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# **Cardiovascular Comorbidities are the Main Predictors of Cardiac Reverse Remodeling Following Kidney Transplantation**

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**Running title:** Comorbidities and cardiac reverse remodeling following kidney transplantation

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## **Introduction**

Chronic kidney disease in end-stage renal disease (ESRD) is associated with progressive deteriorations in left ventricular (LV) structure and function <sup>1</sup>, leading to an increased risk of mortality. Kidney-related factors (*e.g.*, hemodynamic overload, biochemical mediator and uremic toxins) are associated with these deteriorations <sup>2,3</sup>, but cardiovascular (CV) comorbidities -which are frequent in patients with ESRD- may also contribute to cardiac remodeling <sup>4</sup>.

Kidney transplantation (KT) is associated with improvements in LV function, structure and prognosis in patients with ESRD <sup>5,6</sup>. KT can reverse kidney-related factors, whereas CV related factors persist or exacerbate thereafter, leading to the association with cardiac remodeling. However, which CV comorbidities or kidney-related factors have a noteworthy impact on the LV reversibility is scarcely studied. We aimed therefore to determine the associations of CV comorbidities or renal related factors with changes in cardiac function and structure following KT.

## **Methods**

### **Study population**

This was a single-center substudy of the prospective DIVAT (computerized and VAlidated data in Transplantation) French database of transplanted patients <sup>7</sup>. The study was approved (CNIL no. 891735), and written informed consent was obtained from the participants. We enrolled 56 patients undergoing their first KT in Lorraine University Hospital from 2007 to 2015 who had available echocardiographic data at both prior and after KT ((median=24 [14-36] months). This cohort study was conducted in accordance with the Declaration of Helsinki.

Hypertension was defined as systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg or the prescription of anti-hypertensive medication <sup>8</sup>, and diabetes was defined by the prescription of anti-diabetes medication. Coronary artery disease was defined as

a prior history of myocardial infarction or coronary intervention (*i.e.*, coronary artery bypass graft surgery or percutaneous coronary intervention), while patients hospitalized for worsening HF were considered as a prior history of HF. Valvular heart disease was defined as moderate or severe stenosis/regurgitation according to recent guidelines <sup>9</sup>.

### **Echocardiography**

Echocardiographic examinations were performed (Vivid 7/Vivid 9, GE Vingmed Ultrasound, Horten, Norway) with a 2.5-MHz transducer, with the obtained data analyzed offline using dedicated automated software (Echo PAC PC version 110.1.0, GE Healthcare). All echocardiographic parameters were reanalyzed by a single operator blinded to all clinical variables and the timing of echocardiography (*i.e.*, prior to or following the KT). The LV volume and LV ejection fraction (LVEF) were measured using the biplane Simpson's method, and the LV mass index (LVMI) was measured from 2D standard views. Diastolic function was assessed by pulsed-wave Doppler and tissue Doppler imaging <sup>9</sup>.

### **Statistical analysis**

Data are expressed as mean  $\pm$  SD values for continuous variables and as number (percentage) values for categorical variables. Multivariable linear regression analysis was performed to assess the associations of CV or renal related factors with changes in echocardiographic parameters from pre- to post-KT after adjustment for age, hemoglobin and an estimated glomerular filtration rate  $<45$  ml/min/m<sup>2</sup> in the post-KT. A selection procedure was used to retain factors associated with a p-value $<0.10$  in each model. A p value of  $<0.05$  was considered significant. Statistical analysis was performed using SAS (version 9.4, SAS Institute, Cary, NC).

### **Results**

Mean age was  $48 \pm 15$  years and a majority of patients were male (73.2%) and had hypertension (98%). Diabetes mellitus (DM) was observed in 16.1% prior KT and 23.2% post KT. Mean LVMI and LVEF in prior KT were  $105.9 \text{ g/m}^2$  and 63.9%, respectively. Their LVMI and LVEF were  $105.9 \pm 33.1 \text{ g/m}^2$  and  $63.9 \pm 10.8\%$ , respectively, prior to KT. LVEF improved significantly to  $69.6 \pm 7.8\%$  ( $p < 0.01$ ) post-KT, whereas there were no significant overall changes in LVMI or diastolic parameters (**Table 1**).

### **Associations of Cardiovascular and Renal Comorbidities with Changes in Echocardiographic Parameters**

DM and other cardiovascular comorbidities were the main predictors of changes in echocardiographic features (**Table 2**).

In multivariable analysis, a history of valvular heart disease was associated with a significantly smaller reduction in LVMI ( $\beta = -27.3$ ,  $p = 0.04$ ), a history of coronary artery disease (CAD) or heart failure (HF) was associated with a smaller increase in LVEF ( $\beta = 7.17$ ,  $p = 0.02$ ), and DM was associated with smaller improvement in E wave,  $e'$  and  $E/e'$  ( $\beta = -0.19$ ,  $p = 0.05$  and  $\beta = 4.15$ ,  $p < 0.01$  and  $\beta = -5.00$ ,  $p < 0.01$ , respectively) (**Table 2**). In contrast, KT rejection was significantly associated only with LV diastolic diameter changes and there was no echocardiographic parameter associated with eGFR (**Table 2**).

### **Discussion**

The main finding of this study is that histories of valvular heart disease, CAD or HF, and DM are associated with smaller improvements in cardiac structure and function following KT. Taken together, the present findings emphasize the clinical importance of CV comorbidities — rather than kidney-related variables—in the cardiac remodeling that occurs following KT.

### **Changes in LV structure and function following KT**

In the present study, majority of patients had hypertension, which may be explained by an ESRD population<sup>10,11</sup>. In addition, a minority of patients had comorbidities and cardiac vascular risk factors: This relatively low-risk profile may be influenced by the selection of renal transplant recipients since patients with a high-risk profile may not be suitable renal transplant candidates.

Our results are not in line with previous reports focusing on changes in LVMI and diastolic parameters following KT<sup>5,12</sup>. LV reverse remodeling following KT may presumably need a progressive LV remodeling prior to KT. In the current study, patients had less cardiac remodeling illustrated by less cardiac comorbidities (*i.e.*, CAD or HF), smaller LV mass and better diastolic function compared to previous reports<sup>5</sup>, which could limit the potential for reverse remodeling. In contrast, we observed a significant improvement in LVEF following KT despite the LVEF being normal at baseline, which suggests that systolic function can improve after removing the exposure to uremic toxins<sup>5</sup> and to variations in intravascular volume related to dialysis. These findings support that LVEF may represent an early reversible function in the process of cardiac remodeling in patients with ESRD, especially in the absence of myocardial damage due to cardiac events such as CAD or HF.

### **Associations of Cardiovascular Comorbidities with Changes in Left Ventricular Diastolic Function and Structure**

DM contributes to different types of LV remodeling such as LV hypertrophy, diastolic dysfunction and impaired systolic function, which is associated with a higher incidence of most CV outcomes<sup>13,14</sup>. Specifically, diastolic dysfunction may derive from the myocardial deposition of collagen and advanced glycation end products as well as relative myocardial hypertrophy<sup>15</sup>. Although ESRD provides progressive cardiac remodeling, the present study found that DM, either prior to or after KT, predicted the absence of subsequent diastolic function recovery (associations with the E wave,  $e'$ , and  $E/e'$ ). These findings suggest that cardiac damage can persist in patients with DM despite large decreases in uremic toxins and the optimization of hemodynamics.

## **Clinical implications**

The present results suggest that CV comorbidities (and not kidney-related factors) are key to the cardiac changes following KT. This observation would suggest that clinicians should expect limited “favorable” reverse cardiac remodeling following KT in patients with CV comorbidities. However, further research is needed to determine whether medication (*e.g.* anti-diabetes drugs or inhibitors of the renin-angiotensin-aldosterone system) have a different impact on cardiac remodeling according to CV co-morbidities.

## **Limitations**

This was a retrospective cohort study, and hence was subject to the limitations inherent in observational data. Causality cannot be inferred. The size of the cohort also may reduce the statistical power. In addition, we had available echocardiographic data at a median of 24 months after KT, and this time period was not associated with changes in cardiac function/structure in this study (all  $p$ -Value $>0.1$ ); however, different results may be observed with longer follow-up. Majority of our population had hypertension, whereas the number of patients with comorbidities or cardiovascular risk factors was small. Our results thus may only be applicable to populations with similar profile. Certain important variables, *e.g.* systolic blood pressure, hemoglobin A1c, proteinuria and treatment for comorbidities were not available. Finally, we had no control group matched with age, sex and end-stage renal disease.

## **Conclusion**

Cardiovascular comorbidities such as valvular heart disease, CAD or HF, and DM were associated with smaller improvements in cardiac structure and function following KT.

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### **Table 1. Patients Characteristics between Pre and Post Kidney Transplantation**

eGFR, estimated glomerular filtration rate; IVST, intraventricular septal thickness; E/A, ratio of peak early and late diastolic velocities;  $e'$ , early diastolic velocity of the mitral annulus;  $E/e'$ , ratio of early mitral inflow velocity and mitral annular early diastolic velocity.

### **Table 2. Associations of Clinical Characteristics with Changes in Echocardiographic Parameters between Pre- and Post-Kidney Transplantation**

Changes in echocardiographic parameters were calculated as (pre-KT) – (post-KT).

LVMI, left ventricular mass index; LVDD, left ventricular diastolic diameter; LVPW, left ventricular posterior wall; LVEF, left ventricular ejection fraction;  $e'$ , early diastolic velocity at the mitral annulus;  $E/e'$ , ratio of early mitral inflow velocity and early diastolic velocity at the mitral annulus; DT, deceleration time of E wave; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; KT, kidney transplantation; CAD, coronary artery disease; HF, heart failure; eGFR, estimated glomerular filtration rate.

**Table 1. Patients Characteristics between Pre and Post Kidney Transplantation**

	<b>Pre-transplantation</b>	<b>Post-transplantation</b>	<b>p-Value</b>
	Mean ± SD / n (%)	Mean ± SD / n (%)	
<b>Demographic parameters</b>			
Transplant Age, yrs	48.3 ± 15.1	—	
Male, N (%)	41 (73.2 %)	—	
Body mass index, kg/m <sup>2</sup>	24.5 ± 6.2	—	
<b>Comorbidities</b>			
Hypertension, N (%)	55 (98.2 %)	44 (83.0 %)	<b>&lt;0.01</b>
Diabetes mellitus, N (%)	9 (16.1 %)	13 (23.2 %)	0.21
Dyslipidemia, N (%)	26 (46.4 %)	27 (48.2 %)	0.82
Current smoker, N (%)	10 (17.9 %)	—	
Valvular disease, N (%)	8 (14.3 %)	—	
Coronary artery disease, N (%)	6 (10.7 %)	—	
Heart failure, N (%)	10 (17.9 %)	—	
<b>Causal nephropathy</b>			
Diabetes	4 (7.1 %)	—	
Hypertension/renovascular disease	3 (5.4 %)	—	
Glomerulonephritis	13 (23.2 %)	—	
Polycystic kidney disease	7 (12.5 %)	—	
<b>Dialysis method, N (%)</b>			
Peritoneal dialysis	12 (21.4 %)	—	
Hemodialysis	44 (78.6 %)	—	
<b>Type of donor</b>			
Living donor	—	11 (19.6 %)	
Standard criteria donor	—	28 (50.0 %)	
Expanded criteria donor	—	17 (30.4 %)	
<b>Immunosuppressive regimen</b>			
Rituximab	—	1 (1.8 %)	
Corticosteroid	—	11 (19.7 %)	
Lymphocyte-depletive agent	—	3 (5.4 %)	
<b>Rejection</b>			
	—	16 (28.6 %)	
<b>Type of rejection</b>			
Borderline	—	10 (17.9 %)	
Cellular	—	5 (8.9 %)	
Humoral	—	1 (1.8 %)	
<b>Laboratory findings</b>			
Hemoglobin, g/dL	—	13.3 ± 2.0	
eGFR, ml/min/1.73m <sup>2</sup>	—	56.8 ± 21.2	
<b>Echocardiographic parameters</b>			
LV mass index, g/m <sup>2</sup>	105.9 ± 33.1	114.0 ± 35.3	0.13
LV diastolic diameter, cm	4.8 ± 0.6	4.9 ± 0.7	0.55
IVST, cm	1.1 ± 0.3	1.1 ± 0.3	0.61
LV posterior wall, cm	1.1 ± 0.3	1.1 ± 0.2	0.43
LV ejection fraction, %	63.9 ± 10.8	69.6 ± 7.8	<b>&lt;0.01</b>
E wave, m/s	0.8 ± 0.2	0.8 ± 0.2	0.63
A wave, m/s	0.7 ± 0.2	0.7 ± 0.2	0.21
E/A	1.2 ± 0.6	1.2 ± 0.5	0.40
Deceleration time of E, ms	212.5 ± 68.6	202.3 ± 44.3	0.45
e', cm/s	10.7 ± 4.0	10.8 ± 2.9	0.85
E/e'	8.0 ± 3.2	7.2 ± 3.8	0.17

**Table 2. Associations of Clinical Characteristics with Changes in Echocardiographic Parameters between Pre- and Post-Kidney Transplantation**

		Cardiovascular risk factor/comorbidities				Kidney related factors		
		Age>50 years	Diabetes mellitus		CAD or HF	Valvular disease	Rejection	eGFR
			pre-KT	post-KT				
LV structure	LVMI, g/m <sup>2</sup>	—	—	—	—	$\beta=-27.3$ $p=0.04$	—	—
	LVDD, cm	—	—	—	$\beta=-0.40$ $p=0.07$	—	$\beta=-0.41$ $p=0.05$	—
	LVPW, cm	—	$\beta=-0.15$ $p=0.06$	—	—	—	—	—
Systolic function	LVEF, %	—	—	—	$\beta=7.17$ $p=0.02$	—	—	—
Diastolic function	E wave, m/sec	—	$\beta=-0.19$ $p=0.05$	—	—	—	—	—
	e', cm/sec	—	—	$\beta=4.15$ $p<0.01$	—	—	—	—
	E/e'	—	—	$\beta=-5.00$ $p<0.01$	—	—	—	—
	DT, msec	$\beta=32.19$ $p=0.03$	—	—	—	—	—	—
RV function	TAPSE, cm	$\beta=-0.21$ $p=0.01$	—	—	—	—	—	—