

Beneficial effect of bilateral native nephrectomy as complete denervation on left ventricular mass and function in renal transplant recipients

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KEY WORDS

bilateral nephrectomy,
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ABSTRACT

INTRODUCTION Left ventricular hypertrophy (LVH) is a risk factor for cardiovascular morbidity and mortality in renal transplant recipients. The development of LVH is connected with excessive activation of the sympathetic nervous system. A bilateral nephrectomy is an example of complete renal denervation.

OBJECTIVES The aim of this study was to evaluate the effect of pretransplant bilateral native nephrectomy on left ventricular mass and function during a long-term follow-up of patients after kidney transplantation. **PATIENTS AND METHODS** The study group consisted of 32 renal transplant recipients who had previously undergone pretransplant bilateral native nephrectomy. The control group involved 32 recipients with preserved native kidneys, matched for age, sex, creatinine levels, estimated glomerular filtration rate, immunosuppressive treatment, and the time of renal replacement therapy. All patients were evaluated by echocardiography, and 16 patients—by cardiac magnetic resonance (CMR). In addition, all patients had their arterial blood pressure (BP) and metabolic markers measured.

RESULTS In comparison with controls, the study group had lower systolic BP ($P = 0.048$) and received a lower number of antihypertensive agents ($P = 0.001$). Lipid and hemoglobin levels were similar in both groups. The study group had a lower left ventricular mass index (LVMI; $P = 0.001$) and left atrial volume index (LAVI; $P = 0.004$). The left ventricular mass evaluated by CMR was also lower in the study group ($P < 0.001$). Mild left ventricular diastolic dysfunction (LVDD) was more frequent in the study group compared with the control group ($P < 0.001$).

CONCLUSIONS In a long-term follow-up of patients after kidney transplantation, the bilateral native nephrectomy before transplantation was associated with a lower LVMI and LAVI as well as a lower grade of LVDD. These patients had lower systolic BP and used fewer antihypertensive drugs.

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INTRODUCTION Left ventricular hypertrophy (LVH) and cardiac fibrosis are major risk factors for premature cardiovascular morbidity and mortality in chronic kidney disease (CKD).^{1,2} LVH leads to diastolic dysfunction, congestive heart failure, arrhythmias, and sudden death. It develops early in the course of CKD and is found

in more than half of patients with CKD stage 3 and nearly all patients (90%) with CKD stage 5.³ The mechanisms underlying LVH are multifactorial and include hypertension, extracellular volume overload, arterial stiffness, dyslipidemia, diabetes, inhibition of nitric oxide, endothelial dysfunction, inflammation, anemia, and activation

of the activity of the renin–angiotensin–aldosterone and sympathetic nervous systems.^{2,4} The excessive activation of the sympathetic nervous system is observed from the early stage of CKD, during progression, to the end stage of renal disease (ESRD), as well as after kidney transplantation (KTx).^{5–9}

After successful KTx, the risk of cardiovascular disease is reduced as compared with patients maintained on dialysis, but remains 3- to 5-fold higher than in the general population. It is a consequence of persistent ischemic cardiovascular disease and cardiac hypertrophy. Cardiac hypertrophy is caused mainly by increased blood pressure (BP) triggered by hyperactivity of the sympathetic nervous system from native kidneys and the side effects of immunosuppressive treatment.¹⁰

The overactivity of the sympathetic nervous system damages the cardiovascular system through numerous pathways such as the activation of the renin–angiotensin–aldosterone system, arrhythmogenic effect of noradrenaline, acceleration of atherosclerosis via vasoconstriction, as well as proliferation and migration of smooth muscle cells and fibroblasts in coronary and peripheral vasculature.¹⁰

Excessive sympathetic nervous activity may be reduced by percutaneous, catheter-based endovascular ablation of renal sympathetic nerves.¹¹ Efficient and complete elimination of sympathetic nervous hyperactivity is also a consequence of bilateral nephrectomy. Bilateral nephrectomy in patients on renal replacement therapy, beside normalization of sympathetic activity, leads to the removal of circulating renal renin and to the decrease in systemic activity of the renin–angiotensin–aldosterone system.¹² Some investigators observed a decrease in BP after renal removal, but the effect on cardiac remodeling has not been studied in the adult population.¹³

The aim of this study was to evaluate the effect of pretransplant bilateral native nephrectomy on the morphology and function of the left ventricle (LV) in a long-term follow-up of patients after KTx.

PATIENTS AND METHODS **Participants** From 1999 to 2011, 986 patients underwent KTx at our transplant center. Of these patients, 38 had their native kidney removed before KTx, during the time of maintenance dialysis treatment. Six patients were excluded from the study because of valvular heart disease and retransplantation. The remaining 32 patients (mean age, 51.72 ± 14.46 years) constituted the study group. Native bilateral nephrectomy was performed due to autosomal-dominant polycystic kidney disease in 16 patients, refractory hypertension in 2 patients, vesicoureteral reflux in 5 patients, focal segmental glomerulosclerosis with large proteinuria in 3 patients, urolithiasis in 2 patients, trauma in 2 patients, and cancer in 2 patients.

Patients underwent nephrectomy at a mean time of 114 months before the study.

The control group included 32 kidney recipients with preserved native kidneys (mean age, 51.94 ± 12.97 years). Controls were matched for age, sex, the cause of renal failure, estimated glomerular filtration rate (eGFR), immunosuppressive treatment, and time after KTx. All patients received kidneys from deceased donors. Patients were treated with triple immunosuppressive therapy consisting of calcineurin inhibitor, mycophenolate mofetil or azathioprine, and prednisone, except for 6 patients in the study group and 5 in the control group, who were treated with mammalian target of rapamycin (mTOR) inhibitors. The levels of tacrolimus and cyclosporine were similar in both groups.

In all patients, arterial BP, pulse pressure, metabolic markers, and allograft function were evaluated during the first and third month and every 3 months until the end of the follow-up (median time in the study group, 95 months [range, 54.5–115.5]; and in the control group, 91 months [range, 57.5–132.5]; $P > 0.05$). The average of the measurements of the examined parameters was used for calculations. We also compared these parameters between the 2 groups before KTx and after 3, 6, and 12 months as well as each year from 2 to 10 years. After this period, it had not been compared because of an insufficient number of patients in the groups.

The eGFR was calculated by the Modification of Diet in Renal Disease formula. An echocardiographic examination and cardiac magnetic resonance (CMR) were performed after a mean time of 92.2 months after KTx in the study group and 98.4 months after KTx in the control group ($P = 0.66$).

Echocardiography and cardiac magnetic resonance All patients underwent echocardiography using the Vivid4 GE Medical System (GE Healthcare, Tirat Carmel, Israel), with a 2.5-MHz transducer ultrasound system. All echocardiography measurements were obtained according to the recommendations of the American Society of Echocardiography and European Association of Echocardiography.^{14,15}

Left ventricular mass (LVM) was calculated from the end-diastolic septal wall thickness (SWTd), end-diastolic LV diameter (LVEDd), and end-diastolic posterior wall thickness (PWTd), using the following formula:

$$\text{LVM} = 0.8\{1.04[(\text{LVEDd} + \text{SWTd} + \text{PWTd})^3 - (\text{LVEDd})^3]\} + 0.6.$$

The LVM was indexed for the body surface area (BSA). A cut-off value of 115 g/m² or lower for men and of 95 g/m² or lower for women was used for the upper limit of the normal LVM index (LVMI).

In order to classify the pattern of the LV geometry, the relative wall thickness (RWT) was calculated according to the following formula: $\text{RWT} = (2\text{PWTd})/\text{LVEDd}$.

TABLE 1 Demographic and clinical characteristics of the study groups

Parameter	Study group	Control group	P value
female sex	20 (62.5)	19 (59)	0.8
age, y	51.72 ± 14.46	51.94 ± 12.97	0.9
BSA, m ²	1.77 ± 0.23	1.78 ± 0.24	0.8
BMI, kg/m ²	25.18 ± 4.9	25.06 ± 3.8	0.9
time after binephrectomy, y	9.5 ± 6.1	0	0
time of dialysis, mo	52.81 ± 44.69	33.44 ± 44.76	0.003
time of kidney replacement therapy, mo	145.00 ± 69.99	128.53 ± 72.29	0.4
creatinine, μmol/l	143.2 ± 61	143.2 ± 48.6	0.9
eGFR, ml/s	0.76 ± 0.22	0.74 ± 0.24	0.8
Hg, μmol/l	8.28 ± 1.178	7.96 ± 1.17	0.3
total cholesterol, mmol/l	5.3 ± 1.04	5.34 ± 1.27	0.9
triglycerides, mg/l	1.72 ± 0.74	1.62 ± 0.75	0.6
DM	2 (6.25)	2 (6.25)	1.000
SBP, g/l	16.74 ± 2.19	17.74 ± 1.73	0.048
DBP, kPa	10.30 ± 1.42	10.72 ± 1.15	0.2
PP, kPa	6.43 ± 1.44	7.01 ± 1.42	0.1
HR, bpm	64 ± 12	62 ± 15	0.6
number of antihypertensive agents	1.38 ± 1.10	2.47 ± 1.50	0.001
mTOR treatment	6 (18.75)	5 (15.63)	0.7

Data are presented as mean ± standard deviation or number (percentage) of patients.

Abbreviations: BMI, body mass index; BSA, body surface area; DM, diabetes mellitus; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hg, hemoglobin; HR, heart rate; mTOR, mammalian target of rapamycin inhibitors; PP, pulse pressure; SBP, systolic blood pressure

The normal pattern of the LV geometry was defined for the normal LVMI and RWT of 0.42 or lower, and the concentric remodeling—for the normal LVMI and RWT of more than 0.42. The concentric LVH was classified for an increased LVMI and RWT of more than 0.42, and the eccentric one—for RWT of 0.42 or lower. The LV ejection fraction (LVEF) was measured by the biplane Simpson's method on the 4-chamber apical view.

The left atrial volume (LAV) was measured by the area-length method. The LAV was indexed to the BSA. The cut-off point was up to 34 ml/m² for LAV enlargement.

The Doppler echocardiography was performed in a 4-chamber view and obtained peak of the early (E), late (A) diastolic transmitral velocity, E/A ratio, deceleration time of mitral E wave (DT), and isovolumic relaxation time.

Tissue Doppler imaging was used for the measurements of systolic and diastolic velocities of the mitral annulus such as peak mitral annular systolic velocity (s), peak early diastolic velocity (e), and peak late diastolic velocity (a) from the septal and lateral sides. All parameters were calculated as the average of measurements taken in 3 consecutive cardiac cycles. The ratio of peak early transmitral velocity to the peak mitral annular early diastolic velocity (E/e) was calculated separately for the lateral and septal annulus sides, and then for the average of both velocities.

An average E/e ratio of 8 or lower was considered as an indicator of normal left atrial (LA) pressure, and of 13 or higher—as high LA pressure.

An increased LA pressure was defined as an average E/e ratio exceeding 8, but not exceeding 13 in the case of a simultaneous presence of the LAV enlargement.

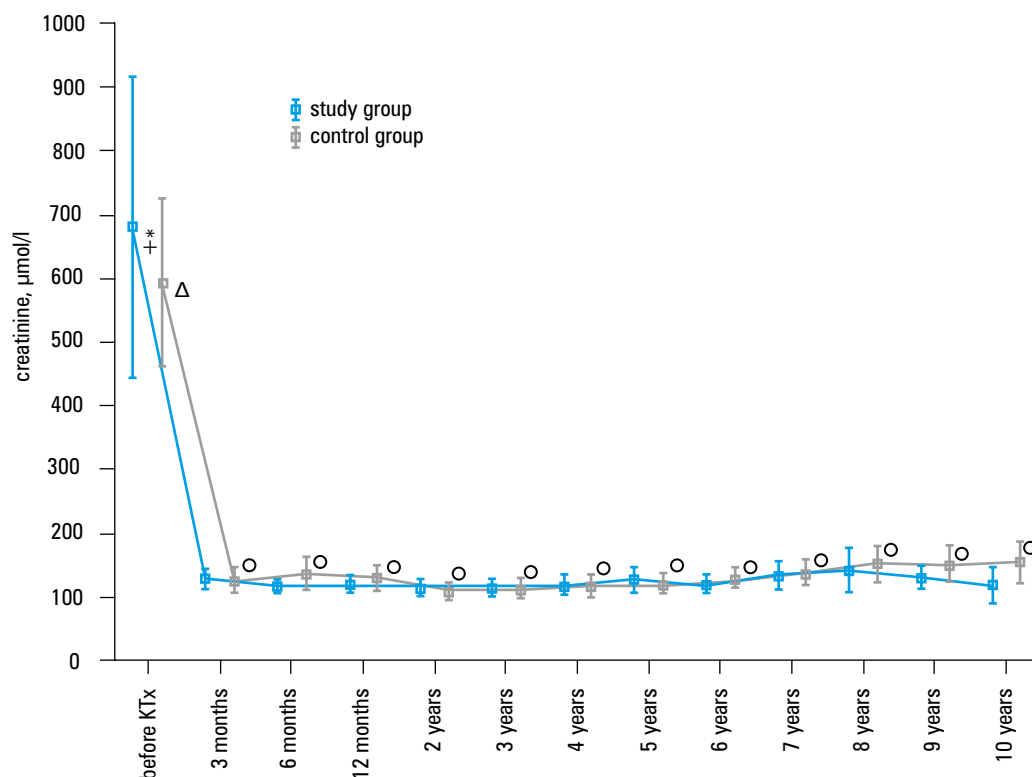
The presence of LV diastolic dysfunction (LVDD) was defined as a LAVI of up to 34 ml/m² and velocity of lateral e of less than 10 cm/s and septal e of less than 8 cm/s. The E/A ratio, DT, and the average E/e ratio were used to classify LVDD into 3 grades: 1) mild: with an E/A ratio of less than 0.8, DT above 200 ms, and an average E/e ratio of 8 or lower; 2) moderate: with an E/A ratio between 0.8 and 1.5, DT between 160 and 200 ms, and an average E/e ratio of more than 8 but less than 13; and 3) severe: with E/A exceeding 2, DT below 160 ms E/e, and an average E/A ratio of 13 or higher.

Diastolic function was graded on a 4-point scale: 1, normal diastolic function of the LV; 2, mild LVDD; 3, moderate LVDD; and 4, severe LVDD.

CMR was performed only in 16 patients from both groups (9 patients in the study group, 7 patients in the control group) by using a 1.5 Tesla scanner (Signa HDxt, GE Healthcare). Both breath-held cardiac-gated dynamic (2- and 4-chamber planes and short-axis slices) and static ("dark blood") sequences were obtained.

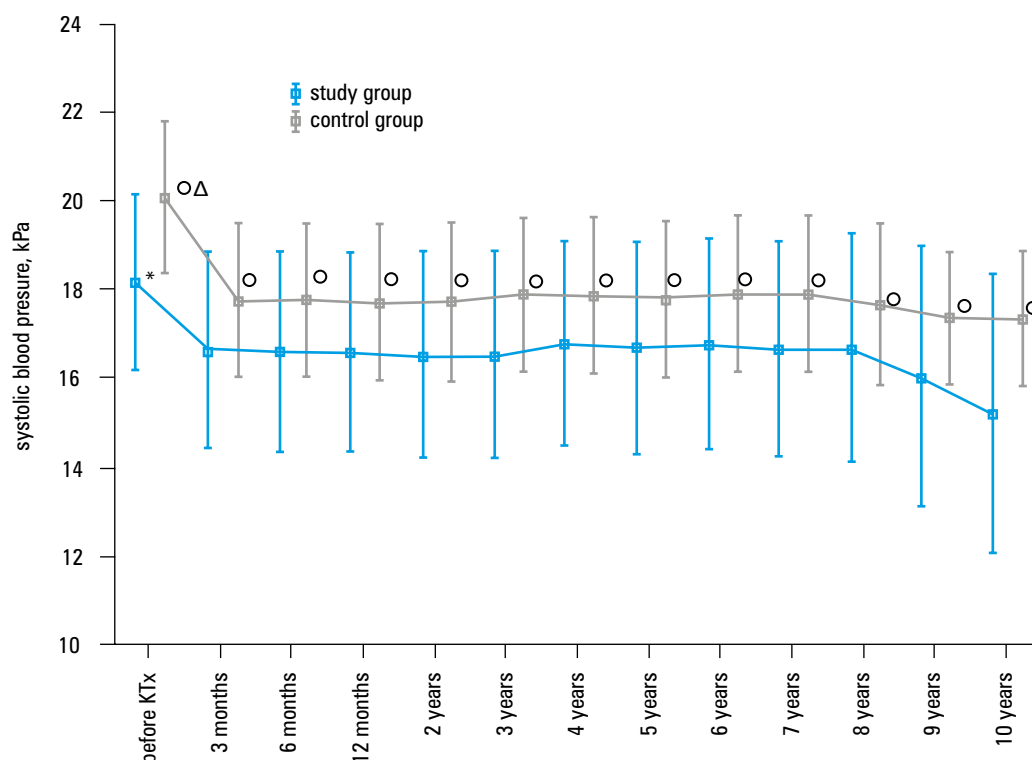
The basic acquisition parameters were as follows: slice thickness, 8 mm; the gap, 2 mm; the field of view, 34 cm; and number of excitations, 1. All images were analyzed, and the measurements were taken using the Advantage Work station

FIGURE 1 Serum creatinine levels in the study and control groups at investigated time points (data are presented as mean $\pm$ standard deviation)



- Δ in the control group, serum creatinine level was significantly higher before transplantation than at each time point after transplantation (KTx) ($P < 0.001$)
- in both study groups, serum creatinine level was similar at each time point after KTx ($P = NS$)
- * in the study group, serum creatinine level was significantly higher before KTx than at each time point after KTx ($P < 0.001$)
- + before KTx, serum creatinine level was significantly higher in the study than in the control group ($P = 0.02$)

FIGURE 2 Systolic blood pressure (SBP) in the study and control groups at investigated time points (data are presented as mean $\pm$ standard deviation)



- Δ in the control group, SBP before transplantation (KTx) was higher than at each time point after KTx ($P < 0.01$)
- * in the study group, SBP was lower than in the control group at each time point ($P < 0.05$)
- in the study group, SBP before KTx was higher than at each time point after KTx ($P < 0.02$) and was lower than in the control group before KTx ($P = 0.01$)

TABLE 2 Echocardiographic parameters of the left ventricle and left atrium in the study groups

Parameter	Study group	Control group	P value
LVEDd, mm	49.51 ± 5.89	50.25 ± 6.04	0.6
SWTd, mm	13.09 ± 1.58	14.40 ± 1.91	0.004
PWTd, mm	10.79 ± 1.09	11.67 ± 1.08	0.002
LAV, ml	64.28 ± 13.20	76.00 ± 20.74	0.009
LAVI, ml/m ²	36.11 ± 4.28	42.46 ± 9.57	0.001
LVM, g	231.97 ± 59.54	271.22 ± 80.20	0.03
LVMI, g/m ²	129.78 ± 22.80	150.48 ± 32.19	0.004
EF, %	61.66 ± 2.15	62.25 ± 2.11	0.3
RWT	0.44 ± 0.06	0.47 ± 0.05	0.04
RWT > 0.42	51	90	< 0.001

Data are presented as mean ± standard deviation or percentage of patients.

Abbreviations: EF, ejection fraction; LAV, left atrial volume; LAVI, left atrial volume index; LVEDd, left ventricular end-diastolic diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; PWTd, end-diastolic posterior wall thickness; RWT, relative wall thickness; SWTd, end-diastolic septal wall thickness

version 4.4 (GE Healthcare) supplied with a semi-automated cardiac analysis software.

LV measurements including wall thickness and internal dimensions were obtained using the short-axis view basally to the tips of the papillary muscles. The intraventricular septal thickness was defined as the distance between the right and left endocardial surfaces at the end of diastole. LV volumes and mass were calculated using the method of summation of slices at the end-systolic and end-diastolic phases of the study.

Statistical analysis Continuous variables were presented as means and standard deviations and compared with the *t* test or the Mann–Whitney test, according to their distribution. Discrete variables were presented as numbers and percentages and compared with the χ^2 test.

Additionally, we used a multivariate linear regression model to assess the associations of the independent variables such as sex, age, bilateral nephrectomy, time of kidney replacement therapy, treatment with mTOR inhibitors, and eGFR with the LVMI as a dependent variable.

P values of less than 0.05 were considered statistically significant.

RESULTS Clinical and demographic characteristics

The clinical and demographic data of the study groups are shown in **TABLE 1**. During the study, cardiovascular events such as myocardial infarction or percutaneous coronary intervention were observed in 3 patients from the study group and 5 patients from the control group (*P* = 0.04).

We did not observe any differences in metabolic parameters between the groups at the examined time points. The serum creatinine level significantly decreased after KTx in both groups (*P* < 0.001) but did not differ between the study and control groups at the investigated time points (nonsignificant; **FIGURE 1**). At all compared time points, systolic BP was lower in the study group compared with the control group (*P* < 0.05;

FIGURE 2). Diastolic BP and pulse pressure were similar in both groups at all time points.

Nephrectomized patients received a mean of 1.4 antihypertensive drugs: mainly calcium channel blockers (90%) and β -blockers (40%). Patients from the control group received a mean of 2.4 antihypertensive drugs: β -blockers (90%), calcium channel blockers (90%), angiotensin-converting enzyme inhibitors (28%), and α 2-blockers (32%). At the time of cardiac evaluation, most patients had CKD stage 3.

Echocardiographic and cardiac magnetic resonance parameters of the left ventricle

LV and LA parameters derived from 2-dimensional and M-mode echocardiography are shown in **TABLE 2**. The mean LVMI was lower in the study group than in the control group by 20.7 g/m² (*P* = 0.004). The LAVI of less than 34 ml/m² was observed in 6 patients: 4 in the study group (12.5%) and 2 in the control group (6.25%).

In the study group, 1 patient had a normal LV pattern, and 3 patients had concentric remodeling. In the control group, 2 patients had concentric remodeling. In nephrectomized patients, eccentric and concentric LVH occurred with a similar frequency (40% vs 47%). In the control group, concentric LVH was significantly more frequent and was found in 84% of the patients, but eccentric LVH—only in 9% of the patients.

Left ventricular diastolic function A lateral, septal, and average E/e ratio exceeding 8 was significantly more common in patients with preserved native kidneys. These patients also showed LAV enlargement, which indicated an increase of LA pressure.

In both groups, there were no patients who had an average E/e ratio of higher than 13. The Doppler echocardiography parameters of the LV inflow and tissue Doppler imaging parameters are presented in **TABLE 3**.

Six patients (4 nephrectomized and 2 from the control group) had normal LVM, LAV, and LV

TABLE 3 Doppler echocardiographic parameters of left ventricular inflow and tissue Doppler imaging parameters in the study groups

Parameter	Study group	Control group	P value
mitral valve E, cm/s	71.06 ± 16.48	76.56 ± 15.18	0.2
mitral valve A, cm/s	82.72 ± 16.43	75.75 ± 13.56	0.07
mitral valve E/A ratio	0.88 ± 0.24	1.05 ± 0.31	0.02
deceleration time of mitral E, ms	222.13 ± 49.18	184.75 ± 22.59	<0.001
IVRT, ms	93.23 ± 16.66	101.03 ± 9.14	0.02
e lat, cm/s	10.07 ± 3.22	8.84 ± 2.42	0.08
a lat, cm/s	10.10 ± 2.01	9.76 ± 2.41	0.5
s lat, cm/s	10.55 ± 12.9	8.50 ± 2.20	0.4
E/e lat	7.31 ± 1.61	8.94 ± 2.23	<0.001
e sep, cm/s	8.19 ± 2.71	7.35 ± 2.25	0.2
a sep, cm/s	9.84 ± 1.84	9.40 ± 2.17	0.4
s sep, cm/s	7.69 ± 1.75	7.55 ± 1.67	0.730
E/e sep	9.03 ± 2.15	10.8 ± 2.23	0.003
E/e avr	8.07 ± 1.82	9.71 ± 1.76	0.001
E/e avr > 8	10 (31)	27 (84)	<0.001

Data are presented as mean ± standard deviation or number (percentage) of patients.

Abbreviations: a, peak mitral annular late diastolic velocity; avr, average of lateral and septal side; e, peak mitral annular early diastolic velocity; E/e ratio, peak transmitral early diastolic velocity to peak annular mitral early velocity ratio; IVRT, isovolumic relaxation time; lat, lateral side; s, peak mitral annular systolic velocity; sep, septal side

diastolic function and were younger than 40 years old. There were no patients with severe LVDD in any of the groups. The differences between the groups were related to the incidence of mild and moderate LVDD. The percentage of patients with LVH and mild LVDD was higher in the study group than in the control group (56.25% and 12.50%, respectively; $P < 0.001$), whereas the percentage of patients with moderate LVDD was higher in the control group than in the study group (81.3% and 31.3%, respectively, $P < 0.001$).

Cardiac magnetic resonance parameters of the left ventricle The parameters obtained by CMR are shown in **TABLE 4**. End-diastolic LVM was lower by a mean of 45 g and end-systolic LVM was lower by a mean of 63 g (30%) in nephrectomized patients compared with controls ($P = 0.001$ and $P = 0.004$, respectively). The difference in LVM between the groups was higher than that estimated by echocardiography.

Multivariate regression analysis A multivariate regression analysis was performed to identify clinical factors related to a higher LVMI. The studied variables were age, sex, history of bilateral nephrectomy, duration of kidney replacement therapy, history of treatment with mTOR inhibitors, and eGFR. The analysis revealed that a lower LVMI was independently associated with a history of bilateral nephrectomy ($P = 0.003$), but a higher LVMI was associated with male sex ($P = 0.004$) and older age ($P = 0.01$) (**TABLE 5**). The remaining parameters, namely, eGFR, duration of renal replacement therapy, and treatment with mTOR inhibitors, were not associated with the LVMI.

DISCUSSION Our study showed that renal transplant recipients who underwent a pretransplant native bilateral nephrectomy had better control of systolic BP and lower LVM than patients with preserved kidneys. Moreover, these patients had lower LVDD and a lower frequency of concentric LVH. The beneficial effect of the procedure on the cardiovascular system was observed in the long-term follow-up of patients after native kidney removal and KTx. We compared cardiac parameters of patients with those of a well-matched control group. The results of CMR were obtained from a small group of patients, but we decided to present them because they showed a significant difference.

Our earlier study on a smaller group of renal transplant patients ($n = 11$) also suggested that bilateral native nephrectomy before KTx improved BP control and reduced the LVM.¹⁶ The present study, using various echocardiographic and CMR parameters, confirmed the initial finding and provided some insight into the relationship between bilateral nephrectomy and LV morphology and function.

The prevalence of LVH was lower in nephrectomized patients than in patients with native kidneys, although nephrectomized patients had longer time of dialysis before KTx. It is well known that dialysis leads to LVH. The longer time of dialysis in the study group was connected with 2 procedures of nephrectomy, which were not performed at one time. Some investigators reported that KTx leads to regression of LVH,¹⁷⁻¹⁹ while others—that LVH persists or can develop de novo.²⁰⁻²³ The difference in the outcome was associated with renal allograft function, anemia, resistant

TABLE 4 Cardiac magnetic resonance parameters of the left ventricle in the study groups

Parameter	Study group	Control group	P value
SWTd, mm	11.5 ± 2.2	15.4 ± 2.1	0.005
EF, %	63.3 ± 7.9	62.8 ± 17.6	0.9
end-diastolic LVM, g	109.3 ± 30.3	150.2 ± 34.0	0.03
end-systolic LVM, g	125.1 ± 37	183.0 ± 41.3	0.01
LVEDd, mm	50.4 ± 7.3	55.8 ± 7.7	0.2
LVESd, mm	32.5 ± 6.6	35.2 ± 9.7	0.5

Abbreviations: LVESd, left ventricular end-systolic diameter; others, see [TABLE 2](#)

TABLE 5 Multivariate regression analysis of independent factors for left ventricular mass index in renal transplant recipients

Parameter	β coefficient	Standard error of β	P value
age	0.64	0.24	0.01
male sex	19.81	6.68	0.004
bilateral nephrectomy	– 20.03	6.38	0.003
duration of renal replacement therapy	0.01	0.05	0.976
treatment with mTOR inhibitors	2.51	8.44	0.767
eGFR	0.02	0.24	0.928

Abbreviations: see [TABLE 1](#)

hypertension, sympathetic activity, and the side effects of immunosuppressive treatment.

The regression of LVH had a favorable and independent effect on cardiovascular survival in a population of patients with hypertension and in patients with ESRD. London et al²⁴ found that a decrease in LVM by 10% translated into a decrease in mortality risk from cardiovascular causes by 28% over a 5-year follow-up of patients treated with hemodialysis.²⁴ They calculated that a 1-g decrease in LVM translated to a decrease in the risk for cardiovascular mortality by 1%.

High mortality from cardiovascular diseases in renal transplant patients compared with the general population was associated with LVH.^{25,26} Our multivariate regression analysis showed that bilateral nephrectomy was an independent predictor of a lower LVMI; however, LVH was associated with male sex and older age. The time of replacement therapy, eGFR, and treatment with mTOR inhibitors did not affect the LVMI.

Patients with concentric LVH have a relatively high incidence of adverse cardiovascular and noncardiovascular events compared with patients with eccentric LVH.^{27,28}

LVH and the presence of intermyocardial fibrosis, specific for patients with CKD, impair diastolic LV function. Previous studies have shown a correlation between increasing LV mass with increasing LVDD and filling pressure.²⁹ The average E/e ratio, an indicator of LA pressure, was increased in patients with native kidneys than in those without. Numerous studies have shown a correlation of the E/e ratio with adverse events after acute myocardial infarction, hypertensive cardiomyopathy, and ESRD.^{30–33} The velocity of e is dependent on changes of preload, afterload,

and sympathetic tone.¹⁵ The LAV is more useful for the evaluation of chronically increased LV filling pressure and for detecting diastolic heart failure than the E/e ratio is.^{34,35} In the general population, LA enlargement is considered an indicator of diastolic burden and a predictor of atrial fibrillation, stroke, congestive heart failure, and cardiovascular death.^{36,37} Patel et al³⁸ showed that LA dilation before KTx was significantly associated with reduced posttransplant survival, while elevated LAV was associated with death independently from LVH.³⁸

In the present study, patients after bilateral nephrectomy had a significantly lower LA volume and significantly fewer patients had moderate LVDD compared with patients with native kidneys. Therefore, we postulated that bilateral nephrectomy ameliorated LVDD in our patients, and the improvement has been maintained throughout the follow-up. LV systolic function in our study was similar (LVEF >60%) in nephrectomized patients before KTx and in patients with native kidneys.

Bilateral nephrectomy in patients with ESRD included on the waiting list for KTx is an uncommon procedure and is performed mainly in patients with malignancies, with complications of autosomal-dominant polycystic kidney disease, and in specific cases as a prerequisite for KTx. This surgical procedure is associated with a significant burden for the patient. In addition, in patients with residual renal function, nephrectomy removes the beneficial effect of residual diuresis.

Numerous investigators have shown that bilateral nephrectomy reduces muscle sympathetic nerve activity and the total body noradrenaline spillover; therefore, it is a suitable model to test

the effects of complete sympathetic renal denervation (RD) on the cardiovascular system in patients after KTx.^{5,9}

Zoccali et al⁷ demonstrated an association between noradrenaline spillover and LVM in patients with ESRD, independent of other risk factors. Similarly, Penne et al³⁹ showed a correlation between the index of sympathetic overactivity and cardiovascular events independent of GFR and BP in patients with CKD.

Numerous clinical studies have shown that the reduction of renal sympathetic activity by RD in addition to BP lowering significantly reduced LVM and improved LV diastolic function in patients with resistant hypertension.^{40–41} An estimate based on the data from the Symplicity HTN-2 trial indicates that RD reduces cardiovascular mortality by 30% and all-cause mortality by 15%, compared with standard therapy predicted for 10 years.⁴² Patients with CKD were excluded from those studies despite evidenced hyperactivity of the sympathetic nervous system among such patients.

Hering et al⁶ performed a bilateral RD in 15 patients with resistant hypertension and CKD stages 3–4. The results of their study showed that RD was safe (did not deteriorate renal function) and improved BP control. Additionally, they observed an increase in hemoglobin concentrations and reduction in proteinuria and peripheral arterial stiffness index.

Our results of bilateral nephrectomy as a complete elimination of sympathetic activity encouraged us to perform RD in kidney transplant recipients with resistant hypertension. We performed a bilateral native renal nerve ablation using a radiofrequency catheter in a 58-year-old patient, 8 years after KTx, with refractory hypertension and cardiac hypertrophy.⁴³ The procedure caused a decrease in systolic and diastolic BP (measured with 24-hour ambulatory BP monitoring and average office BP) and reduced the LVMI by 24 g/m² as assessed by CMR. Kidney allograft function was stable during a 1-year follow-up. It might confirm the contribution of sympathetic activity from native kidneys to hypertension in renal transplant patients and also suggest that the denervation performed after KTx may be efficient in a selected group of recipients; however, the issue requires further studies.

RD in renal transplant patients may not be technically feasible owing to narrow renal arteries (<4 mm) and reduced renal blood flow in the native kidneys, which undergo progressive atrophy during dialysis treatment and posttransplant period. Schlaich et al⁴⁴ attempted to perform denervation in 12 patients with ESRD and uncontrolled BP but the procedure could not be performed in 3 cases due to atrophic renal arteries, while in another 2 patients, the ablation was aborted because of a rapidly rising temperature due to reduced renal blood flow.⁴⁴

Longer duration of renal replacement therapy makes RD less technically feasible; therefore,

the procedure should be performed in selected patients during the early period of dialysis treatment. Furthermore, early implementation of the procedure might improve patients' survival after transplantation. It was shown that high BP after dialysis sessions was associated with higher mortality in kidney transplant recipients.⁴⁵

RD has attracted considerable interest in recent years, which has weakened after the publication of the results from the Symplicity HTN-3 trial,⁴⁶ a blinded, randomized controlled trial, with a sham-operation group, including 535 patients with refractory hypertension. The study failed to reach the primary efficacy endpoint, defined as a reduction of systolic BP to 5 mmHg or higher after RD.⁴⁶ An incomplete ablation of the renal sympathetic nervous system might be one of the culprits of no response to the procedure.

Our findings on the human model of complete elimination of sympathetic overactivity support performing RD in patients with ESRD to prevent harmful effects of sympathetic hyperactivity on the cardiovascular system in kidney transplant recipients. It is particularly worth considering while interventions used to reduce LVH in patients with normal renal function are less successful in patients with ESRD.

Conclusions Renal transplant recipients who had undergone bilateral nephrectomy before KTx have lower LVM and lower grade of LVDD in a long-term follow-up after transplantation. The incidence of concentric LVH was also lower in these patients than in those with preserved native kidneys. Patients after bilateral nephrectomy had lower systolic BP and used fewer antihypertensive agents. These results might support performing native RD during maintenance dialysis and before KTx in order to improve cardiac structure and function.

Contribution statement MO, MB, and MK conceived the idea for the study. MO and MB contributed to the design of the research. All authors were involved in data collection. MO and DZ analyzed the data. All authors edited and approved the final version of the manuscript.

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Korzystny efekt obustronnej natywnej nefrektomii jako kompletnej denerwacji na masę i funkcję lewej komory u pacjentów po przeszczepie nerki

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SŁOWA KLUCZOWE

biorcy nerek,
dysfunkcja
rozkurczowa,
obustronna
nefrektomia, przerost
lewej komory

STRESZCZENIE

WPROWADZENIE Przerost mięśnia lewej komory serca jest czynnikiem ryzyka zgonu oraz chorób sercowo-naczyniowych u pacjentów po przebytych przeszczepie nerki. Rozwój przerostu lewej komory związany jest z nadmierną aktywacją układu współczulnego. Obustronna natywna nefrektomia jest przykładem całkowitej denerwacji nerek.

CELE Celem pracy była ocena efektu przedtransplantacyjnej obustronnej natywnej nefrektomii na masę i funkcję lewej komory w długoterminowej obserwacji pacjentów po przeszczepie nerki.

PACJENCI I METODY Grupa badana składała się z 32 biorców nerki po przebytej przedtransplantacyjnej obustronnej natywnej nefrektomii. Grupa kontrolna składała się z 32 biorców nerki z zachowanymi własnymi nerkami, dobranych pod względem wieku, płci, stężenia kreatyniny, poziomu współczynnika przesączania kłębuszkowego, terapii immunosupresyjnej i czasu leczenia nerkozastępczego. Wszystkim pacjentom wykonano badanie echokardiograficzne, a 16 z nich miało wykonany rezonans magnetyczny serca. U wszystkich pacjentów mierzono także ciśnienie tętnicze i parametry metaboliczne.

WYNIKI W porównaniu z grupą kontrolną grupa badana miała niższe wartości skurczowego ciśnienia tętniczego ($p = 0,048$) i była leczona mniejszą ilością leków hipotensyjnych ($p = 0,001$). Stężenia lipidów i hemoglobiny były podobne w obu grupach. Wskaźnik masy lewej komory oraz objętości lewego przedsionka był niższy w grupie badanej (odpowiednio $p = 0,001$ i $p = 0,004$). Masa lewej komory oceniana w rezonansie magnetycznym serca była również niższa w grupie badanej ($p < 0,001$). Łagodna dysfunkcja rozkurczowa lewej komory częściej występowała w grupie badanej ($p < 0,001$).

WNIOSKI W obserwacji długoterminowej pacjentów po przeszczepie nerki obustronna nefrektomia własnych nerek wykonana przed przeszczepem wiązała się z występowaniem niższego wskaźnika masy lewej komory, niższego wskaźnika objętości lewego przedsionka oraz niższym stopniem dysfunkcji rozkurczowej lewej komory. Pacjenci ci mieli niższe wartości skurczowego ciśnienia tętniczego oraz stosowali mniejszą liczbę leków hipotensyjnych.

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