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Received: 13 April 2021 | Revised: 18 August 2021 | Accepted: 24 September 2021

DOI: 10.1111/sdi.13028

ORIGINAL ARTICLE

Seminars in Dialysis WILEY

High-flow arteriovenous fistula and hemodynamic consequences at 1 year after kidney transplantation

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Abstract

Introduction: There are only scarce data regarding the cardiovascular impact of arteriovenous fistula after kidney transplantation depending on fistula flow.

Methods: We performed a single-center, prospective, cohort study including 49 patients with a functional fistula at 1 year from kidney transplantation. Patients were convened for a clinical work-up, a biological analysis, a fistula's Doppler ultrasonography and an echocardiography. Main judgment criterion was comparison of echocardiography parameters between patients with relative (fistula flow >1 L/min and a fistula flow/cardiac output ratio >20%), absolute high-flow fistula (fistula flow >2 L/min) and normal-flow fistula.

Results: High-flow fistula frequency was 69%. Significantly higher left ventricular end-diastolic and systolic diameters were observed in this group compared with the normal-flow fistula group (53 ± 6 vs. 48 ± 7 mm; $p = 0.04$ and 33 ± 6 vs. 28 ± 8 mm; $p = 0.02$) and between the absolute and relative high-flow fistula subgroups (56 ± 6 vs. 51 ± 6 mm; $p = 0.009$ and 35 ± 6 vs. 31 ± 5 mm; $p = 0.01$). The study showed no other significant differences.

Conclusions: This study showed a significantly higher but not pathological left ventricular end-diastolic and systolic diameters values in patients with high-flow fistula compared with patients with normal-flow fistula and between patients with respectively absolute and relative high-flow fistula.

1 | INTRODUCTION

Kidney transplantation (KT) is a major substitution technique for end-stage renal disease (ESRD). However, prior to KT, most patients undergo other substitution techniques including hemodialysis (HD). HD achievement necessitates a good vascular access, arteriovenous fistula (AVF), being the reference vascular access.[1,2]

However, AVF is not exempt from hemodynamic and cardiovascular effects. Some authors suggest that AVF promotes hemodynamical and cardiac anatomical abnormalities, particularly left ventricular hypertrophy (LVH), high-flow AVF (HF-AVF), or even high-output cardiac failure (HOCF).[3–6] Studies analyzing these abnormalities due to patent AVF are carried out in ESRD patients, mostly on HD therapy, what constitutes a bias of interpretation about the direct AVF impact on the cardiovascular system. Indeed, pronounced intravascular volume variations occurring during thrice-weekly HD therapy combined to chronicle hyperuremic state impact dramatic hemodynamical parameters, leading independently to serious cardiovascular abnormalities.[7,8] In contrast, only few studies[9,10] analyzing AVF hemodynamic consequences are carried out in KT recipients (KTRs), whose main characteristic is to benefit from a well-functioning kidney, thus ensuring a more efficient and stable sodium–water homeostasis.[11,12]

Theoretically, patients no longer require their vascular access after successful KT. However, there is no consensus as to the benefit of AVF closure after KT. Long-term AVF could possibly lead to severe

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cardiovascular complications, and some authors showed a regression of LVH after AVF closure,[9,10,13–15] without demonstrating a clear impact on KT morbidity and mortality. Moreover, none of these studies distinguished groups with normal-flow AVF (NF-AVF) versus HF-AVF. Few studies carried out in HD patients may suggest that HF-AVF has a higher cardiovascular risk than NF-AVF.[6,16,17] Nevertheless, this population exhibits poor vascular capital and, as a result, often has trouble in creating a new AVF. KDOQI Clinical Practice Guideline for vascular access 2019[1] reminded us to consider the medical situation and potential life span of each KTR before considering an AVF closure, because of the potential need of a future HD.

In this study, we aimed to know if functional renal graft at 1 year was able to protect heart from hemodynamic consequences of HF-AVF compared with NF-AVF.

2 | PATIENTS AND METHODS

This single-center, prospective, noninterventional study was performed in the nephrology-transplantation department at the Nouvel Hôpital Civil in Strasbourg, France. All adult KT patients with a functional native AVF at 1 year from KT were consecutively included between February 2013 and November 2015. All patients with either a prosthetic or AVF loss during the first year post-KT, an altered left ventricular ejection function (LVEF) (<40%) and a significant valvulopathy were excluded.

All patients who met the inclusion and exclusion criteria were convened at 1-year post-KT at our Nephrology Functional Exploration unit, with the following examinations performed on the same day: a clinical work-up, including pre-KT data (morphology, AVF data, cumulative HD time, KT characteristics, cardiovascular comorbidities), a blood sample with graft function evaluation (measured glomerular filtration rate [GFR] with Iohexol clearance, estimated GFR with modification of diet in renal disease [MDRD] formula) and brain natriuretic peptide (BNP) plasma level measurement, an electrocardiogram (ECG) as well as blood-pressure (BP) monitoring (mean of 12 measurements).

AVF Doppler ultrasonography (SonoSite-M Turbo™, Fujifilm™, USA), performed by two consecutive single operators (measuring conditions are summarized in Table S1) who measured the diameter and flow volume in the brachial artery in order to calculate Q_{AVF}.

Doppler echocardiography (Vivid-9™, General Electric™, USA) was performed by a single operator. Echocardiographic examination included measurement of left ventricular (LV), right ventricular (RV), systolic, and diastolic functions, in two-dimensional, M-mode examinations, Doppler and tissue Doppler imaging (TDI) analysis. Left ventricular mass index (LVMi) was calculated according to the standard equation: $LVMi = 0.8 \times 1.04 \times [(IVS + LVID + PWT)^3 - LVID^3] + 0.6$ g. LVEF was calculated using the biplane Simpson's method. RV systolic function was calculated using the RV fractional shortening (RVFS). Measured parameters included maximal Doppler velocity of early mitral and tricuspid inflows (Em and Et, respectively), late mitral and tricuspid inflows (Am and At, respectively), and calculations of Em/Am and Et/At ratios. All right Doppler flows were recorded in end-expiratory time. Early diastolic DTI velocities of the mitral (Eam) and tricuspid (Eat) annulus were measured at the lateral systolic mitral annulus and at the lateral tricuspid annulus respectively, from the apical 4-chamber view, allowing a noninvasive estimation of LV and RV filling pressures, respectively. Systolic pulmonary arterial pressure (sPAP) was assessed by continuous wave Doppler using tricuspid regurgitation, while right arterial pressure (RAP) was estimated by measuring the inferior vena cava (IVC) diameters. Cardiac output (CO) and pulmonary output (PO) were calculated after measuring LV and RV outflow tract diameters in the parasternal long axis view in systole on the one hand and the left and right outflow tract velocity time integral (VTI) by pulsed wave Doppler on the other, respectively. Each measurement at a given site was performed over 3 consecutive cardiac cycles, the results of which were subsequently averaged.

All subjects gave their informed consent to the study and for the use of clinical and biological data. The study was exempt from approval from an ethics' board.

The main judgment criterion was comparisons of hemodynamic data obtained by echocardiography, between NF-AVF and HF-AVF groups and between relative HF-AVF (HFr-AVF) and absolute HF-AVF (HFa-AVF) subgroups. Other judgment criteria included Q_{AVF} frequency and HOCF prevalence. The Basile and al.[6] definition of HF-AVF was used, which distinguishes relative HF-AVF (HFr-AVF with a Q_{AVF} > 1 L/min and a Q_{AVF}/CO > 20%) and absolute HF-AVF (HFa-AVF with a Q_{AVF} > 2 L/min). HOCF was defined by a cardiac index above 3.9 L/min/m^2 associated with chronic heart failure (CHF) symptoms with New York Heart Association (NYHA) grade ≥ 2/4 and/or water–salt overload.

Quantitative data are described as mean, median, variance, standard deviation (SD), and standard error when appropriate. Qualitative data are described according to their frequency for each modality. Comparisons between quantitative and qualitative data were performed with Student's t test or Wilcoxon test when appropriate and χ^2 test, respectively; correlation between echocardiographic data and Q_{AVF} was performed with Pearson's test for distribution. The α error was set at 5%. All statistical analyses were performed using the SPSS software package, (SPSS Inc., USA).

3 | RESULTS

Among the 178 KTR transplanted between February 2013 and November 2015, 49 were ultimately included in the study (Supporting Information S1). General population characteristics at inclusion are reported in Table 1.

There were no differences regarding clinical characteristics, ECG analysis, Holter BP measurements and biological data between the HF-AVF and NF-AVF groups, nor between the HFa-AVF and HFr-AVF subgroups (Table 2). In the whole studied cohort, mean Q_{AVF} was 1,600 ± 684 ml/min (558–3,266) and HF-AVF frequency was 69%. Mean Q_{AVF} in the NF-AVF and HF-AVF groups were respectively 959 ± 274 ml/min and 1,883 ± 616 ml/min, significantly

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TABLE 1 General population characteristics at inclusion

Characteristics	Mean ± *SD* (min and max) or frequency
Demographic	
Age (years)	57 ± 12 (27–77)
Ratio men/women	2
Cumulative dialysis time before KT (months)	47 ± 25 (8–111)
Native Kidney Disease (%)	
• Interstitial tubular nephropathy	32
• Glomerular nephropathy	20
• ADPKD	18
• Diabetic nephropathy	14
• Vascular nephropathy	6
• Other	10
CVD risk factors (%)	
• HBP	96
• Smoking habit (% active)	53 (35)
• Diabetes	41
• Coronary artery disease	12
Clinical characteristics	
NYHA	1.5 ± 0.5
BP systolic / diastolic (mmHg)	146 ± 18 / 81 ± 10
AVF characteristics	
Upper-arm localization (%)	73.5
Duration of use (months)	55 ± 27 (13–138)
Aneurysmal / previous angioplasty (%)	29 / 13
Treatment	
Number of antihypertensive drugs (≥3 in %)	1.8 ± 1.3 (22)
Biological characteristics	
Creatinine (μmol/L)	141 ± 53 (54–295)
Iohexol clearance (ml/min)	49 ± 16 (19–77.6)
MDRD GFR (ml/min/1.73 m^2)	49 ± 17 (20–86)
BNP (ng/L)	240 ± 328 (2–1,284)

Abbreviations: ADPKD, autosomal dominant polycystic disease; AVF, arteriovenous fistula; BNP, brain natriuretic peptide; BP, blood pressure; CVD, cardiovascular disease; GFR, glomerular filtration rate; HBP, high blood pressure; KT, kidney transplantation; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MDRD, modification of diet in renal disease; NYHA: New York Heart Association; SD, standard deviation.

different ($p < 0.001$). In the HF-AVF group, HFa-AVF frequency was 38%, while HFr-AVF frequency was 62%, with a mean Q_{AVF} of 2,543 ± 329 and 1,474 ± 320 ml/min, respectively, significantly different ($p < 0.001$).

Echocardiographic examinations revealed LVH in 69% of patients. Relatively but significantly higher left ventricular end-diastolic (LVEDD) and left ventricular end-systolic (LVESD) diameters were observed in the HF-AVF group compared with NF-AVF group (53 ± 6 vs. 48 ± 7 mm; $p = 0.04$ and 33 ± 6 vs. 28 ± 8 mm; $p = 0.02$, respectively, Table 3 and Figure 1) with a poor but significant correlation with Q_{AVF} (LVEDD $r = 0.45$; $p = 0.001$ and LVESD $r = 0.35$; $p = 0.02$). LVEDD and LVESD were also relatively but significantly higher in the HFa-AVF subgroup compared with the HFr-AVF subgroup (56 ± 6 vs. 51 ± 6 mm; $p = 0.009$ and 35 ± 6 vs. 31 ± 5 mm; $p = 0.01$, respectively, Table 4 and Figure 1).

The CO index was significantly increased in NF-AVF group when compared with HF-AVF group (3.4 ± 0.5 vs. 3.1 ± 0.6 L/min/m^2, $p = 0.01$, respectively) but remained in the normal range. There was no significant correlation between CO and duration of AVF use. Mean CO index was 3.2 ± 0.6 L/min/m^2, with two patients having a cardiac index below 2.1 L/min/m^2. In five patients (11%) with high CO, whose mean Q_{AVF} was 1,628 ± 321 ml/min, four of them were in the HFr-AVF subgroup, while the fifth patient was in the NF-AVF group; this latter patient presented with vitamin B6 deficiency and mild anemia. Only two patients fulfilled the HOCF criteria. There was no significant association between high CO and clinical, biological, or echocardiographic characteristics.

According to estimation of LV filling pressure recommendations,[14] left atrial pressure (LAP) was increased in 20% of patients, all of whom had LVH. Mean PO was 4.9 ± 1.2 L/min (with PO/CO ratio in the normal range) and no patient presented RV dilatation nor RV systolic dysfunction. RAP estimated echographically by IVC diameters was increased in 12% of patients, and pulmonary hypertension (PHTN) was found in 14%, all of presumed post-capillary origin. Nevertheless, IVC diameter did not differ between the HFa-AVF and the HFr-AVF subgroups (15.5 ± 3 vs. 13.1 ± 4.8 mm; $p = 0.08$) and was in normal ranges (Table 4). Mean LVFP, stroke volume (SV), right chamber, IVC sizes, and RV filling pressures were in normal ranges and comparable between groups (Table 3, Figure 2, and Supporting Information S2). None of the patients had a significant valvular heart disease.

4 | DISCUSSION

In the present study, we observed a significant increase in diastolic and systolic LV sizes in the HF-AVF group compared to the NF-AVF group, and in HFa-AVF subgroup compared with the HFr-AVF subgroup respectively, with weak but significant correlations between Q_{AVF} and both LVEDD and LVESD. Interestingly in HF-AVF group, HFr-AVF or HFa-AVF subgroups, mean LVFP, SV, right chamber, IVC sizes, and RV filling pressures were in normal ranges and comparable with NF-AVF group. We also observed a similar and moderate increase of mean plasma BNP level, in all patients' groups.

Mechanistically, AVF is the anastomosis between a noncompliant arterial sector with high pressure and a capacitive venous sector with a low pressure. The consequence is a shunt of the capillary network in parallel, thus promoting arterial steal to the AVF due to its low resistance.[18] Indeed, this considerable increase of arterial flow in the AVF[19] will increase the shear stress applied to the endothelial cells, favoring NO synthesis and then vasodilatation of both arterial and venous sectors, which causes a collapse of the AVF resistance

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TABLE 2 Comparison of demographic, clinical and biological characteristics between NF-AVF and HF-AVF groups and between HFr-AVF and HFa-AVF groups

Characteristics	Mean ± *SD* or number (frequency)			Mean ± *SD* or number (frequency)		
	NF-AVF ($N = 15$)	HF-AVF ($N = 34$)	*p*	HFr-AVF ($n = 21$)	HFa-AVF ($n = 13$)	*p*
Demographic						
Age (years)	61 ± 13	56 ± 12	0.2	56 ± 28	59 ± 29	0.2
Ratio men/women	1.5	2.4	0.4	1.6	12	0.07
Mean HD time (months)	43 ± 24	49 ± 25	0.5	51 ± 27	45 ± 23	0.6
CVD risk factors	2.7 ± 1	2.5 ± 1.3	0.5	2.3 ± 1.5	2.8 ± 1.2	0.4
Antihypertensive drugs	2 ± 1.2	1.7 ± 1.3	0.5	1.6 ± 1.2	2 ± 1.4	0.5
Clinical						
Mean NYHA	1.5 ± 1	1.5 ± 0.5	0.2	1.5 ± 0.5	1.5 ± 1	0.4
Salt–water overload	6 (40)	9 (26)	0.4	3 (14)	6 (46)	0.08
SBP (mmHg)	150 ± 21	145 ± 17	0.4	142 ± 16	150 ± 19	0.2
DBP (mmHg)	82 ± 11	81 ± 10	0.8	79 ± 10	84 ± 9	0.2
Mean duration of AVF use (months)	50 ± 25	57 ± 28	0.4	56 ± 28	59 ± 29	0.7
Biological						
Creatinine (μmol/L)	143 ± 53	139 ± 53	0.8	128 ± 50	157 ± 56	0.3
Iohexol clearance (ml/min)	42 ± 13	50 ± 16	0.06	50 ± 17	50 ± 15	0.9
MDRD GFR (ml/min/1.73m^2)	46 ± 17	51 ± 18	0.4	54 ± 19	45 ± 15	0.1
BNP (ng/L)	232 ± 379	244 ± 310	0.51	230 ± 296	265 ± 340	0.69

Abbreviations: AVF, arteriovenous fistula; BNP, brain natriuretic peptide; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HD, hemodialysis; HF-AVF: high-flow AVF; HFa-AVF, absolute high-flow AVF; HFr-AVF, relative high-flow AVF; NF-AVF, normal-flow AVF; MDRD, modification of diet in renal disease; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

(R_{AVF}).[20] Such a significant hemodynamic change is well explained by two main physical laws:

- When blood is pumped from the LV to the arteries, it generates pressure. According to Poiseuille's law: $\Delta P = CO{\cdot}R$ (ΔP: pressure difference; R: resistance), equivalent to $MAP = CO{\cdot}TSVR$ (MAP: mean arterial pressure; TSVR: total systemic vascular resistance) when transposed into the CV system.
- Further, according to Ohm's law in a parallel circuit: $1/TSVR = 1/R_{AVF} + 1/SVR$, TSVR is always lower than the value of the lowest resistance, R_{AVF} in the present case. Consequently, MAP decreases because of the lowering of TSVR ($\downarrow MAP = CO{\cdot}\downarrow TSVR$). This decrease in MAP by lowering the resistances leads to a decrease in organ perfusion.

In a rat model of AVF, an aorto-cava fistula placement resulted in an early decrease in MAP.[21] Indeed, as a consequence of this decrease in MAP, neurohumoral and sympathetic compensatory mechanisms appear the first days after AVF creation.[22] The salt and water retention promoted by the activation of the renin–angiotensin–aldosterone system (RAAS) combined with a venous return increase generated directly by the AVF, leads to SV increase. This SV increase dilates the cardiac cavities and promotes plasma increases in ANP and BNP, peaking between 150 and 160% at D10 of AVF, as Iwashima et al. reported.[16]

Another compensatory mechanism is sympathetic activation, thereby promoting increases in HR and LV inotropism. According to Franck–Starling's law, these increases in HR, inotropism, and SV will promote an increase in CO to compensate for organ hypoperfusion (Figure 3). In an uremic animal model of femoral AVF by chemical adenine nephrectomy,[23] cardiac response to the chronic volume overload showed not only a significant increase of the LVEDV in AVF-healthy and AVF-CKD rats in comparison with shams, but also increased SV and heart rates (HRs), contributing to a significant increased CO, more pronounced in AVF-CKD rats. The appearance over time of an eccentric then concentric (mixed) LVH participates to diastolic dysfunction by LVFP increasing. These adaptive mechanisms are beneficial in the short term by maintaining SV after AVF placement, and they became deleterious in the long term by promoting fibrosis.[24]

In 24 pre-dialysis patients, Dundon observed by cardiac MRI significant increases in SV, CO, LV diameters, and LV mass of the left and right cardiac chamber 6 months after AVF creation, in comparison with measurements performed before AVF.[19]

In our study, while remaining within normal range, we observed a significant LV enlargement in HF-AVF group in comparison with NF-AVF group, as described also by Iwashima et al.[16] and Korsheed et al.[17] in pre-dialysis patients. However, LVMi and h/r ratio, while increased, were not significantly higher in the HF-AVF group in comparison with the NF-AVF group.

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TABLE 3 Comparison of echocardiographic characteristics between NF-AVF and HF-AVF groups

Characteristics	Mean ± *SD* or number (frequency)			
	Total	**NF-AVF ($N = 15$)**	**HF-AVF ($N = 34$)**	***p***
LV morphology				
LVEDD / LVESD (mm)	51 ± 7 / 31 ± 7	48 ± 7 / 28 ± 8	53 ± 6 / 33 ± 6	0.04 / 0.02
LVMi (g/m^2)	134 ± 44	127 ± 48	137 ± 42	0.5
h/r	0.49 ± 0.14	0.52 ± 0.16	0.47 ± 0.13	0.3
LVH	34 (69)	10 (67)	24 (70)	0.8
Concentric / eccentric LVH	22 (65) / 1 (3)	8 (80) / 0	1 (58) / 1 (4)	0.4 / 0.51
Mixed LVH	11 (32)	2 (20)	9 (38)	0.3
Concentric / eccentric remodeling	7 (14) / 1 (2)	3 (20) / 1 (7)	4 (12) / 0	0.5 / 0.1
RV morphology				
RVEDS / BSA (cm^2/m^2)	9.3 ± 2.1	9.7 ± 2.3	9.1 ± 2	0.4
RVESS / BSA (cm^2/m^2)	4.2 ± 1.3	4.5 ± 1.5	4.1 ± 1.2	0.3
IVC diameter (mm)	13.8 ± 4.4	13.3 ± 4.8	14.1 ± 4.3	0.6
RA morphology				
RA surface (cm^2)	15.4 ± 4.1	15.6 ± 4.5	15.4 ± 3.9	0.9
Systolic LV function				
LVEF (%)	67 ± 7	69 ± 8	66 ± 6	0.2
CO index ($L/min/m^2$)	3.2 ± 0.6	3.4 ± 0.5	3.1 ± 0.6	0.01
Diastolic LV function				
E/A_{mitral}	0.9 ± 0.4	0.8 ± 0.4	0.9 ± 0.4	0.4
$E/E'_{latéral}$ E/E'_{septal}	8.3 ± 3.5 11.1 ± 3.9	7.7 ± 3.3 10.3 ± 4.5	8.6 ± 3.6 11.5 ± 3.6	0.4 0.4
Ap-Am (ms)	−26 ± 26	−25 ± 23	−26 ± 27	0.9
Systolic RV function				
PO (L/min)	4.9 ± 1.2	5.2 ± 0.8	4.9 ± 1.3	0.5
RVFS (%)	54 ± 10	53 ± 9	55 ± 10	0.6
St-DTI (cm/s) ($n < 10$)	14 ± 3.4 (2)	13.2 ± 3.7 (1)	14.4 ± 3.3 (1)	0.3
TAPSE (mm)	23 ± 6	22 ± 6	24 ± 6	0.3
Diastolic RV function				
$E/A_{tricuspid}$	1.1 ± 0.3	1 ± 0.2	1.2 ± 0.3	0.07
$E/E'_{tricuspid}$ ($n > 6$)	4.5 ± 1.3 (6)	4.6 ± 1.4 (2)	4.5 ± 1.3 (4)	0.68
Arterial pulmonary pressure				
V_{max} IT (cm/s)	257 ± 40	258 ± 52	257 ± 32	0.9
PASP (mmHg) ($n =$ PHTN)	32 ± 9 (7)	33 ± 13 (2)	32 ± 6 (5)	0.7

Abbreviations: AVF, arteriovenous fistula; BSA, body surface area; CO, cardiac output; HF-AVF, high-flow AVF; h/r, thickness/radius ratio of the left ventricle; IVC, inferior vena cava; LV, left ventricle; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; NF-AVF, normal-flow AVF; PASP, pulmonary artery systolic pressure; PHTN, pulmonary hypertension; PO, pulmonary output; RA, right atrial; RV, right ventricle; RVEDS, right ventricular end-diastolic surface; RVESS, right ventricular end-systolic surface; RVFS, RV fractional shortening; SD, standard deviation; St-DTI, tricuspid annular S wave velocity in Doppler tissue imaging; TAPSE, tricuspid annular plane systolic excursion.

These results support a mixt mechanism of LV remodeling, by a LV walls thickening in both groups associated with a significant LV enlargement in HF-AVF group, without reaching abnormal values of LV dilatation. Despite the presence of common confounding factors in both groups, well-known to promote concentric LVH as high BP (96%), diabetes (41%), age (mean age 57 ± 12 years), and 1 year of immunosuppressive therapy,[25] relative LV enlargement observed in HF-AVF group appeared weakly but significantly correlated with Q_{AVF}. However, Cridlig et al.[3] did not find a significant relationship between Q_{AVF} and LV diameters, although the authors described a relationship between Q_{AVF} and LVH. In this latter study, the HF-AVF cut-off used ($Q_{AVF} > 680$ ml/min, disregarding Q_{AVF}/CO) was lower

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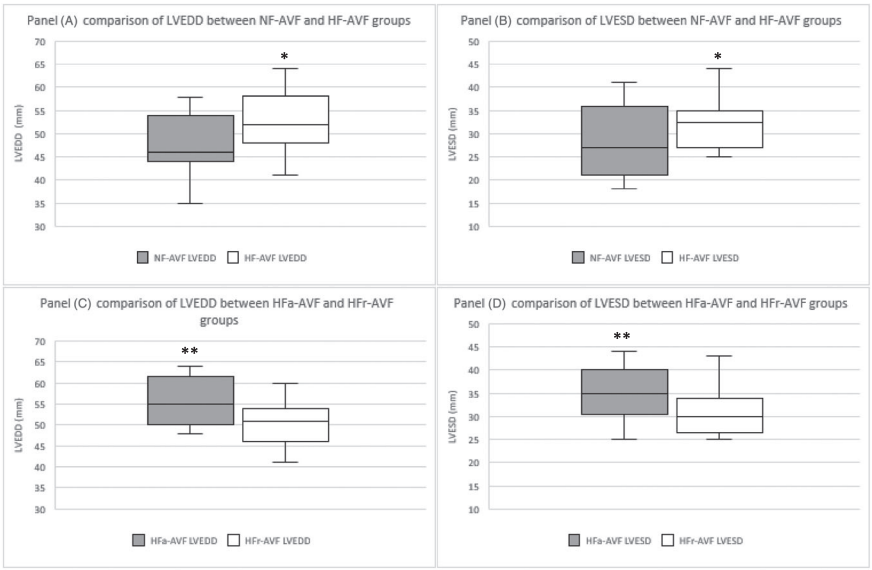

FIGURE 1 Comparisons of left ventricular end-diastolic and end-systolic diameters, between NF-AVF and HF-AVF groups (panels A and B) and between HFa-AVF and HFr-AVF subgroups (panels C and D). AVF, arteriovenous fistula; HF-AVF, high-flow AVF; HFa-AVF, absolute high-flow AVF; HFr-AVF, relative high-flow AVF; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; NF-AVF, normal-flow AVF. Difference between groups: $^{*}p < 0.05$; $^{**}p < 0.01$

than the cut-off used in our study (Q_{AVF} > 2 L/min or Q_{AVF} > 1 L/min with a Q_{AVF}/CO > 20%); in addition, their patients were younger, with only few CVD risk factors, and followed-up over a longer time period (5 years). As in our study, Papasotiriou et al. observed also in stable KTR a mean LVEDD in normal range with a patent AVF.[26] Interestingly, patients who benefited of AVF closure improved cardiac morphology, as a decrease in LVMi due to a significant reduction in LVEDD, and had better kidney graft function.[13,27] These observations support the idea that patent AVF, *a fortiori* with high flow, participate to the trend to dilatation part of LV remodeling, which contributes in turn to the LVMi increase calculated by standard equation.[28]

This might explain a moderate plasma BNP levels increase observed in both groups without a significant difference, due mainly by the presence of a moderate and comparative LVH in these both groups. Moreover, reestablishment of renal function after KT and avoidance of the pronounced intravascular volume variations occurring during thrice-weekly HD therapy consistently reduce BNP variations.[7] A BNP decrease has been reported in a prospective study (19), 3 months after KT in comparison with period before KT, in the presence of AVF (BNP rate 206 ± 200 pg/ml vs. 505 ± 428 pg/ml; $p < 0.01$). The average plasma BNP declined significantly during the first 14 days after surgery. Interestingly, when AVF was surgically ligated in a KT population, a normalization of NT-proBNP values was observed, well correlated with improvement in cardiac chamber dimensions observed by cardiac MRI at baseline and at 6 months.[29] These outcomes are in relation with the relative regression in LVMi observed in studies in the first year after KT, resulting from prevention of uremia and plasma volume overload.[30,31] Except two patients with HOCF, all included patients were asymptomatic, which could be in relation with a better control of volaemia after KT and a better adaptation to the water–salt overload induced by HF-AVF. In addition to the nonpathological left chamber dilatation, this is an argument to avoid ligature procedure in asymptomatic patients.

Another AVF complication classically described is high CO due to HF-AVF, to compensate for organ hypoperfusion. Although our study observed a higher HF-AVF frequency than what was previously described by Basile in HD patients (6), we just identified 15% of patients with high CO. Indeed, high CO classically described in ESRD and HD patients with HF-AVF is thought to be the result of the combined activation of the RAAS and the sympathetic system that our patients probably did not display sustainably, due to physiologic volemic control by a well-functioning renal graft, and the lack of necessary important compensatory mechanisms[32,33] (Figure 3). Nevertheless, we observed that CO index was significantly increased in NF-AVF group compared with the HF-AVF group, but this result is without hemodynamic consequences because both groups' mean values remained strictly in the normal range.

Concerning high HF-AVF frequency observed in our study, one reason is likely linked to our prospective and systematic strategy of recruitment at 1 year after KT, which is probably more closed to the real prevalence of HF-AVF in KTR.

Concerning RV, enlargement and systolic dysfunction are classically described in ESRD patients with patent AVF, which further worsens the patients' prognosis. RV dysfunction is not only impacted by LVFP increase, but it is also directly impacted by the increase in venous return and hyperuremic state[34,35](Figure 3). The well-functioning renal graft of our KTR, regulating efficiently the water–salt balance, might have prevented venous return increase, because we did not observe any IVC dilatation (in relation with RAP level), right chamber enlargement, deterioration of RV function, even in HF-AVF group patients. In other words, the functional graft thus efficiently protects patients from any volodependent mechanisms and from a hyperuremic state.

Study limitations include a lack of echocardiographic parameters before AVF creation and/or before KT would be of great interest. Despite being the largest cohort to this day, the limited number of patients in our study drives to a lack of power.

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TABLE 4 Comparison of echocardiographic characteristics between HFr-AVF and HFa-AVF groups

Characteristics	Mean ± *SD* or number (frequency)		*p*
	HFr-AVF ($n = 21$)	HFa-AVF ($n = 13$)	
LV morphology			
LVEDD / LVESD (mm)	51 ± 6 / 31 ± 5	56 ± 6 / 35 ± 6	0.009 / 0.01
LVMi (g/m^2)	131 ± 39	147 ± 45	0.5
h/r	0.47 ± 0.13	0.47 ± 0.13	0.5
LVH (total)	12 (52)	11 (85)	0.09
RV morphology			
RVEDS / BSA (cm^2/m^2)	9 ± 2	9 ± 2	0.7
RVESS / BSA (cm^2/m^2)	17 ± 5	19 ± 7	0.2
IVC diameter (mm)	13.1 ± 4.8	15.5 ± 3	0.08
RA morphology			
RA surface (cm^2)	15 ± 4.1	16.1 ± 3.7	0.4
Systolic LV function			
LVEF (%)	67 ± 6	65 ± 7	0.2
CO index ($L/min/m^2$)	3.1 ± 0.8	3.1 ± 0.4	0.3
Diastolic LV function			
E/A_{mitral}	0.9 ± 0.3	1 ± 0.5	0.4
$E/E'_{latéral/septal}$	8 ± 3.3 / 10.7 ± 3.3	9.7 ± 4.1 / 12.6 ± 3.9	0.3 / 0.3
Ap-Am (ms)	−26 ± 18	−25 ± 38	0.9
Systolic RV function			
PO (l/min)	5.1 ± 1.2	4.5 ± 1.3	0.4
RVFS (%)	55 ± 8	55 ± 14	0.9
St-DTI (cm/s) ($n < 10$)	14 ± 3	15 ± 4	0.5
TAPSE (mm)	23 ± 4	24 ± 7	0.5
Diastolic RV function			
$E/A_{tricuspid}$	1.2 ± 0.3	1.2 ± 0.4	0.2
$E/E'_{tricuspid}$	4.5 ± 1.5	4.4 ± 1.1	0.9
Arterial Pulmonary Pressure			
V_{max} IT (cm/s)	247 ± 34	275 ± 20	0.3
PASP (mmHg) (n = PHTN)	30 ± 7 (2)	35 ± 5 (3)	0.3

Abbreviations: AVF, arteriovenous fistula; BSA, body surface area; CO, cardiac output; HFa-AVF, absolute high-flow AVF, HFr-AVF, relative high-flow AVF; h/r, thickness/radius ratio of the left ventricle; IVC, inferior vena cava; LV, left ventricle; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; PO, pulmonary output; PASP, pulmonary artery systolic pressure; PHTN, pulmonary hypertension; RA, right atrial; RAP, right atrial pressure; RV, right ventricle; RVEDS, right ventricular end-diastolic surface; RVESS, right ventricular end-systolic surface; RVFS, RV fractional shortening; SD, standard deviation; St-DTI, tricuspid annular S wave velocity in Doppler tissue imaging; TAPSE, tricuspid annular plane systolic excursion.

Moreover, further hemodynamic studies in KTRs with patent AVF and normal renal function led immediately after, as well as years beyond KT, would be necessary to understand the specific cardiovascular effects of AVF and the benefit/risk ratio of AVF ligation. The question of a greater impact and benefit on the LVM reduction after AVF ligation remains open after this study. Indeed, before making the decision to ligate a patent AVF, it is important to note that AVF ligation promotes not only the appearance of beneficial effects but promotes also deleterious effects.[24] Moreover, the decision to ligate must consider the venous capital of the patients. Most patients who undergo a KT will potentially return in HD in the future. The absence of the possibility of a new native vascular access could be even more deleterious.

In conclusion, our study showed a significantly higher but not pathological LVEDD and LVESD values in the HF-AVF group compared with the NF-AVF group, weakly correlated with Q_{AVF}, without any significant differences in other hemodynamical parameters. We observed also a moderate increase of mean plasma BNP level, without any significant difference between groups nor between subgroups.

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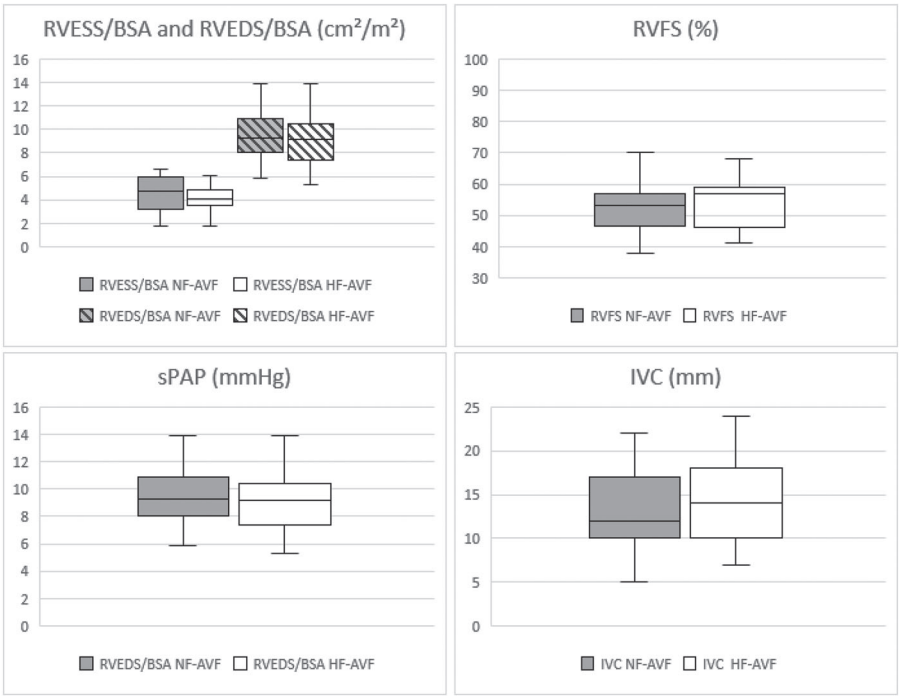

FIGURE 2 Comparisons of right ventricular echocardiographic parameters, systolic pulmonary arterial pressure and inferior vena cava, between NF-AVF and HF-AVF groups. AVF, arteriovenous fistula; HF-AVF, high-flow AVF; IVC, inferior vena cava (expiration); NF-AVF, normal-flow AVF; RVEDS, right ventricular end-diastolic surface; RVESS, right ventricular end-systolic surface; RVFS, right ventricular fraction shortening; sPAP, systolic pulmonary arterial pressure

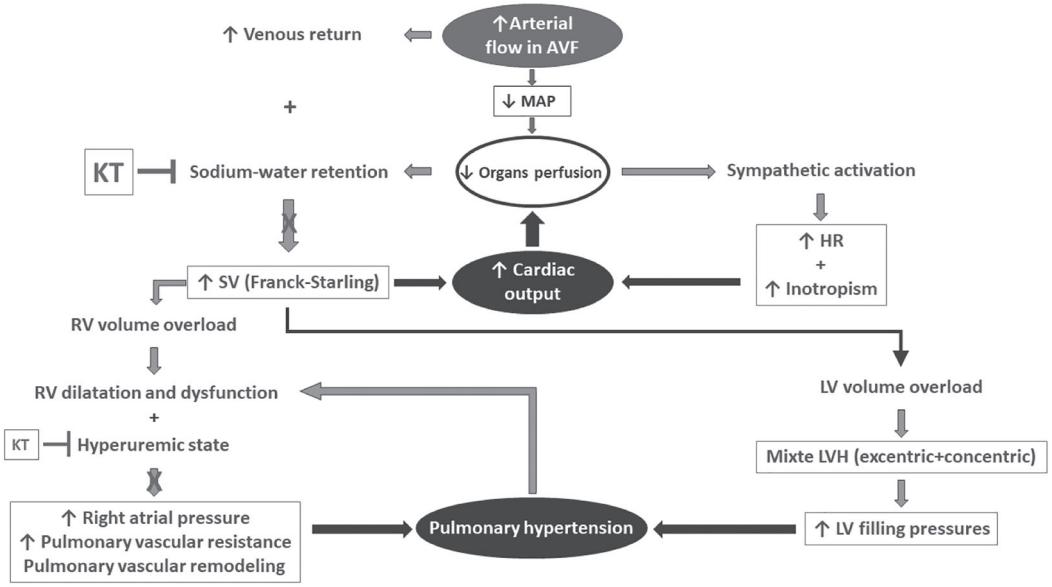

FIGURE 3 Main hemodynamical consequences of AVF and suggestion of KT mechanisms reducing these effects. AVF, arteriovenous fistula; HR, heart rate; KT, kidney transplantation; LV, left ventricle; LVH, left ventricular hypertrophy; MAP, mean arterial pressure; RV, right ventricle; SV, stroke volume

The deleterious cardiovascular effects of AVFs classically described in ESRD and HD patients are thought to be secondary to compensatory volodependent mechanisms. These deleterious cardiovascular effects seemed to have been prevented in our KT population. We hypothesized that the absence of sodium–water retention is linked to the presence of a well-functioning renal graft, even in the presence of HF-AVF. It could be in relation with a global protective effect at 1 year of functional renal grafting on the cardiovascular system in the presence of patent AVF, independently of Q_{AVF}.

ACKNOWLEDGMENTS

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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CONFLICT OF INTEREST

The authors declare no financial support related to this work.

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