Supplementary Online Content

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eMethods. Supplemental Methods

Study Design

Clinical and demographic data, body mass index (BMI) and smoking history (ever or never) were recorded. Ethnicity data was provided by the participants. This information was collected for baseline demographic data only. Assessment of co-morbidities included a history of (1) CVD (defined as non-fatal myocardial infarction, acute coronary syndrome requiring hospitalization, percutaneous coronary intervention, coronary artery bypass graft or stroke) or (2) diabetes (defined as use of oral hypoglycemic agent or insulin). Antihypertensive medication use was recorded.

Biochemical measures included highly sensitive-C-reactive protein (hs-CRP), albumin-corrected calcium, phosphate, intact parathyroid hormone (iPTH) and serum creatinine concentrations. Glomerular Filtration Rate was estimated by six-variable Modification of Diet in Renal Disease equation[17].
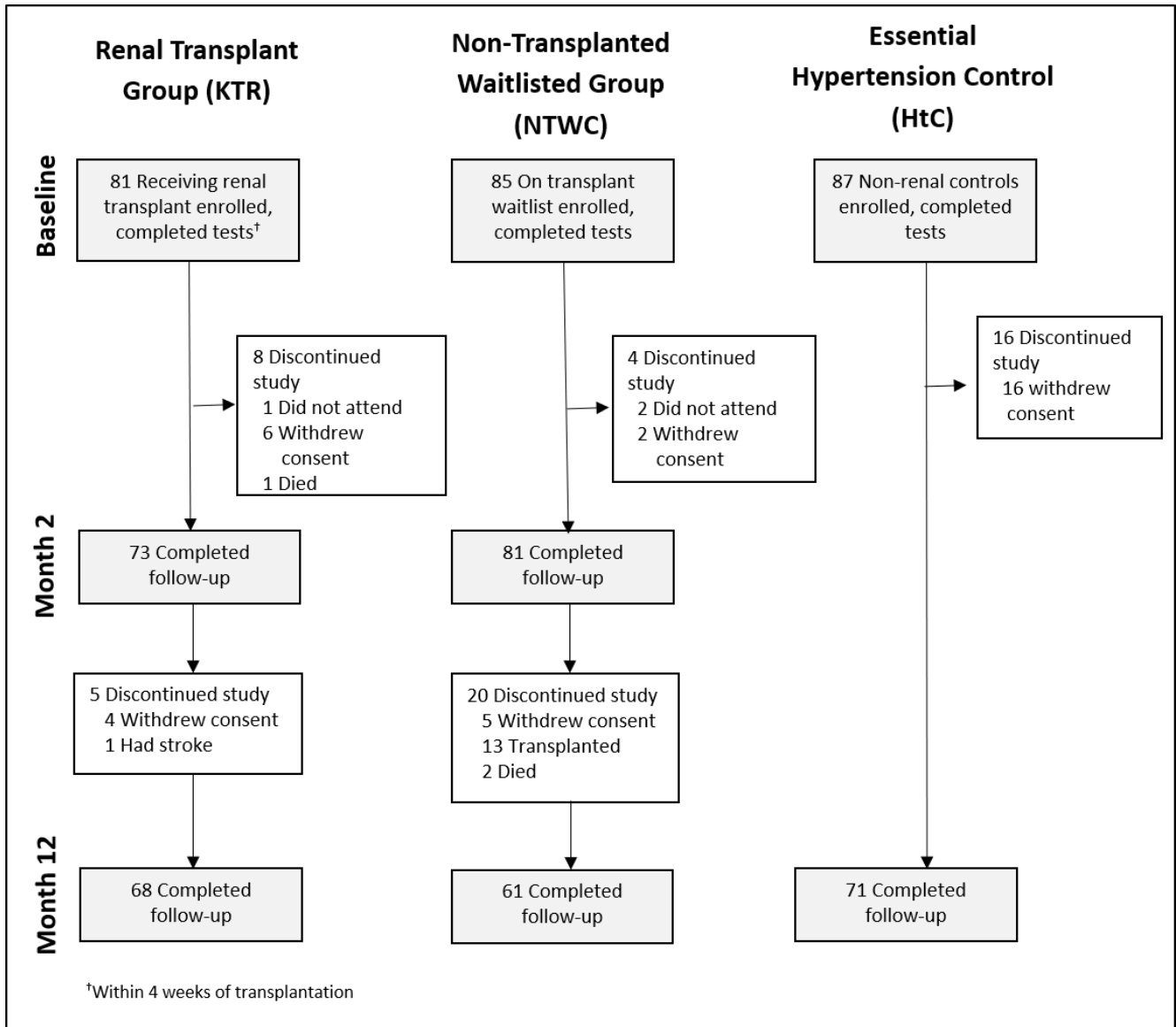
CPET assessment

CPET was conducted using an electronically braked, upright cycle ergometer incorporating individualized work rate and continuous 12-lead ECG recording. The equipment was calibrated prior to each assessment. Care was taken to ensure participants understood the maximal exercise test protocol and to brief against premature cessation of pedalling or incremental loading due to symptoms of lactic acidosis. Participants rested for 3 minutes followed by 3 minutes of unloaded pedalling prior to workload increments, continuing until symptom-limited volitional fatigue. Continuous breath-by-breath gas exchange analysis (VIASYS, MasterScreen CPX®, Hoechberg, Germany) was performed. The VO_2 at the point of anerobic threshold (VO_2AT) was determined by the V-slope method in conjunction with analyses of the ventilatory equivalents and end-tidal gas tension plots[20]. VO_2max was measured as the highest VO_2 achieved during the final 20-second averaging of peak exercise. An experienced blinded investigator carried out all exercise testing. Anerobic threshold and maximal ventilator reserve were indexed to body weight.

Echocardiography

Two-dimensional, Doppler and tissue Doppler transthoracic echocardiography were performed using Vivid 7 (GE Healthcare, Horten, Norway). Calculations included LV mass, LV volumes, left atrial (LA) volume and LVEF according to quantitative biplane Simpson's method. Mass and volume measures were indexed to body surface area. Sequential tissue Doppler imaging of the lateral and septal annular sites were obtained from the apical 4-chamber view. The ratio of early transmitral flow velocity to averaged annular (septal and lateral) mitral velocity (E/mean e') was taken as a non-invasive estimate of LV filling pressure. All measurements were undertaken according to the American Society of Echocardiography[21] and analyzed offline (EchoPac, GE Healthcare) by a blinded investigator. Brachial blood pressure was measured following 10 minutes of supine rest by oscillometric sphygmomanometer (Omron 705IT, Omron Healthcare, Kyoto, Japan).

Supplemental eFigure 1: Number of patients enrolled and completed study

Renal Transplant Group (KTR)

Non-Transplanted Waitlisted Group (NTWC)

Essential Hypertension Control (HtC)

Baseline

81 Receiving renal transplant enrolled, completed tests[†]

85 On transplant waitlist enrolled, completed tests

87 Non-renal controls enrolled, completed tests

8 Discontinued study
  1 Did not attend
  6 Withdrew consent
  1 Died

4 Discontinued study
  2 Did not attend
  2 Withdrew consent

16 Discontinued study
  16 withdrew consent

Month 2

73 Completed follow-up

81 Completed follow-up

5 Discontinued study
  4 Withdrew consent
  1 Had stroke

20 Discontinued study
  5 Withdrew consent
  13 Transplanted
  2 Died

Month 12

68 Completed follow-up

61 Completed follow-up

71 Completed follow-up

[†]Within 4 weeks of transplantation

Supplemental eFigure 2: Changes in echocardiographic measures before and after kidney transplantation (adjusted).
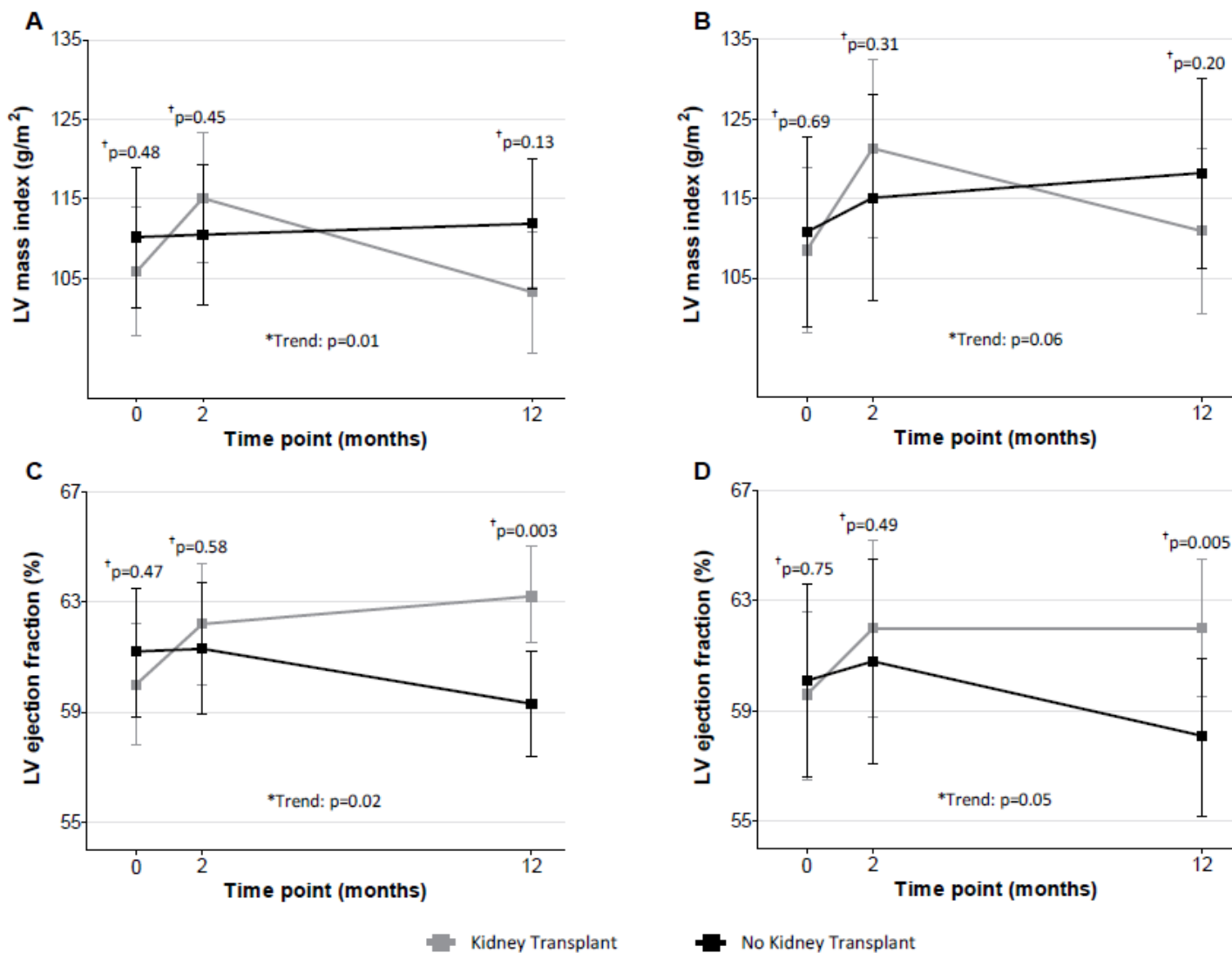
Changes in LV mass index and LV ejection fraction over time at baseline (before transplant), 2-months and 12-months follow-up (A, C, unadjusted comparison; B, D, adjusted for age, BMI, gender, smoking, diabetes, cardiovascular disease, duration of antihypertensive therapy, beta-blocker, hemoglobin and dialysis duration. †p-value for comparison between 2 groups at each respective time point. *p-value for comparison between 2 groups for changes over time.

SUPPLEMENTAL RESULTS

Supplemental eTable 1: Laboratory measures at baseline, 2-months and 12-months follow-up (unadjusted).

Variables	Patient Group	Time point			p-value[1]
		Baseline	**Month 2**	**Month 12**	
eGFR, ml/min/1.73m²	**Transplanted**	9.6 ± 4.1	55.3 ± 17.0	59.1 ± 18.4	<0.001
	Non-transplanted	8.9 ± 4.8	9.2 ± 5.0	9.1 ± 4.3	
	Control	92.5 ± 15.0	-	92.2 ± 18.2	
	p-value[2]	<0.001	<0.001	<0.001	
Calcium, mmol/L	**Transplanted**	2.2 ± 0.2	2.3 ± 0.2	2.3 ± 0.2	0.10
	Non-transplanted	2.3 ± 0.2	2.2 ± 0.2	2.3 ± 0.2	
	Control	2.2 ± 0.1	-	2.2 ± 0.1	
	p-value[2]	0.47	0.63	0.05	
Phosphate, mmol/L	**Transplanted**	1.7 ± 0.5	0.9 ± 0.2	0.9 ± 0.2	<0.001
	Non-transplanted	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	
	Control	1.1 ± 0.3	-	1.1 ± 0.2	
	p-value[2]	<0.001	<0.001	<0.001	
***iPTH**, pmol/l	**Transplanted**	3.0 ± 1.1	2.1 ± 0.6	2.0 ± 0.6	<0.001
	Non-transplanted	3.0 ± 1.2	3.1 ± 1.2	3.1 ± 1.0	
	Control	1.2 ± 0.4	-	1.3 ± 0.3	
	p-value[2]	<0.001	<0.001	<0.001	
***hsCRP**, mg/l	**Transplanted**	0.9 ± 1.3	0.3 ± 1.3	0.7 ± 1.2	0.07
	Non-transplanted	1.2 ± 1.3	1.2 ± 1.3	1.3 ± 1.3	
	Control	0.4 ± 1.0	-	0.4 ± 1.0	
	p-value[2]	<0.001	<0.001	<0.001	
Hemoglobin, g/dl	**Transplanted**	11.8 ± 1.4	11.9 ± 1.5	13.2 ± 1.5	<0.001
	Non-transplanted	11.7 ± 1.4	11.5 ± 1.2	11.2 ± 1.4	
	Control	14.2 ± 1.2	-	14.2 ± 1.1	
	p-value[2]	<0.001	0.08	<0.001	

Data are presented as mean $\pm$ standard deviation. *Log-transformed prior to analysis. [1]Comparison of (time *x* group) interaction between the two renal groups using repeated measures ANOVA. [2]Comparison between all available groups at each respective time point

Supplemental eTable 2: Baseline cardiovascular characteristics.

I) Functional cardiovascular parameters as assessed by cardiopulmonary testing (CPET).

Variables	Advanced CKD			Non-CKD Control (HtC)	p-value[2] (3-group comparison)
	Transplanted (KTR)	Non-transplanted (NTWC)	p-value[1] (KTR vs NTWC)		
VO$_2$max, ml min^{-1} kg^{-1}	20.7 ± 5.8	18.9 ± 4.7	0.03	24.9 ± 7.1	<0.001
VO$_2$max absolute, ml min^{-1}	1495.9 ± 553.1	1427.3 ± 391.6	0.42	1979.0 ± 725.2	<0.001
VO$_2$AT, ml min^{-1} kg^{-1}	11.8 ± 2.3	11.4 ± 2.3	0.23	14.8 ± 3.8	<0.001
VO$_2$AT absolute, ml min^{-1}	846.4 ± 235.1	859.0 ± 172.9	0.51	1168.5 ± 400.5	<0.001
Maximal work load, Watt	115.3 ± 50.7	105.2 ± 36.7	0.09	156.4 ± 61.8	<0.001
Endurance time, min	10.3 [9.0, 11.7]	10.3 [8.9, 11.7]	0.96	11.7 [10.5, 12.8]	<0.001
O$_2$ pulse, ml min^{-1}	10.1 [8.4, 12.9]	11.1 [8.8, 13.5]	0.63	11.7 [9.4, 14.7]	0.009
HRmax, beat min^{-1}	139.0 ± 22.9	132.1 ± 26.9	0.08	155.1 ± 18.5	<0.001
HRmax, %predicted	78.5 ± 12.0	77.5 ± 15.5	0.65	93.0 ± 9.8	<0.001
RER at peak exercise	1.2 ± 0.1	1.3 ± 0.1	0.02	1.2 ± 0.1	<0.001
RER at VO$_2$AT	0.9 ± 0.1	0.9 ± 0.1	0.05	0.9 ± 0.1	<0.001

II) Echocardiographic measures.

	Advanced CKD			Non-CKD Control (HtC)	p-value[2] (3-group comparison)
	Transplanted (KTR)	Non-transplanted (NTWC)	p-value[1] (KTR vs NTWC)		
LV mass index, g/m^2	104.9 ± 36.1	113.8 ± 37.7	0.07	87.8 ± 16.9	<0.001
LV geometry			0.67		<0.001
Normal geometry	14 (17.3)	17 (20.0)	-	27 (32.5)	-
Concentric remodelling	32 (39.5)	27 (31.8)	-	41 (49.4)	-
Concentric hypertrophy	24 (29.6)	31 (36.5)	-	7 (8.4)	-
Eccentric hypertrophy	11 (13.6)	10 (11.8)	-	0 (9.6)	-
LV diameter, cm	4.6 (0.7)	4.7 (0.7)	0.35	4.5 (0.5)	0.08
LVEDVI, ml/m^2	48.2 ± 16.7	51.0 ± 17.7	0.30	44.4 ± 10.2	0.02
LVESVI, ml/m^2	19.8 ± 8.6	20.6 ± 10.9	0.55	14.9 ± 4.6	<0.001
LV ejection fraction, %	60.1 ± 8.6	61.4 ± 8.9	0.43	66.1 ± 5.9	<0.001
*E/mean e'	2.0 [1.8, 2.3]	2.1 [1.9, 2.3]	0.34	2.1 [1.9, 2.2]	0.23
LA diameter, cm	3.5 ± 0.7	3.7 ± 0.8	0.03	3.7 ± 0.5	0.10
LA volume index, ml/m^2	25.8 [19.1, 30.5]	25.9 [18.9, 37.1]	0.17	25.4 [19.9, 28.7]	0.10

Data are presented as mean ± standard deviation, median [interquartile range], and n(%) for LV geometry. *Log-transformed prior to analysis. **I)** VO_2max, oxygen consumption at peak exercise; VO_2AT, oxygen consumption at the point of anerobic threshold; HR, heart rate at peak exercise; RER, respiratory exchange ratio of CO_2 production to O_2 consumption. **II)** LV, left ventricular; LVEDVI, LV end-diastolic volume index; LVESVI, LV end-systolic volume index; LA, left atrium; E/mean e' , the ratio of peak early transmitral ventricular filling velocity to averaged septal and lateral annular mitral velocity; LA, left atrium. P–value[1]: by independent-samples t-test or Kruskal-Wallis test for 2-group comparison between KTR and NTWC; P-value[2]: ANOVA, Kruskal-Wallis test or χ^2 (categorical variables) for 3-group comparison.

Supplemental eTable 3: Baseline characteristics of patients lost to follow-up during the 12-month study period

A) Demographic and laboratory data

Variables	Advanced CKD Transplanted (KTR)	Non-transplanted (NTWC)	Non-CKD Control (HtC)	p-value
Number of subjects	13	24	16	
Male, n (%)	4 (30.7)	11 (45.8)	6 (37.5)	0.66
Age, years	41.1 ± 14.6	48.1 ± 14.3	51.6 ± 9.1	0.10
BMI, kg/m^2	25.0 ± 3.7	26.5 ± 5.4	28.3 ± 4.2	0.16
Hypertension, n (%)	10 (76.9)	20 (83.3)	16 (100)	0.15
Smoking (Ever), n (%)	5 (38.5)	12 (50.0)	8 (50.0)	0.77
Diabetes, n (%)	2 (15.4)	3 (12.5)	0 (0)	-
Cardiovascular disease, n (%)	1 (7.7)	2 (8.3)	0 (0)	-
Dialysis status, n (%)				-
Predialysis	3 (23.1)	4 (16.7)	-	-
Hemodialysis	9 (69.2)	17 (70.8)	-	-
Peritoneal dialysis	1 (7.7)	3 (12.5)	-	-
Dialysis duration, months	41.9 ± 35.2	37.5 ± 40.3	-	-
Laboratory				-
Creatinine, μmol/l	485.0 [460.0, 768.0]	674.0 [428.5, 754.0]	67.0 [59.0, 84.0]	<0.001
eGFR, ml/min/1.73m^2	9.9 ± 4.5	9.0 ± 4.9	91.6 ± 10.9	<0.001
Albumin, g/l	44.0 [41.0, 47.0]	44.0 [41.0, 46.5]	47.0 [46.0, 47.0]	0.03
*hsCRP, mg/l	1.3 ± 0.9	1.3 ± 1.4	0.2 ± 0.9	0.01
Hemoglobin, g/dl	11.9 [11.2, 13.2]	11.9 [10.8, 12.7]	13.9 [12.8, 14.6]	<0.001

BMI, body mass index; eGFR, estimated glomerular filtration rate; hsCRP, highly sensitive C-reactive protein. Data are presented as mean ± standard deviation, median [interquartile range] or frequencies (%).*Log-transformed prior to analysis. P–value by ANOVA, Kruskal-Wallis or χ^2-test for 3-group comparison.

B) Cardiovascular parameters as assessed by CPET and echocardiography

Variables	Advanced CKD			Non-CKD Control (HtC)	p-value[2] (3-group comparison)
	Transplanted (KTR)	Non-transplanted (NTWC)	p-value[1] (KTR vs NTWC)		
VO$_2$max, ml min^{-1} kg^{-1}	18.3 ± 5.5	18.4 ± 4.8	0.99	22.1 ± 5.0	0.07
VO$_2$max absolute, ml min^{-1}	1245.6 ± 416.1	1339.7 ± 420.1	0.52	1724.4 ± 561.6	0.02
VO$_2$AT, ml min^{-1} kg^{-1}	11.0 ± 2.6	11.3 ± 2.7	0.73	12.7 ± 2.2	0.16
VO$_2$AT absolute, ml min^{-1}	751.8 ± 222.0	815.3 ± 181.8	0.36	988.5 ± 271.9	0.02
RER at peak exercise	1.2 ± 0.1	1.3 ± 0.1	0.06	1.2 ± 0.1	0.05
LV mass index, g/m^2	91.2 ± 47.2	115.9 ± 44.9	0.13	92.3 ± 17.0	0.12
LV ejection fraction, %	61.5 ± 7.6	61.6 ± 9.8	0.98	64.7 ± 5.3	0.51
*E/mean e'	2.1 ± 0.3	2.2 ± 0.3	0.29	2.0 ± 0.2	0.18

Data are presented as mean $\pm$standard deviation. *Log-transformed prior to analysis. VO$_2$max, oxygen consumption at peak exercise; VO$_2$AT, oxygen consumption at the point of anerobic threshold; RER, respiratory exchange ratio of CO_2 production to O_2 consumption. LV, left ventricular; E/mean e', the ratio of peak early transmitral ventricular filling velocity to averaged septal and lateral annular mitral velocity. P–value[1]: by independent-samples t-test for 2-group comparison between KTR and NTWC; P-value[2]: ANOVA for 3-group comparison.

Supplemental eTable 4: Cardiovascular functional and hemodynamic measures

Variables	Patient Group	Time point			p-value[1]
		Baseline	Month 2	Month 12	
Cardiovascular functional changes					
HRmax, beat min^{-1}	Transplanted	139.0 ± 22.9	142.8 ± 23.4	140.5 ± 25.8	0.25
	Non-transplanted	132.1 ± 26.9	130.8 ± 24.0	124.4 ± 20.9	
	Control	155.1 ± 18.5	-	152.3 ± 19.3	
	p-value[2]	<0.001	0.002	<0.001	
HRmax, % predicted	Transplanted	78.5 ± 12.0	80.5 ± 11.9	79.8 ± 12.8	0.48
	Non-transplanted	77.5 ± 15.5	77.9 ± 15.7	74.0 ± 12.0	
	Control	93.0 ± 9.8	-	92.3 ± 10.6	
	p-value[2]	<0.001	0.26	<0.001	
RER at peak exercise	Transplanted	1.2 ±0.1	1.3 ± 0.1	1.2 ± 0.1	0.15
	Non-transplanted	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	
	Control	1.2 ± 0.1	-	1.2 ± 0.1	
	p-value[2]	0.04	0.49	0.003	
Resting hemodynamic measures					
Systolic BP, mmHg	Transplanted	136.2 ± 20.2	138.8 ± 14.8	137.4 ± 14.8	0.26
	Non-transplanted	133.1 ± 20.8	130.5 ± 21.2	135.1 ± 19.0	
	Control	141.5 ± 13.2	-	138.8 ± 13.1	
	p-value[2]	0.01	0.01	0.40	
Diastolic BP, mmHg	Transplanted	81.8 ± 11.7	80.8 ± 11.0	81.4 ± 10.5	0.74
	Non-transplanted	78.7 ± 12.3	78.4 ± 12.5	80.7 ± 12.8	
	Control	85.7 ± 9.9	-	82.8 ± 8.5	
	p-value[2]	<0.001	0.22	0.49	
Mean arterial pressure, mmHg	Transplanted	100.0 ± 12.9	100.1 ± 9.6	100.0 ± 9.6	0.56
	Non-transplanted	96.8 ± 13.8	95.8 ± 14.0	98.8 ± 13.5	
	Control	104.3 ± 9.5	-	101.5 ± 8.2	
	p-value[2]	<0.001	0.03	0.34	

Data are presented as mean with standard deviation. *Log-transformed prior to analysis. [1]Comparison of time *x* group interaction between the two renal groups using ANOVA. [2]Comparison between all available groups at each respective time point