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Original Paper

Improved Left Ventricular Structure and Function After Successful Kidney Transplantation

Bernd Hewing[a,b] Anna Maria Dehn[a] Oliver Staeck[c] Fabian Knebel[a,b] Sebastian Spethmann[a] Karl Stangl[a,b] Gert Baumann[a] Henryk Dreger[a,b] Klemens Budde[c] Fabian Halleck[c]

[a]Medizinische Klinik m.S. Kardiologie und Angiologie, Charité-Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany; [b]DZHK (German Center for Cardiovascular Research), partner site Berlin, Germany; [c]Medizinische Klinik für Nephrologie, Charité-Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany

Key Words
Kidney transplantation • Speckle tracking echocardiography • Cardiorenal syndrome • Left atrial strain • LV hypertrophy

Abstract
Background/Aims: Cardiac changes observed in chronic kidney disease patients are of multifactorial origin including chronic uremia, hemodynamics or inflammation. Restoration of renal function by kidney transplantation (KTX) may reverse cardiac changes. Novel echocardiographic methods such as speckle tracking echocardiography (STE) allow early and sensitive detection of subtle changes of cardiac parameters. We evaluated changes of cardiac structure and function after KTX by advanced echocardiographic modalities. ***Methods:*** Thirty-one KTX recipients (female n=11) were evaluated by medical examination, laboratory testing and echocardiography before and after KTX (median follow-up 19 months). Left ventricular (LV) and right ventricular (RV) diameters and function were assessed by echocardiographic standard parameters. Longitudinal 2D strain of the LV (GLPS) and left atrium (LA) was determined by 2D STE. ***Results:*** After KTX, median serum creatinine level was 1.3 mg/dl (IQR, 1.2-1.5). Systolic blood pressure decreased significantly after KTX. Echocardiography showed a significant reduction in LV end-diastolic septal and posterior wall thickness and LV mass index after KTX, which was accompanied by an improvement of GLPS. There were no relevant changes in parameters of LA (reservoir, conduit or contractile) function, LV diastolic or RV function after KTX. ***Conclusion:*** LV hypertrophy reversed after successful KTX and was accompanied by an improvement in longitudinal LV function as assessed by STE. Diastolic function and STE-derived LA function parameters did not change significantly after KTX.

Bernd Hewing, MD

Charité-Universitätsmedizin Berlin, Charité Campus Mitte, Medizinische Klinik m.S. Kardiologie und Angiologie, Charitéplatz 1, 10117 Berlin (Germany)
Tel. +49-30-450613305, Fax +49-30-450513905, E-Mail bernd.hewing@charite.de

Introduction

Cardiac and renal function are closely related and chronic kidney disease (CKD) represents a major risk factor for cardiovascular (CV) disease. Based on the concept of a cardiorenal syndrome (CRS), which was first introduced systematically in 2008, acute or chronic kidney dysfunction can cause acute or chronic heart dysfunction and vice versa [1]. CKD evokes structural and functional cardiac changes such as left ventricular hypertrophy (LVH), LV dilation, and LV systolic and diastolic dysfunction. Increased blood pressure, volume overload and in particular the uremic milieu with its toxins contribute to these alterations [2-4]. While cardiac changes are initially adaptive they may aggravate with progressing CKD, finally leading to cardiac failure. Restoration of renal function after kidney transplantation (KTX) disrupts the negative cardiorenal interplay and may reverse some of the cardiac changes seen with CKD [5, 6]. KTX was shown to reduce cardiac mortality and the risk for development of chronic heart failure (CHF) compared with long-term dialysis [7].

Recent advances in echocardiographic methods such as tissue Doppler imaging and strain analyses by speckle tracking echocardiography (STE) allow an earlier and more sensitive detection of subtle changes of myocardial function. So far, data derived from these advanced echocardiographic modalities in KTX patients are scarce. Therefore, we evaluated changes of cardiac structure and function after KTX by advanced echocardiographic modalities.

Material and Methods

Study design

The study comprises a retrospective analysis of a single-center prospective data base (Ethics Committee of the Charité-Universitätsmedizin Berlin: EA1/048/14 and EA1/330/14). The study complied with the Declaration of Helsinki. 469 kidney transplant recipients of the KTX Outpatient Department of the Charité-Universitätsmedizin Berlin, Germany who received KTX during the years 2010-2014 were screened and were included into the study when they had a comprehensive and suitable echocardiographic examination in our echocardiography laboratory within 210 days before kidney transplantation. Patients with transplant failure after KTX were excluded. Thus, thirty-one patients were included in the final analysis. All kidney recipients were CKD stage V according to KDIGO at the time of baseline echocardiography before KTX. Medical history assessment, physical examination including office blood pressure measurements with mercury sphygmomanometer (in the seated position), laboratory testing and echocardiography were performed before and after KTX at the follow-up visits.

Patients generally received standard immunosuppressive protocol including induction therapy (anti-interleukin-2 receptor antibody), calcineurin inhibitor (CNI), mycophenolate and steroids. One patient received a CNI-free immunosuppressive regimen with belatacept. Tapering of steroids was performed intending steroid-free regime after the first year if no former rejection episodes had occurred.

Biochemical studies

Blood samples were collected from cubital veins before and after KTX. Standard laboratory parameters were obtained from EDTA blood and serum after centrifugation by established assays in the hospital's laboratory. Spontaneous urinary protein excretion was quantified by turbidimetric protein assay with the biuret method (Labor Berlin - Charité Vivantes Services GmbH). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation.

Echocardiography and Doppler measurements

Echocardiography was performed by experienced physicians of the echocardiography laboratory of the Cardiology Department, Charité-Universitätsmedizin Berlin, Germany. Echocardiographic parameters were obtained in the left decubitus position according to the recommendations of the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) [8, 9] using Vivid 7

Dimension and Vivid E9 (GE Vingmed, Horton, Norway, M4S or M5S transducer). Three beats were stored digitally and analyzed offline (EchoPac PC, GE Vingmed, Horton, Norway). Cardiac dimensions were acquired by M-Mode echocardiography or directly from 2D images according to the recommendations of ASE and EACVI [8, 9]. LV mass was calculated using the Devereux formula and was indexed to the calculated body surface area (BSA) using the Mosteller formula [9, 10]. LV mass indices of 43-95 g/m^2 for women and 49-115 g/m^2 for men were considered as normal ranges using the linear method [9]. LA volumes were obtained based on the recommendation of ASE and EACVI [9] and indexed to BSA. LVEF was obtained using the Auto-EF tool (GE Vingmed, Horton, Norway) as previously described [11]. The frame rate for tissue Doppler (TDI) measurements was >100/s. Transmitral pw-Doppler inflow at the tips of the mitral leaflets was measured to obtain E wave velocity, E wave deceleration time (DT), A wave velocity and E/A ratio [12]. Average peak early diastolic velocity (E´) was obtained from the septal and lateral sides of the mitral annulus in the apical four-chamber view with proper pulsed-wave TDI settings. Systolic (S´) and late diastolic velocity (A´) as well as the isovolumic relaxation time (IVRT) were quantified using pulsed-wave TDI at the septal insertion site of the mitral leaflet in the apical four-chamber view. The E/E´ ratio was calculated to estimate LV filling pressures [13, 14]. The position of the sample volume for velocity and TDI strain measurements was manually positioned in the myocardium throughout the cardiac cycle. Tricuspid annular plane systolic excursion (TAPSE) was acquired by M-Mode echocardiography according to Kaul et al. [15] and longitudinal velocity of excursion (RV S´) was assessed by pulsed-wave TDI positioning the sample volume for velocity in the basal free right ventricular wall [8].

2D speckle tracking strain analysis

For longitudinal strain analyses of the left atrium (LA) and left ventricle (LV), standard 2D ultrasound images were recorded with a frame rate between 60 and 80 frames per second (fps) from the apical long axis, two- and four-chamber views. The recordings were digitally stored for offline analysis (EchoPac PC) as previously described [16-18]. Briefly, LV global longitudinal peak systolic strain (GLPS) was assessed by a semi-automatic algorithm for tracking of the left ventricular myocardial wall which was divided into 18 segments [17]. LA function comprises three separate components - reservoir (for pulmonary inflow during ventricular systole), conduit (for passive LA emptying during early diastole) and contractile function (for active LA emptying in the late diastole) - which can be determined separately and specifically by strain analysis (see [18] and [19] for further details). LA longitudinal strain was assessed by 2D STE of the LA septal and lateral basal segments in the apical four-chamber view. The timing of end ventricular systole was defined by aortic valve closure using the aortic valve click obtained by cw-Doppler flow recordings in the LV outflow tract. After manual tracing of endocardial borders of the atrial septum as well as lateral and superior walls, the software automatically traced the region of interest. To optimize tracking, the region of interest width was adjusted when necessary. The trigger was put at the onset of the QRS complex. Peak positive strain (R_{LA}), strain during early diastole (E_{LA}) and strain during atrial contraction (A_{LA}) were determined and LA reservoir (R_{LA}), conduit (R_{LA}–E_{LA}) and contractile function (E_{LA}–A_{LA}) were calculated [18, 20].

Statistical analysis

Results are expressed as arithmetic mean and standard deviation (SD) or, if not normally distributed variables, as median with interquartile ranges (IQR) for continuous variables and as frequency distributions for dichotomous variables. Accordingly, paired T-test or Wilcoxon-test were used for comparison of paired observations. Categorical variables were compared with chi-squared tests. Multivariate logistic regression models using stepwise backward elimination including the variables changes in systolic blood pressure, changes in body mass index and changes in heart rate were created to identify factors that were independently associated with an improvement of GLPS and reduction of LV mass index. For the evaluation of interobserver variability, intraclass correlation coefficient was calculated using GLPS measurements from ten randomly selected study participants assessed by two echocardiographers. One experienced observer calculated GLPS on two consecutive days for analysis of the intraobserver variability. Statistical analyses were performed using SPSS v23.0 (IBM Corporation, Armonk, NY, USA) software; $p<0.05$ was considered statistically significant.

Table 1. General characteristics of study participants before (pre) and after (follow-up) kidney transplantation (KTX)

Parameter	Pre	Follow-up	*P value*
Serum creatinine [mg/dL]	7.7 [6.1-10.4]	1.3 [1.2-1.5]	*<0.001*
Body mass index [kg/m^2]	25.4 ± 4.2	25.5 ± 4.3	*0.760*
Blood pressure [mmHg]			
Systolic	140.4 ± 20.0	130.6 ± 14.2	*0.020*
Diastolic	82.2 ± 14.5	84.2 ± 10.2	*0.464*
Heart rate [per min]	72.7 ± 10.7	70.2 ± 10.7	*0.299*
C-reactive protein [mg/L]	1.0 [0.4-5.0]	1.2 [0.4-6.9]	*0.695*
Antihypertensive medication [average no. of pills]	3.0 ± 1.6	1.9 ± 1.3	*0.017*
Beta-blockers, n [%]	19 [61]	18 [58]	
ACE inhibitors, n [%]	18 [58]	5 [16]	
Angiotensin-receptor blockers, n [%]	4 [13]	7 [23]	
Calcium-channel blockers, n [%]	15 [48]	13 [42]	
Loop diuretics, n [%]	16 [52]	6 [19]	
Thiazides, n [%]	5 [16]	0 [0]	
Alpha-receptor blockers, n [%]	7 [23]	2 [6]	
ASA, n [%]	4 [13]	4 [13]	
Immunosuppression after KTX			
Mycophenolate, n [%]	-	31 [100]	
Calcineurin inhibitor, n [%]	-	30 [97]	
Belatacept, n [%]	-	1 [3]	
Steroids, n [%]	-	31 [100]	

Data are expressed as mean ± SD, median with IQR, or frequencies. ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid.

Results

Detailed characteristics of the 31 kidney recipients before and after KTX are shown in Table 1. Mean age at KTX was 44 years (range: 19-85 years), 11 recipients were female, 20 received a cadaveric and 11 a living kidney donation. Underlying causes for end-stage renal disease (ESRD) were glomerulonephritis (n=15), polycystic kidney disease (n=6), other (n=8) and unknown (n=2). Twenty-three patients received maintenance dialysis before KTX with a median time on dialysis of 33.5 [10.0-72.3] months and 8 patients received preemptive KTX. At KTX, coronary artery disease was prevalent in n=4, peripheral artery disease in n=4 and diabetes mellitus in n=3 patients. None of the patients had a history of transient ischemic attack (TIA) or stroke. Median follow-up after KTX was 19.0 [13.0-32.0] months. Serum creatinine and systolic blood pressure were significantly lower after KTX (Table 1). At follow-up, mean eGFR was 59.6 ± 19.0 ml/min and median spontaneous urinary protein excretion was 69.0 [41.0-223.0] mg/L.

Echocardiography

All patients had sinus rhythm at the time of echocardiographic evaluation. LV end-diastolic septal and posterior wall thickness decreased significantly after KTX (Table 2). Accordingly, there was a significant reduction of LV mass index reaching normal ranges after KTX (Table 2). GLPS improved significantly after KTX within normal ranges, while the increase in LVEF did not reach statistical significance *(P = 0.058)* (Table 3). LV diastolic function parameters did not change significantly after KTX, but there was a trend *(P = 0.066)* towards a lower E/E' ratio after KTX. LA dimensions and LA reservoir, conduit and contractile function did not change significantly after KTX (Table 2 and 4). There were no significant changes in RV parameters after KTX (Table 2 and 3).

Table 2. Two-dimensional echocardiographic data before (pre) and after (follow-up) kidney transplantation (KTX)

Parameter	Pre	Follow-up	*P value*
IVSD [mm]	12.4 ± 2.1	11.5 ± 2.0	*<0.001*
LVPWD [mm]	11.1 ± 2.3	10.1 ± 1.8	*<0.001*
LVEDD [mm]	48.3 ± 7.4	47.3 ± 6.2	*0.252*
LVESD [mm]	29.1 ± 6.8	27.8 ± 5.8	*0.267*
LV mass index [g/m^2]	112.2 [88.7-150.6]	103.8 [78.4-113.8]	*0.001*
female	99.2 [78.1-128.9]	79.0 [72.8-107.9]	*0.080*
male	121.8 [93.8-153.5]	106.3 [85.8-117.2]	*0.008*
LAD [mm]	37.0 [34.0-41.0]	38.0 [32.0-43.0]	*0.976*
Diastolic LA volume index [mL/m^2]	31.7 [28.1-37.6]	33.0 [28.6-38.0]	*0.575**

Data are expressed as mean ± SD or median with IQR. IVSD, end-diastolic septal wall thickness; LV, left ventricular; LVPWD, end-diastolic LV posterior wall thickness; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; LAD, left atrial diameter; *n=24.

We observed an association between pre-transplant systolic blood pressure and both the improvement of GPLS (Spearman's rho: 0.482, *P* = 0.006) and the reduction of LV mass index (Spearman's rho: 0.307, *P* = 0.093) after KTX. The extent of systolic blood pressure reduction after KTX showed a non-significant trend for prediction of improvement of GLPS (RR 1.5, 95% confidence interval [CI] 1.0-2.2, *P* = 0.084 per 10 mmHg) and the reduction of LV mass index (RR 1.6, 95% CI 1.0-2.6, *P* = 0.055 per 10 mmHg).

Intra- and interobserver variability of GLPS measurements was 0.96 (95% CI 0.86-0.99) and 0.93 (95% CI 0.65-0.98), respectively.

Table 3. Changes in echocardiographic data of left ventricular (LV) systolic and diastolic and right ventricular (RV) function before (pre) and after (follow-up) kidney transplantation (KTX)

Parameter	Pre	Follow-up	*P value*
Systolic LV function			
GLPS [%]	-18.4 ± 2.8	-19.4 ± 2.3	*0.028*
LVEF [%]	58.6 ± 7.8	61.2 ± 7.2	*0.058*
LV S' [cm/s]	7.5 ± 1.5	7.6 ± 1.3	*0.797*
Diastolic LV function			
E [m/s]	0.70 [0.56-0.83]	0.70 [0.50-0.80]	*0.121*
A [m/s]	0.66 [0.56-0.95]	0.60 [0.50-0.90]	*0.183*
E/A	1.08 ± 0.37	1.15 ± 0.50	*0.291*
E' [cm/s]	9.50 ± 2.73	9.48 ± 2.84	*0.977*
E/E'	7.8 [6.1-9.9]	7.0 [5.6-10.1]	*0.066*
A' [cm/s]	9.41 ± 2.44	9.15 ± 1.92	*0.519*
DT [ms]	206.4 ± 47.6	213.6 ± 53.7	*0.443*
IVRT [ms]	96.7 ± 29.8	89.3 ± 25.6	*0.235*
RV function			
TAPSE [mm]	23.3 ± 6.2	23.2 ± 5.6	*0.880*
RV S' [cm/s]	12.9 ± 2.5	12.7 ± 2.9	*0.494*

Data are expressed as mean ± SD or median with IQR. GLPS, left ventricular global longitudinal peak systolic strain; LVEF, left ventricular ejection fraction; LV S', peak systolic velocity of the basal septal segment; E, peak transmitral E wave velocity; A, peak transmitral A wave velocity; E/A, ratio of transmitral E to transmitral A; E', early diastolic annular velocity averaged from measurements in the septal and lateral mitral valve annulus; A', late diastolic annular velocity measured in the septal mitral valve annulus; E/E', ratio of peak early transmitral diastolic velocity to early averaged annular velocity; DT, deceleration time of the transmitral E wave; IVRT, isovolumic relaxation time; TAPSE, tricuspid annular plane systolic excursion; RV S', peak systolic velocity of the basal RV free wall segment.

Table 4. Left atrial (LA) strain before (pre) and after (follow-up) kidney transplantation (KTX)

Parameter	Pre	Follow-up	*P value*
Reservoir function (R_{LA}) [%]	44.8 ± 13.8	44.2 ± 9.3	*0.818*
Conduit function (R_{LA}-E_{LA}) [%]	27.4 ± 12.1	24.3 ± 8.3	*0.063*
Contractile function (E_{LA}-A_{LA}) [%]	18.7 ± 5.8	20.9 ± 5.5	*0.100*

Data are expressed as mean ± SD. Values are averaged from septal and lateral basal LA segments. R_{LA}, LA peak positive strain; E_{LA}, LA strain during early diastole; A_{LA}, strain during atrial contraction.

Discussion

LVH is the most commonly observed cardiac change in CKD patients, which is a result of multiple factors including chronic uremia (which also induces cardiac fibrosis), hemodynamic changes (such as systemic hypertension and volume overload) and changes in the inflammatory, metabolic or hormonal status [21, 22]. While LVH initially represents an adaption to maintain cardiac function it may become maladaptive as it progresses with continuing CKD finally resulting in systolic or diastolic dysfunction, which is associated with a poor prognosis [23].

In accordance with previous studies [5, 22, 24, 25], we were able to show that restoration of renal function by KTX ameliorated blood pressure control after KTX and significantly reversed LVH. Of note, all of the investigated 31 kidney transplant recipients in the present study were successfully transplanted (defined as the absence of maintenance dialysis since the date of KTX and a significant improvement of GFR). We found that improvement of renal function after KTX was accompanied by a significant reduction of antihypertensive medication indicating that better hypertension control was not an independent factor contributing to reduction of LVH. Although not reaching statistical significance in our small cohort, levels of systolic blood pressure before KTX and the decrease in systolic blood pressure over KTX seem to be key determinants for the reversal in LVH in line with the findings of [22, 26]. In hypertensive (non-ESRD) patients under antihypertensive treatment a reduction in LV mass is directly linked to prognosis including lower rates of CV mortality, stroke, myocardial infarction, and all-cause mortality [27].

Improvement of LV systolic function (as determined by LVEF assessment) after KTX was shown in patients with moderately reduced LV systolic function and occurs within a relatively short-term follow-up after KTX [5, 28]. In the present study, most patients had preserved or mildly impaired LVEF before KTX, which might explain why we observed only a slight, non-significant increase in LVEF. However, LV longitudinal function as assessed by STE (GLPS) improved significantly after KTX. Again, reasons for the improvement of LV function after KTX are multifactorial and complementary including the removal of uremic toxins, reversal of LVH, hemodynamic changes and restoration of inflammation [2, 24, 26, 29]. We observed that patients with higher systolic blood pressure before KTX benefit the most from transplantation in terms of improvement of GLPS. LV strain of longitudinal shortening as assessed by STE is predominantly influenced by subendocardial fibers. It is more suited to detect subtle changes of LV function than LVEF, which mainly depends on radial and circumferential deformation caused by mid-myocardial and epicardial fibers [17, 20]. GLPS is affected by the composition of the interstitial myocardium including the extent of myocardial fibrosis [30] and was shown to be a robust and independent predictor for all-cause mortality in patients with severe CKD and impaired LV function [31]. Furthermore, GLPS assessed after KTX was shown to be a prognostic marker for CV events [32]. The prognostic value of changes of GLPS over KTX on future CV events has not been evaluated so far and should be addressed in further studies.

Diastolic dysfunction is frequent in patients with ESRD as a result of LVH and cardiac fibrosis [2]. However, in line with previous studies [22, 25] we did not detect a significant

improvement in diastolic function parameters after KTX. In contrast to both mentioned studies, which based their classification of diastolic function solely on the mitral inflow pattern, we evaluated diastolic function by complementary utilization of tissue Doppler analyses as currently recommended [33] and by additional assessment of STE-derived LA strain.

Limitations

The study comprises a sample of an ESRD population with rather low prevalence of CV disease, relatively low LV mass index and preserved LV function. Thus, some of our findings might have been more pronounced in more diseased patients and with a bigger sample size. Furthermore, a control group of age- and sex-matched ESRD patients not undergoing KTX with repeated echocardiographic evaluations was not included in the study protocol.

Conclusions

Within a mid-term follow-up after successful KTX, we observed a significant reversal of LV hypertrophy. This was accompanied by a significant improvement in longitudinal LV function as assessed by STE. Diastolic function and STE-derived LA function parameters did not change significantly after KTX. These findings highlight the dynamic interplay of the cardiorenal axis and support the application of advanced echocardiographic modalities such as STE for the evaluation of cardiac function in this patient population.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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