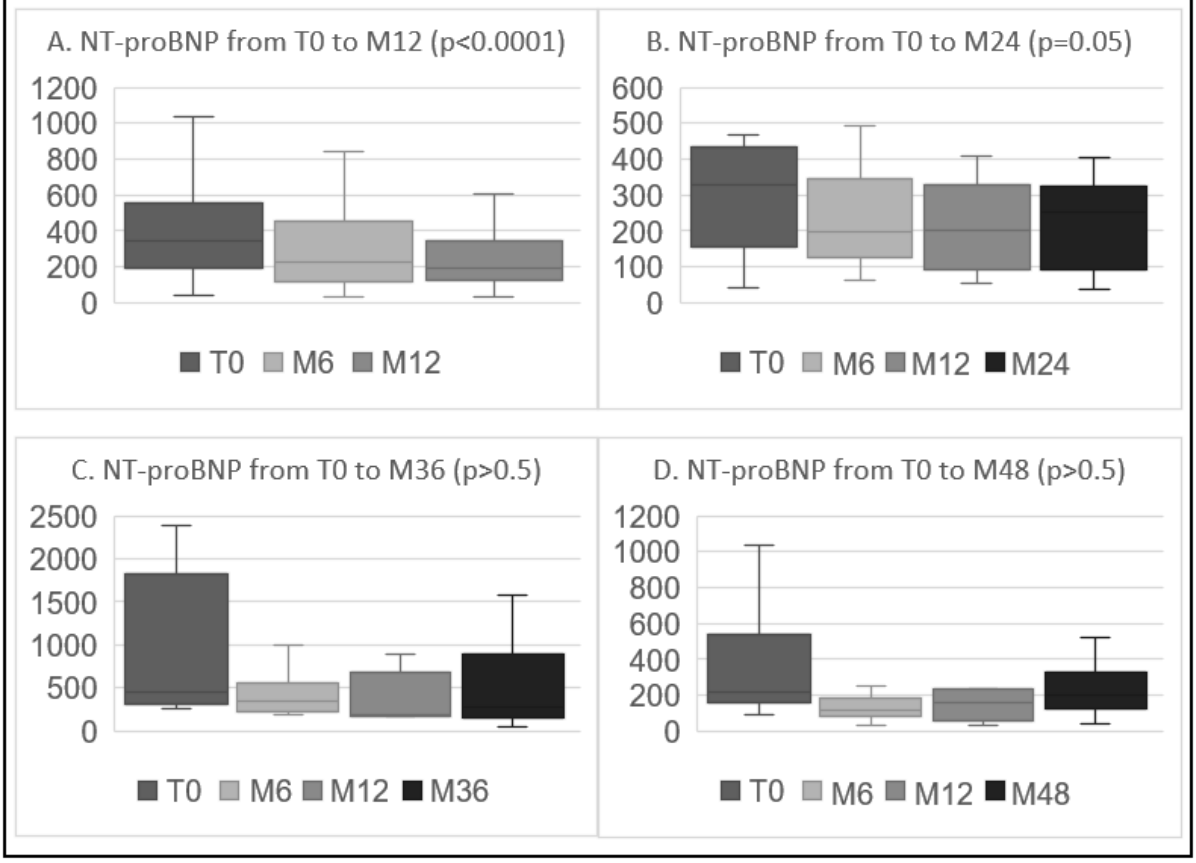

Figure 2.