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Factors associated with changes in echocardiographic parameters following kidney transplantation

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Abbreviations:

ACEI: angiotensin converting enzyme inhibitor

ARB: angiotensin II receptor blocker

ATG: antithymocyte globulin

AVF: arteriovenous fistula

BMI: body mass index

CV: cardiovascular

DSA: donor-specific antibodies

ECD: extended criteria donor

EPO: erythropoietin

KT: kidney transplantation

LAVI: left atrial volume index

LDL: low density lipoprotein

LVEF: left ventricular ejection fraction

LVH: left ventricular hypertrophy

LVMI: left ventricular mass index

NODAT: new onset diabetes after transplant

PTH: parathyroid hormone

SCD: standard criteria donor

TTE: transthoracic echocardiography

Abstract

Background: Chronic kidney disease leads to cardiac remodelling of multifactorial origin known as "uraemic cardiomyopathy", the reversibility of which after kidney transplantation (KT) remains controversial. Our objectives were to assess, in the modern era, changes in echocardiographic parameters following KT and identify predictive clinical and biological factors associated with echocardiographic changes.

Methods: One hundred six patients (mean age 48 ± 16 , 73% male) who underwent KT at the University Hospital of Nancy between 2007 and 2018 were retrospectively investigated. Pre- and post-KT echocardiography findings (8.6 months before and 22 months after KT on average, respectively) were centralised, blind-reviewed and compared.

Results: A majority of patients (60%) had either a left ventricular (LV) ejection fraction $<50\%$, at least moderately abnormal LV mass index or left atrial (LA) dilatation at pretransplanted echocardiography. After KT, LV remodelling and diastolic doppler indices did not significantly change whereas LA volume index (LAVI) increased (35.9 mL/m^2 post-KT vs. 30.9 mL/m^2 pre-KT, $p=0.006$). Advancing age, cardiac valvular disease, delayed graft function, lower post-KT haemoglobin, and more severe post-KT hypertension were associated with higher LAVI after KT. Higher post-KT serum creatinine, more severe post-KT hypertension and lower pre-KT blood calcium levels were associated with a deterioration in LAVI after KT.

Discussion/Conclusion: Adverse remodelling of the left atrial volume occurred after KT, predominantly in patients with lower pre-KT blood calcium, poorer graft function and post-KT hypertension. These results suggest that a better management of modifiable factors such as pre-KT hyperparathyroidism or post-KT hypertension could limit post-KT cardiac remodelling.

Introduction:

Cardiovascular (CV) mortality is one of the leading causes of death in end-stage renal disease (ESRD) patients(1). Excess CV mortality still persists despite kidney transplantation (KT)(2). Chronic kidney disease leads to cardiac remodelling of multifactorial origin (water and sodium overload, activation of the renin-angiotensin-aldosterone system, sympathetic activation and accumulation of uraemic toxins) known as "uraemic cardiomyopathy", which could partly account for this excess mortality rate(3, 4). At the histopathological level, cardiomyopathy specific to ESRD is related to cardiomyocyte hypertrophy and onset of diffuse interstitial fibrosis(5, 6).

The cardiac abnormalities associated with uraemic cardiomyopathy can be detected and monitored by echocardiography. Progressive kidney disease leads to left ventricular hypertrophy (LVH) as well as impaired left ventricular and diastolic function(7).

The reversibility of uraemic cardiomyopathy has been reported in several(8-17), but not all studies(18, 19). Nevertheless, some studies are old(20, 21), or with a limited number of patients(22, 23), or without a control group. Considering these methodological limitations, a recent meta-analysis(24) could only include four studies with a control group, two with echocardiography(22, 25) and two with cardiac magnetic resonance imaging(19, 26). The authors did not observe significant changes in LVH or left ventricular ejection fraction (LVEF) following KT, while diastolic function could not be analysed due to inconsistent reporting(24). Hence, the reversibility of uraemic cardiomyopathy still remains subject to debate.

Given the increase in age of both KT recipients and donors in the past decades(27), it is likely that the evolution of uraemic cardiomyopathy has changed over time. KT recipients are more likely to have cardiac abnormalities not only related to ESRD, but also to age or other comorbidities. Moreover, aging of donors may attenuate the cardiovascular benefit of KT in these patients(28). In addition, because of organ shortage, the mean waiting list time has increased in the past decades(27), such that a prolonged time on dialysis prior to KT may also attenuate the cardiovascular benefit of KT(29).

The objective of this study was to describe the changes in cardiac variables following KT, in the modern era, and identify predictive factors of uraemic cardiomyopathy reversibility using sequential echocardiographic evaluations.

Methods:

- **Study population:**

This retrospective cohort included patients who underwent KT surgery at the Nancy University Hospital between 2007 and 2018. Enrolled patients had pre-transplant echocardiography in the University Hospital echocardiography laboratory during the 24-month period prior to KT and at least one echocardiography after KT (from 3 months to 72 months post-KT). Patients with concomitant heart transplant were excluded.

Clinical data were retrieved from the French DIVAT database (computerised and Validated data in Transplantation) (www.DIVAT.Fr) (French Research Ministry: RC12_0452, latest agreement number: 13334, cohort CNIL number: 891735). The study was approved by the clinical research committee, and written informed consent was obtained from all participants.

- **Collection of clinical and laboratory data:**

The following data were collected:

- *Clinical data prior to KT:* Hypertension, diabetes, coronary artery disease, dyslipidaemia, body mass index (BMI), smoking, type of dialysis (haemodialysis, peritoneal dialysis), preemptive KT, causal nephropathy, arteriovenous fistula (AVF), anti-hypertensive medications, anti-diabetic treatments, erythropoietin (EPO), parathyroidectomy.
- *Kidney transplantation data:* Donor type (living, extended criteria donor (ECD), standard criteria donor (SCD)), induction therapy (antithymocyte globulin (ATG), basiliximab), delayed graft function.
- *Post-transplant clinical data:* Graft rejection, *de novo* donor-specific antibodies (DSA), post-transplant hypertension, diabetes, coronary artery disease, dyslipidaemia, anti-hypertensive medications, anti-diabetic treatments, EPO and immunosuppressive therapy (ciclosporin, tacrolimus, mTOR, azathioprine, belatacept).
- *Laboratory data at the time of pre- and post-echocardiography:* haemoglobin, calcaemia, phosphataemia, vitamin D, parathyroid hormone, LDL cholesterol, and creatininemia. Of note, all laboratory parameters were centrally analyzed as patients included in this echocardiographic study had a biological follow-up before KT in the

University Hospital of Nancy. Moreover, after KT, all biological parameters were collected during the clinical follow-up in the Nephrology department.

Definitions of clinical variables:

Hypertension was defined by the presence of at least one antihypertensive therapy in the patient's treatment regimen. Diabetes was defined by the presence of at least one anti-diabetic treatment. Dyslipidaemia was defined by the presence of at least one lipid-lowering agent. Of note, KT patients were followed at least twice a year in our transplant center, with blood pressure measurement, as well as fasting blood glucose and plasma lipid values measurement at least once a year. Hypertension, diabetes and dyslipidemia were recorded according to the guidelines dedicated to KT patients(30-32). Coronary artery disease was defined by a history of an acute coronary event or history of angioplasty or coronary bypass surgery. Cardiac valvular disease was defined as the presence of moderate to severe valve stenosis or leakage. Heart failure was considered on the basis of the ultrasound report (when LVEF was <50%) and/or a history of hospitalisation for the management of acute heart failure.–Smoking was defined by active smoking or a period of time >3 years since smoking cessation. The presence and type of AVF were reported from the patient's medical history. Fistula flow rate was recorded with an AVF Doppler ultrasound closest to the date of the cardiac ultrasound. Delayed graft function was defined as the need to perform a dialysis session within 7 days following KT. Humoral or cell rejection was based on kidney biopsy results according to the Banff classification system in use at the time of analysis.

- **Echocardiography**

Echocardiograms were performed at the University Hospital of Nancy by experienced cardiologists according to current recommendations using a commercially available standard ultrasound scanner (Vivid 7, E9 or E95, GE Medical Systems, Milwaukee, WI, USA) with a 2.5-MHz transducer, and were all reviewed offline with dedicated software (Echo PAC® PC, GE Healthcare). Of note, every echocardiography was reviewed in a standardised manner by a single operator, blinded from the clinical-biological data. Briefly, conventional functional and structural echocardiographic parameters were measured for both ventricles according to recommendations for cardiac chamber quantification(33). The following diastolic parameters were recorded: maximal early and late mitral inflow velocities with pulsed-wave doppler (PW) (E wave, A wave, A wave duration, E wave deceleration time and E/A ratio),

lateral and septal mitral annular e' velocity with TDI, average E/e' ratio, peak velocity of tricuspid regurgitation jet by continuous-wave Doppler (CW) and left atrial biplane volume index (or 4 chamber volume only if 2C was not available). Every echocardiography was reviewed in a standardised manner by a single operator (EB) with experience in CoreLab review of international trials (The Heart OMics in AGing (HOMAGE) trial (34)).

- **Statistical analysis:**

All analyses were carried out using SAS[®] R9.4 software (SAS Institute, Cary, NC, USA). The bilateral level of significance was set at $p < 0.05$.

Continuous variables are expressed as mean \pm standard deviation while categorical variables are expressed in terms of number and percentage. Comparisons between pre- and post-KT echocardiographic parameters were performed using Student's t test, or Wilcoxon signed-rank test for paired data.

The associations between echocardiographic parameters and exposure variables were studied using univariable and multivariable linear regression models while adjusting for the pre-transplant ultrasound parameter. All exposure variables with a p-value less than 20% in the univariable models were then introduced into the multivariate model. Post-KT echocardiographic variables and changes in echocardiographic variables were adjusted for pre-KT values. A final multivariable model was selected using a stepwise interactive method.

The validity assumptions of the regression models were verified by examining residual distribution and conducting the homoscedasticity test. In addition, the absence of multicollinearity was also verified in all regression models.

Results:

- **Patient characteristics**

A total of 106 patients were studied (mean age 47.7 years, 73% male, 76% first KT). A majority of patients had a history of hypertension (84%) while 13% had diabetes, 9% had coronary artery disease and 6% had prior valve surgery (Table 1). Most patients (76%) were on haemodialysis prior to transplantation with a mean dialysis vintage of 40 months. A majority of patients (69.8%) were treated with at least one drug treatment prior to KT, 47 (45%) of whom were receiving angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB).

At pre-transplant echocardiography, 32% of patients had LVH (LV mass index (LVMI) $> 116\text{g/m}^2$ for men and LVMI $> 100\text{g/m}^2$ for women), 30% had LA dilatation (LA volume index (LAVI) $>34\text{ml/m}^2$), and 15% had a LVEF less than 50% (Supplementary Table 1). A majority of patients (60%) had either a low LVEF, LVH or LA dilatation (Supplementary Table 1).

After KT, most of the patients (95%) were receiving calcineurin inhibitors, mainly tacrolimus. Following KT, haemoglobin levels increased (12.9 vs 11.4 g/dL, $p<0.001$), blood calcium levels increased (2.46 vs. 2.29 mmol/L, $p<0.0001$), while PTH levels decreased (69 pg/mL vs. 391 pg/mL, $p<0.0001$) (Table 2).

- **Clinical and laboratory parameters associated with echocardiographic parameters prior to kidney transplantation**

In univariable analysis, an increased left atrial volume pre-KT was associated with advancing age, the presence of cardiac valvular disease, lower haemoglobin levels and cinacalcet intake (Table 4). In multivariate analysis, increased left atrial volume pre-KT was associated with the presence of cardiac valvular disease ($\beta=0.309$, $p=0.008$), and to a lesser extent with age (for ten-year increments, $\beta=0.062$, $p=0.02$) and a lower haemoglobin level (for 1 g/dL, $\beta=-0.086$, $p=0.011$).

- **Clinical and laboratory parameters associated with echocardiographic parameters after kidney transplantation**

In multivariable analysis, the presence of cardiac valvular disease ($\beta=0.322$, $p=0.0005$), and to a lesser extent the prescription of at least one anti-hypertensive treatment

($\beta=0.191$, $p=0.032$), delayed graft function ($\beta=0.145$, $p=0.040$), and advancing age (for ten-years increments $\beta=0.058$, $p=0.030$), were associated with a higher left atrial volume after KT. Higher post-transplant haemoglobin levels were associated with a lower post-transplantation left atrial volume ($\beta=-0.041$, $p=0.014$).

- **Impact of KT on echocardiographic parameters and cardiac structural and functional parameters**

Pre-transplant and post-transplant echocardiographies were performed on average at 8.6 months before KT and 22 months after transplantation, respectively.

There were no statistically significant differences between pre- and post-transplant echocardiography with regard to LV and RV systolic function parameters. There was no significant LV remodelling with similar diastolic function profile.

There was a significant increase in left atrial volume index after KT in comparison to the pre-KT evaluation (35.9 mL/m² vs. 30.9 mL/m², $p = 0.006$) (Table 3).

- **Predictive factors associated with echocardiographic changes after kidney transplantation**

When taking into consideration the changes in LA volumes from pre- to post-transplantation in multivariable analysis, higher pre-transplant calcaemia was associated with reverse LA remodelling ($\beta=-2.479$, $p=0.0001$), whereas higher post-transplant creatinine ($\beta=0.346$, $p=0.007$) and taking hypertension therapy ($\beta=0.614$, $p=0.017$) were significantly associated with adverse LA remodelling (Table 5).

Discussion:

In the present study, we found that a majority of patients (60%) had some degree of cardiopathy before KT, based on accepted LVEF, LVMI or LAVI thresholds(35, 36). Following KT, a significant adverse left atrial remodelling was observed at 2 years, with no other significant changes in other echocardiographic parameters. This adverse atrial remodelling occurred mostly in patients with lower pre-KT blood calcium, poorer graft function and a higher degree of hypertension. Of note, cardiac valvular disease, and to a lesser extent age at KT and haemoglobin levels were associated with higher LAVI either in dialysis or after KT, but was not associated with changes after KT.

- **Baseline echocardiographic parameters of the population**

When compared to previously published reports, the echocardiographic characteristics of our population was overall similar: mean LVEF was 59%, as in most previous studies(37), mean LAVI was 31 ml/m², similar to previous published studies(37), and in line with the previously published mean LA diameters ranging from 35 mm to 43 mm(38). The mean LVMI in our study was 103 g/m², similar to what was reported by Sahagun-Sanchez et al.(23), but which is lower than in most previous reports. However, we can observe that earliest reports (before 2020) reported LVMI 140 g/m² to 160 g/m² (25), and that studies published more recently reported LVMI 120 g/m² to 130g/m² (10) whereas LVMI was approximately 120 g/m² in the reanalysis of the recently published TRITON study(39).

- **Absence of left ventricular hypertrophy reversibility**

In this cohort, there was no post-transplant decrease in left ventricular mass. Although a number of previously published studies identified an improvement in LVH following KT(24), the methodological quality of the evidence was described as poor in a systematic assessment performed by Pickup et al.(24). Among the available evidence, only 4 could be meta-analysed in which no significant decrease in left ventricular mass was identified(24).

Patients reported herein had an overall lower baseline left ventricular mass index prior to KT (102.8g/m²) when compared to previous studies(24). This low initial ventricular mass index may have favoured the absence of a decrease in post-transplant left ventricular mass, given that baseline LVM has been associated with mass regression in post-KT follow-up in several studies(11, 40).

- **Left atrial remodelling following KT**

In line with a previous report (41), we observed a significant increase in left atrial volume index after KT. The fact that LAVi increases after KT, even though patients are likely more decongested and have lower systemic venous pressure after KT than when on dialysis, suggest that cardiopathy actually continue to worsen despite KT.

In contrast, Zapolski *et al.*(17) showed a decrease in left atrial volume index from 34.6 mL/m² 1 month after KT to 27.6 mL/m² 36 months after KT, concomitant with an improvement in atrial contractility. This initial rapid decrease was hypothesised to be related to a change in haemodynamic conditions (reduction in pre-load) while the long-term decrease may have resulted from the reversibility of uraemic cardiomyopathy. However, in this latter study, which included <50 patients, post-transplant measurements were taken as reference, whereas in the present study echocardiographic measurements performed before transplantation were considered as reference. Other studies also reported a decrease in left atrial volume or diameter after KT(37, 38), although these small-sized studies (both with <50 patients) investigated short-term changes (either 3 months or 12 months).

Increased left atrial volume is generally a marker of diastolic function although other parameters of diastolic function (E/A, e', E/e') did not significantly change after KT. These results suggest that the increase in LAVI following KT is most likely related to atrial remodelling. Of note, patients with pre-KT cardiac disease (coronary or valvular disease) were not excluded, which may explain the persistence of cardiac remodelling after KT, due to persisting CV causes. As expected, cardiac valvular disease was a strong predictor of increased LAVI either before or after KT. However, it was not associated with LAVI changes after KT, possibly because it is not affected by KT itself.

- **Clinical importance of left atrial dilatation and its relevance in the setting of kidney transplantation**

Left atrial dilatation is recognized as a prognosis factor for cardiovascular morbidity (42); (43). It is considered as a surrogate marker of the left ventricular diastolic dysfunction and is associated with CV events in the general population (44), patients with CV history (myocardial infarction, heart failure, stroke) 32762920, (43), as well as chronic kidney disease or end-stage renal disease (45), (46). In the setting of KT, it has been previously reported that the left atrial volume at the time of the inscription on the waiting list was associated with patient survival after KT (47). Moreover, in more than 500 KT patients, the LA volume at the time of the KT was associated with long-term survival (48). Finally, the

regression of LA volume during follow-up after KT is associated with a better survival among KT (49). Interestingly, two recent substudies of the TRITON study (50), reported that the autologous bone marrow-derived mesenchymal stromal cell (MSC) therapy with withdrawal of calcineurin inhibitors improved systemic blood pressure control in KT recipients (39), and prevented progressive LA dilation and dysfunction in the first 6 months after KT (51).

- **Factors associated with changes in left atrial volume index**

In the present study, lower graft function (higher creatinine) and post-KT hypertension were associated with a deterioration in left atrial volume after KT. Conversely, the absence of low blood calcium level prior to KT (reflecting the absence of severe hyperparathyroidism) was associated with a greater decrease in left atrial volume after KT. Cardiac vascular disease, age, low haemoglobin level, and delayed graft function and were also associated with a higher post-KT left atrial volume.

Haemoglobin variations have previously been reported as associated with left atrial volume variations(52, 53). In contrast, the association of blood calcium levels with left atrial remodelling is a novel finding and raises the hypothesis of a possible association between severe hyperparathyroidism and cardiac remodelling. Further investigations are required to confirm (and better understand) this association. In this study, cinacalcet intake prior to transplantation was associated in univariable analysis with higher pre-KT-LAVI, while low pre-KT calcaemia as well as an elevated post-KT level of blood parathormone were consistently associated with a deterioration in left atrial volume after transplantation. It could be assumed that calcium-phosphorus balance and hyperparathyroidism may be partly related to changes in LAVI. Primary hyperparathyroidism is associated with increased cardiovascular mortality(54) and is known to affect cardiovascular function(55). This hyperparathyroidism leads to ventricular hypertrophy and induces myocardial and heart valve calcification. Purra *et al.* reported higher LVMI and a higher degree of diastolic dysfunction(56) in patients with primary hyperparathyroidism compared to controls. Similarly, Kepez *et al.* reported more advanced diastolic dysfunction and reduced left atrial conduit and reservoir function(57) in patients with primary hyperparathyroidism. Persistent hyperparathyroidism after KT is also a predictor of mortality(58). We can hypothesise that severe hyperparathyroidism before KT may promote cardiac fibrosis and consequently adverse atrial remodelling. This hypothesis needs to be evaluated in dedicated prospective studies.

- **Limitations**

This is a single-centre retrospective study with no control group. Only patients followed at the Nancy University Hospital after KT were included in order to centrally review echocardiographic exams. The congestion status of patients on chronic haemodialysis prior to KT was not recorded during pre-transplant ultrasound imaging. While volume overload could have had an impact on echocardiographic measurements, the correction of fluid overload, however, should have led to a decrease in LAVI after KT. LV strain, which may be very relevant in this population, could not be retrospectively assessed in this study. In addition, as our protocol requires only one echocardiogram per-year before transplant, echocardiographic data was not available immediately before KT but on average 8 months before. Moreover, hypertension, diabetes and dyslipidemia were defined as the need, according to guidelines relevant to KT, to treat patients for these conditions(30-32). Analyses were not adjusted on blood pressure, fasting glucose or cholesterol blood levels, as some patients were already treated in order to avoid multi-collinearity issues. Kidney transplant patients undergoing surgery for the second or third time were included in this study. Considering the potentially harmful effect of kidney transplantation on the myocardium (the use of immunosuppressive therapy in particular), these patients may have a reduced capacity for cardiac remodelling while undergoing subsequent transplantation.

- **Clinical implications**

In light of our results, we can hypothesize that a better management of pre-KT hyperparathyroidism, as well as better management of post-KT anaemia and blood pressure control may be associated with decreased cardiac remodelling after KT. Prospective studies are needed to properly assess these therapeutic strategies following KT. Of note, international Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease(30) already recommend a target of <130/80 mmHg following KT, despite the absence of dedicated randomized trials that evaluated the impact of different blood pressure targets on cardiovascular morbidity or mortality.

Conclusion:

We report a significant left atrial remodelling after kidney transplantation, with no change in other cardiac parameters. This deleterious evolution may be partly related to poor post-KT kidney graft function, hypertension after KT, and possibly to an insufficient control of hyperparathyroidism prior to KT.

Disclosure of interests:

Pr GIRERD received personal fees from Novartis, Pfizer, Astra Zeneca, Boehringer, Vifor, Bayer and Lilly. All other authors declared no competing interest.

Tables

Table 1: Patient characteristics

Characteristics	N	Mean ± SD / n (%)
Pre-transplant variables		
Demographic characteristics		
Age at transplant (years)	106	47.7 ± 15.7
BMI (kg/m ²)	106	25.5 ± 5.1
Gender (male)	106	77 (72.6 %)
Time to TTE		
Dialysis vintage before KT (months)	102	40.3 ± 36.6
Duration between pre-transplant TTE and KT (months)	106	8.6 ± 6.5
Duration between KT and post-transplant TTE	106	21.9 ± 14.9
Duration between pre-transplant and post-transplant TTE	106	30.4 ± 15.6
Cardiovascular risk factors and comorbidities		
Hypertension	106	89 (84.0 %)
Diabetes	106	14 (13.2 %)
Cardiac valvular disease	106	21 (19.8 %)
Valvular surgery	106	6 (5.7 %)
Coronary artery disease	106	9 (8.5 %)
Heart failure	106	14 (13.2 %)
Parathyroidectomy before KT	106	7 (6.6 %)
Nephropathy:		
Glomerulonephritis (except IgA nephropathy)	106	22 (20.8 %)
Uropathy	106	17 (16.0 %)
Autosomal dominant polycystic kidney disease	106	13 (12.3 %)
Other	106	12 (11.3 %)
IgA nephropathy	106	11 (10.4 %)
Nephroangiosclerosis	106	6 (5.7 %)
Diabetic	106	6 (5.7 %)
Chronic Tubulointerstitial Disease	106	3 (2.8 %)
Type of dialysis		
Peritoneal dialysis	106	11 (10.4 %)
Haemodialysis	106	81 (76.4 %)
Peritoneal dialysis before haemodialysis	106	10 (9.4 %)
Preemptive KT	106	4 (3.8 %)
Graft variables		
Donor:		
Living	106	16 (15.1 %)
ECD	106	35 (33.0 %)
SCD	106	55 (51.9 %)
Rank of the graft		
1	106	81 (76.4%)
2	106	22 (20.8 %)
3	106	3 (2.8 %)
Post-transplant variables		
Hypertension	106	78 (73.6 %)
Diabetes	106	13 (12.3 %)
Dyslipidaemia	106	73 (68.9 %)
Pulmonary embolism	106	5 (4.7 %)
Acute coronary syndrome	106	5 (4.7 %)
de novo DSA	106	10 (9.4 %)
Rejection	106	26 (24.5 %)
Parathyroidectomy after KT	106	6 (5.7 %)
AVF:		
Type		

Distal	106	47 (44.3 %)
Proximal	106	25 (23.6 %)
Flow rate		
<2L/Min	66	58 (87.9 %)
≥2L/Min	66	8 (12.1 %)
AVF closure during follow-up	106	16 (15.1 %)

AVF: arteriovenous fistula, BMI: body mass index, DSA: donor-specific antibodies, ECD: extended criteria donor, KT: kidney transplantation, SCD: standard criteria donor, TTE: transthoracic echocardiography.

Table 2: Evolution of laboratory and clinical parameters following transplantation

Characteristics:	<i>Pre-transplant</i>	<i>Post-transplant</i>	<i>Change</i> (Δ <i>Post-transplant - Pre-transplant</i>)	
	Mean \pm SD / n (%)	Mean \pm SD / n (%)	Mean \pm SD	P-value
<u>Laboratory parameter</u>				
Haemoglobin (g/dL)	11.4 \pm 1.3	13.0 \pm 2.2	0.1 \pm 0.2	<0.001
Calcium (mmol/L)	2.29 \pm 0.16	2.46 \pm 0.17	0.1 \pm 0.03	<0.0001
Phosphorus (mmol/L)	1.72 \pm 0.11	1.02 \pm 0.05	- 0.04 \pm 0.05	< 0.0001
Vitamin D (ng/mL)	29.1 \pm 3.4	23.5 \pm 2.0	- 0.6 \pm 1.2	<0.0001
PTH (pg/mL)	391.1 \pm 372.9	69.1 \pm 66.6	-19.6 \pm 23.1	<0.0001
LDL cholesterol (g/L)	1.1 \pm 0.1	1.2 \pm 0.1	0.01 \pm 0.03	0.08
Creatinine (μ mol/L)	-	141.0 \pm 69.3	-	-
eGFR (mL/min)	-	51.4 \pm 4.0	-	-
<u>Drug treatments</u>				
Immunosuppressive therapy				
CNI	-	101 (95%)	-	-
Ciclosporin	-	25 (23.6%)	-	-
Tacrolimus	-	76 (71.7%)	-	-
mTOR	-	4 (3.8%)	-	-
Azathioprine	-	5 (4.7%)	-	-
Belatacept	-	2 (1.9%)	-	-
Antihypertensive therapy				
Number				
0	32 (30.2%)	23 (21.7%)	-	0.12
1	42 (39.6%)	33 (31.1%)	-	
2	18 (17%)	33 (31.1%)	-	
3	6 (5.7%)	16 (15.1%)	-	
ACEI/ARB	47 (45.2 %)	44 (41.5 %)	-	0.45
Spironolactone	1 (0.9%)	1 (0.9%)	-	1.00
Beta-blocker	40 (37.7%)	53 (50%)	-	0.05
Calcium channel blockers	24 (22.6%)	41 (38.7%)	-	0.038
Loop diuretics	61 (57.5%)	20 (18.9%)	-	<0.0001
Antidiabetic therapy				
Insulin	10 (9.4%)	17 (16%)	-	0.048
EPO				
Patients treated by EPO	74 (69.8%)	9 (8.4%)	-	<0.0001
EPO dose (μ g/month)	86	9	-	<0.0001
Cinacalcet	20 (18.9 %)	0	-	<0.0001

ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, CNI: calcineurin inhibitors, EPO: erythropoietin, eGFR: estimated glomerular filtration rate, LDL: low density lipoprotein, PTH: parathyroid hormone, TTE: transthoracic echocardiography.

Table 3: Evolution of echocardiographic parameters after kidney transplantation

<i>Characteristics</i>	N	<i>Pre-transplant</i>	<i>Post-transplant</i>	<i>Annualised change (Δ post-transplant – pre-transplant)</i>	
		Mean \pm SD	Mean \pm SD	Mean change/year \pm SD	P-value
LV structure and function					
LVMI (g/m ²)	82	102.85 \pm 29.20	105.02 \pm 29.94	0.36 \pm 17.18	0.68
4-cavity LVEF (Simpson) (%)	81	58.68 \pm 9.92	60.8 \pm 10.7	0.17 \pm 8.33	0.21
Biplane LVEF (%)	60	58.18 \pm 9.06	60.7 \pm 8.9	0.70 \pm 6.74	0.20
LVEDVI (mL/m ²)	76	51.87 \pm 16.69	52.66 \pm 17.80	0.87 \pm 14.27	0.99
Mitral S' wave (cm/s)	50	8.19 \pm 2.34	8.5 \pm 2.4	0.02 \pm 1.78	0.70
Diastolic function					
LAVI (mL/m²)	63	30.88 \pm 14.17	35.89 \pm 14.68	4.01 \pm 10.97	0.006
E/A	91	1.04 \pm 0.45	1.14 \pm 0.54	0.06 \pm 0.28	0.12
DT (ms)	91	207.92 \pm 62.26	207.9 \pm 54.0	-3.08 \pm 47.33	0.79
e' velocity (cm/s)	65	9.78 \pm 3.51	10.2 \pm 3.2	0.73 \pm 3.62	0.14
E/e'	63	7.91 \pm 3.29	8.8 \pm 4.5	0.21 \pm 3.07	0.26
Right ventricular quantification					
Tricuspid S' wave (cm/s)	28	11.70 \pm 2.86	13.1 \pm 3.0	0.62 \pm 1.83	0.09
Max TRV (m/s)	34	2.48 \pm 0.42	2.5 \pm 0.4	0.13 \pm 0.38	0.17

TAPSE (mm)	58	22.62 ± 4.96	23.0 ± 5.5	0.04 ± 4.39	0.89
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Left ventricular mass index (LVMI), left ventricular ejection fraction (4-cavity LVEF, biplane LVEF), left ventricular end-diastolic volume index (LVEDVI), mitral valve longitudinal systolic kinetics in tissue Doppler imaging (mitral S' wave), left atrial volume index (LAVI), peak protodiastolic E-wave and protosystolic A-wave velocities on the mitral profile with E/A ratio, E-wave deceleration time (DT), mitral annulus displacement velocity in protodiastole assessed by tissue Doppler imaging (e'-wave), tricuspid valve longitudinal systolic kinetics in tissue Doppler imaging (tricuspid S' wave), peak tricuspid regurgitation velocity (max TRV), tricuspid annulus plane systolic excursion (TAPSE).

Table 4: Association of pre-transplant clinical and laboratory parameters with pre-transplant left atrial volume index

	<i>Factors associated with pre-transplant left atrial volume index</i>			
	Univariable analysis		Multivariable analysis	
	Beta (IC 95% CI)	P-value	Beta (IC 95% CI)	P-value
Hypertension	0.162 ± 0.134	0.23		
Age at transplantation (for 10 years)	0.077 ± 0.029	0.011	0.062 ± 0.027	0.025
BMI (for 10 kg/m ²)	-0.002 ± 0.009	0.81		
Cardiac valvular disease	0.402 ± 0.112	0.0006	0.309 ± 0.113	0.008
Pre-transplant parathyroidectomy	-0.066 ± 0.169	0.7		
ACEI/ARB	0.065 ± 0.097	0.50		
Cinacalcet	0.269 ± 0.122	0.03		
Haemoglobin (g/dl)	-0.104 ± 0.035	0.004	-0.086 ± 0.033	0.011
Calcium (mmol/l)	-0.243 ± 0.301	0.42		
PTH (for 100 pg/mL)	0.012 ± 0.013	0.34		

ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, BMI: body mass index, PTH: parathyroid hormone

Table 5: Factors associated with post-transplant LA volume index and with changes in left atrial (LA) volume index

	<i>Models with post-transplant LA volume index as endpoint</i>				<i>Models with changes in LA volume index as endpoint</i>			
	<i>Univariable analysis</i>		<i>Multivariable analysis</i>		<i>Univariable analysis</i>		<i>Multivariable analysis</i>	
<i>Characteristics</i>	Beta (IC 95% CI)	P-value	Beta (IC 95% CI)	P-value	Beta (IC 95% CI)	P-value	Beta (IC 95% CI)	P-value
Pre-transplant variables								
Hypertension	0.147 ± 0.107	0.17			0.151 ± 0.315	0.63		
Age at transplant (for 10 years)	0.121 ± 0.024	<0.0001	0.058 ± 0.026	0.030	0.168 ± 0.075	0.03		
BMI (for 10 kg/m ²)	0.217 ± 0.075	0.005			0.430 ± 0.207	0.043		
Cardiac valvular disease	0.353 ± 0.099	0.0006	0.322 ± 0.089	0.0005	0.278 ± 0.316	0.38		
Pre-KT Parathyroidectomy	0.179 ± 0.153	0.24			0.418 ± 0.387	0.28		
Pre-KT haemoglobin (g/dl)	-0.005 ± 0.034	0.87			-0.059 ± 0.106	0.58		
Pre-KT calcium (mmol/l)	-0.846 ± 0.254	0.001			-3.240 ± 0.735	<0.0001	-2.479 ± 0.595	0.0001
PTH (for 100 pg/mL)	0.011 ± 0.013	0.42			-0.124 ± 0.061	0.049		
ACEI/ARB	-0.004 ± 0.085	0.96			0.017 ± 0.234	0.94		
Cinacalcet	0.130 ± 0.110	0.24			0.177 ± 0.314	0.58		
Graft variables								
Donor (Reference: Living)								
ECD	0.483 ± 0.111	<0.0001			0.792 ± 0.329	0.019		
SCD	0.109 ± 0.104	0.30			0.126 ± 0.304	0.68		
Delayed graft function	0.196 ± 0.084	0.021	0.145 ± 0.070	0.040	0.419 ± 0.236	0.08		
Induction therapy with ATG	0.209 ± 0.086	0.017			0.308 ± 0.256	0.23		
Post-transplant variables								
Diabetes	0.083 ± 0.126	0.51			0.111 ± 0.347	0.75		
Post-KT parathyroidectomy	0.027 ± 0.230	0.91			-0.031 ± 0.538	0.95		
AVF closure	-0.139 ± 0.121	0.25			-0.356 ± 0.324	0.28		
AVF flow rate (Reference : absence of AVF)								
<2L/Min	0.129 ± 0.091	0.16			0.383 ± 0.268	0.16		
≥2L/Min	0.133 ± 0.151	0.38			0.079 ± 0.403	0.85		
AVF (Reference : distal AVF)								
FAV: absence	-0.188 ± 0.094	0.048			-0.454 ± 0.263	0.09		
FAV: proximal	0.084 ± 0.100	0.40			-0.276 ± 0.320	0.39		
Post-Kt haemoglobin (g/dl)* or delta haemoglobin > median **	-0.064 ± 0.017	0.0003	-0.041 ± 0.016	0.014	-0.611 ± 0.250	0.018		
Post-KT calcium (mmol/l)* or delta calcium > median**	-0.132 ± 0.233	0.57			-0.275 ± 0.237	0.25		
Post-KT PTH (for 100 pg/mL)* or delta PTH**	0.120 ± 0.060	0.049			-0.027 ± 0.010	0.009		
Post-KT creatinine (for 100 µmol/L)	0.201 ± 0.054	0.0004			0.475 ± 0.136	0.0009	0.346 ± 0.123	0.007
CNI	-0.136 ± 0.200	0.50			0.100 ± 0.544	0.85		
ACEI/ARB	-0.004 ± 0.084	0.97			-0.241 ± 0.230	0.30		

Number of antihypertensive therapies ≥ 1	0.188 \pm 0.101	0.067	0.191 \pm 0.088	0.032	0.496 \pm 0.295	0.098	0.614 \pm 0.250	0.017
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ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, ATG: antithymocyte globulin, AVF: arteriovenous fistula, BMI: body mass index, CNI: calcineurin inhibitors, ECD: extended criteria donor, PTH: parathyroid hormone, SCD: standard criteria donor

* For models with post-KT LAVI as endpoint

** For models with changes in LAVI as endpoint

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