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RENAL TRANSPLANTATION IMPROVES CARDIAC FUNCTION

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Abstract
There is mounting evidence that chronic kidney disease is a major contributor to severe cardiac
damage. Although renal transplantation (RT) is an effective strategy in patients with end–stage
renal disease (ESRD), the effects on cardiac function remain unclear. This study determined the
effects of RT on left ventricular (LV) morphology and function in a retrospective longitudinal anal-
ysis of echocardiographic data collected in RT ($n=17$) and maintenance hemodialysis (HD ; $n=19$)
groups from 2003 to 2008.
Echocardiographic data obtained within 6 months and at over 3 years were compared with the data
before transplantation. Improved blood pressure and anemia were observed with RT, but not HD.
In contrast to the HD group, the left ventricular mass index (LVMI) in the RT group was de-
creased from 195.2 ± 52.1 to 162.5 ± 30.8 g/m^2 ($p<0.05$). In addition, the LV ejection fraction
was improved in the RT group from 63.0 ± 17.1% to 79.5 ± 3.3% ($p<0.01$), but not in the HD
group. The rate of reduction of LVMI in the RT group was greater in patients with good control of
hemoglobin.
In conclusion, RT has beneficial effects on LV hypertrophy and function, as well as on ESRD.

Key words : Renal transplantation, Left ventricular hypertrophy, Left ventricular mass
index

Introduction

Chronic kidney disease (CKD) is a risk factor for the
composite outcome of all–cause mortality and cardiovas-
cular disease in the general population[1,2]. The Athero-
sclerosis Risk in Communities Study, Cardiovascular
Health Study, Framingham Heart Study, and Framingham
Offspring Study all provide evidence that CKD is an inde-
pendent risk factor for adverse cardiovascular out-

comes[3,4]. Patients with end–stage renal disease (ESRD),
particularly patients on dialysis, have poor outcomes.
Cardiovascular mortality rates in dialysis patients are
10~30 times greater than in the general population[5,6].
According to the Japanese Society for Dialysis Therapy
survey, there are more than 260,000 patients in Japan on
dialysis, or one person in 500, and this number is expect-
ed to continue to increase.

It has been reported that 75% of patients with ESRD
starting hemodialysis have left ventricular hypertrophy
(LVH), which is a well–established predictor of cardiovas-
cular risk in both patients with ESRD[7] and the general
population[8]. Hypertension is the best–known risk factor
for LVH[9]. In the myocardium, pressure overload leads to
concentric hypertrophy, while volume overload causes
eccentric hypertrophy[10]. The causes of hypertension in

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patients on dialysis are perturbations of the renin-angiotensin system, and volume overload due to decreased urination and renal anemia. These factors also influence the cardiac morphology.

In recent years, angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) have been prescribed for patients with CKD to reduce blood pressure and to protect renal function[11,12]. These medications are known to regress LVH[13,14]. However, it is difficult to use ACE-I or ARB for patients with ESRD because these medications exacerbate renal dysfunction and hyperkalemia.

In patients with ESRD, renal transplantation (RT) is the preferred strategy for improving the outcome and quality of life. In Japan, RT is performed in about 1,000 cases annually[15]. The 1- and 5-year graft survival rates are about 90 and 70%, respectively. The 5-year patient survival rate is about 90%. These data imply RT has a better prognosis than HD. However, very few attempts have been made at the effect of RT on cardiac function.

This study investigated the impact of renal transplantation on left ventricular morphology and function.

Subjects and Methods

Patients

This retrospective longitudinal analysis of echocardiographic data examined the structural changes in left ventricular mass (LVM) from the pre-dialysis stage to the post-transplant years. This study included 19 patients on maintenance hemodialysis (HD group, female : male =8 : 11) and 17 patients who underwent renal transplantation (RT group, female : male=9 : 8) between 2003 and 2008 in Akita, Japan. The RT group was subdivided based on whether the rate of reduction in the LVMI during the post-transplant period was <30% or >30%.

Table 1(B) summarizes the timing of the echocardiograms examined during the study. Echocardiograms were obtained in the immediate pre-transplant period (period 0), after 6 months (period 1), within 6 to 36 months (period 2), and 36 months or more after transplantation (period 3). In the HD group, month 0 indicates the first echocardiogram. Period 0 equaled month 0. The early post-transplant period was uneventful in all patients.

Echocardiographic Measurements

Acuson Sequoia or Aloka 6500 echocardiography machines with a 5-MHz probe were used to obtain tracings that were recorded on sVHS video tape. Echocardiography was performed in the 45° left lateral position, and views that best delineated the interventricular septum and left ventricular posterior wall were chosen in the parasternal long axis view. LVM was calculated using the anatomically validated formula of Devereux and Reicheck[16], as follows :

$$LVM \text{ (g)}=1.04 \text{ } [(IVS+PWLV+LVDd)^3-(LVDd)^3]-13.6$$

where *LVM* is the left ventricular mass (g), *IVS* is the interventricular septal thickness (cm), *PWLV* is the thickness of the posterior wall of the left ventricle (cm), and *LVDd* is the left ventricular internal dimension at the end of diastole (cm). LVM was indexed for the body surface area (BSA ; m^2), as described by Du Bois *et al.*[17].

The ejection fraction (EF), an indicator of left ventricular systolic function, was calculated using the Teicholz formula. The ratio of the peak E wave to the A wave of mitral valve inflow, parameters of left ventricular diastolic function, were evaluated using Doppler ultrasound.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows. Data are expressed as mean values ± SD. The statistical evaluation was performed using Student's paired *t*-test and one-way analysis of variance (ANOVA) followed by a *post hoc* test, with $p<0.05$ considered statistically significant.

Results

Patient characteristics

The characteristics of the study population are summarized in Table 1. The HD group was 42 to 81 years old (mean age 59.7 years) and the RT group was 25 to 65 years old (mean age 44.5 years). The median time on dialysis was 5.2 ± 6.4 years for the HD group and 6.0 ± 1.9 years for the RT group.

Cardiovascular risk factors in the HD group were ane-

Table 1.
(A) Baseline characteristics of the hemodialysis and renal transplant patients.

	HD group	RT group	P value
Gender (female/male)	8/11	9/8	0.773
Age (year)	59.7±10.8	44.5±12.5	<0.01
BMI (kg/m^2)	21.6±3.8	22.1±3.8	0.999
Systolic BP (mmHg)	143.5±17.1	148.4±25.9	0.508
Diastolic BP (mmHg)	78.7±13.1	90.6±12.2	<0.05
Dialysis period (year)	4.9±5.1	6.5±7.0	0.500
Hemoglobin (g/dl)	10.6±2.2	10.1±1.8	0.365
BUN (mg/dl)	49.1±14.2	48.3±19.7	0.879
Creatinine (mg/dl)	8.9±3.8	10.3±3.4	0.287
Uremic acid (mg/dl)	5.8±1.8	5.6±1.6	0.563
HbA1c (%)	6.3±1.5	5.4±1.1	0.066
Medication (%) ACE-I/ARB	73.6	41.2	0.050
β-blocker	31.5	11.8	0.162
Ca antagonist	84.0	64.7	0.187
α-blocker	36.8	5.9	<0.05
tEPO	31.5	5.9	0.095

(B)

Period 0	Period 1	Period 2	Period 3
0	6	36	months
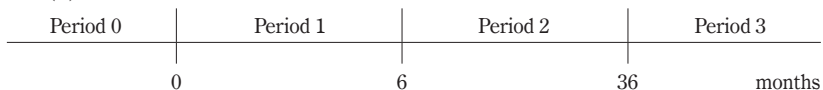
Values are means ± SD. BMI, body mass index ; BP, blood pressure ; ACE-I, angiotensin-converting enzyme inhibitors ; ARB, angiotensin II receptor blockers ; tEPO, erythropoietin therapy. P values are evaluated by Student's paired t-test. (B) The timing of the echocardiography examinations. In the RT group, month 0 means the date of the renal transplant operation. Echocardiography in period 0 was performed as a preoperative examination. In the HD group, month 0 means the first echocardiography examination. Period 0 is equal to month 0.

mia (in 66%), hypertension (58%), diabetes (42%), hyperuricemia (24%), and hypercholesterolemia (19%). In the RT group, they were anemia (in 82%), hypertension (64%), diabetes (12%), hyperuricemia (12%), and hypercholesterolemia (12%). Antihypertensive therapy was taken by 95% of the HD group and 76% of the RT group. The major classes of antihypertensive drugs were prescribed in the HD and RT groups, including angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) (73.6% vs. 41.2% in the respective groups), β-blockers (31.5% vs. 11.8%), calcium antagonists (84.0% vs. 64.7%), and α-blockers (36.8% vs. 5.9%). All of the patients in the RT group took systemic

steroids or immunosuppressive drugs.

Echocardiography

Table 2 shows the echocardiographic parameters during the follow-up period. At period 0, the LVMI in both groups did not differ statistically. In the HD group, the LVMI at period 0 was 193.1 ± 57.7 g/m^2, and it increased to 219.7 ± 53.3 g/m^2 (p<0.05) at period 3 (Fig. 1A). The wall thickness was correlated with LVMI. The interventricular septum thickness (IVST) and posterior wall thickness (LVPWT) were both increased. In the RT group, the LVMI at period 0 was 195.2±52.1 g/m^2 and it decreased to 162.5 ± 30.8 g/m^2 (p<0.05) at period 3.

Table 2.　Echocardiographic parameter comparisons during periods 0 to 3.

	HD group					RT group				
	Period 0	Period 1	Period 2	Period 3	P value	Period 0	Period 1	Period 2	Period 3	P value
LVDd (mm)	51.6±6.6	51.1±8.9	50.9±6.4	49.4±5.1	0.804	51.4±4.2	45.9±4.8	47.9±5.3	41.5±5.4	<0.01
LVDs (mm)	32.1±7.1	34.1±7.9	31.5±6.5	30.3±6.3	0.694	32.7±4.5	30.7±6.6	32.7±8.5	22.3±3.3	<0.01
LVMI (g/m²)	193.1±57.7	183.5±58.4	204.7±63.6	219.7±53.5	0.535	195.2±52.1	166.5±45.9	144.8±37.4	162.5±30.8	<0.05
LAD (mm)	43.2±8.1	45.1±9.1	47.5±6.5	47.1±8.4	0.647	40.9±6.7	41.2±7.4	41.6±6.1	40.3±7.7	0.818
EF %	66.0±14.1	63.2±8.5	64.5±18.6	68.0±11.1	0.539	63.0±17.1	55.8±25.8	63.0±12.9	79.5±3.3	<0.01
E/A	1.15±0.62	0.95±0.34	0.98±0.17	0.69±0.32	0.054	0.92±0.28	0.80±0.22	1.03±0.22	0.95±0.19	0.154
PASP (mmHg)	18.9±10.9	20.3±12.5	24.0±9.7	26.4±12.9	0.457	23.3±6.0	20.9±8.3	16.7±1.5	16.9±0.8	0.05

Values are means ± SD.　LVDd, left ventricular diameter in diastole ; LVDs, LVD in systole ; LVMI, LV mass index ; LAD, left atrial diameter ; EF, ejection fraction ; E/A, the ratio of the peak E wave to the A wave mitral valve inflow using Doppler ultrasound ; PASP, estimated pulmonary artery systolic pressure. P values are evaluated by ANOVA.
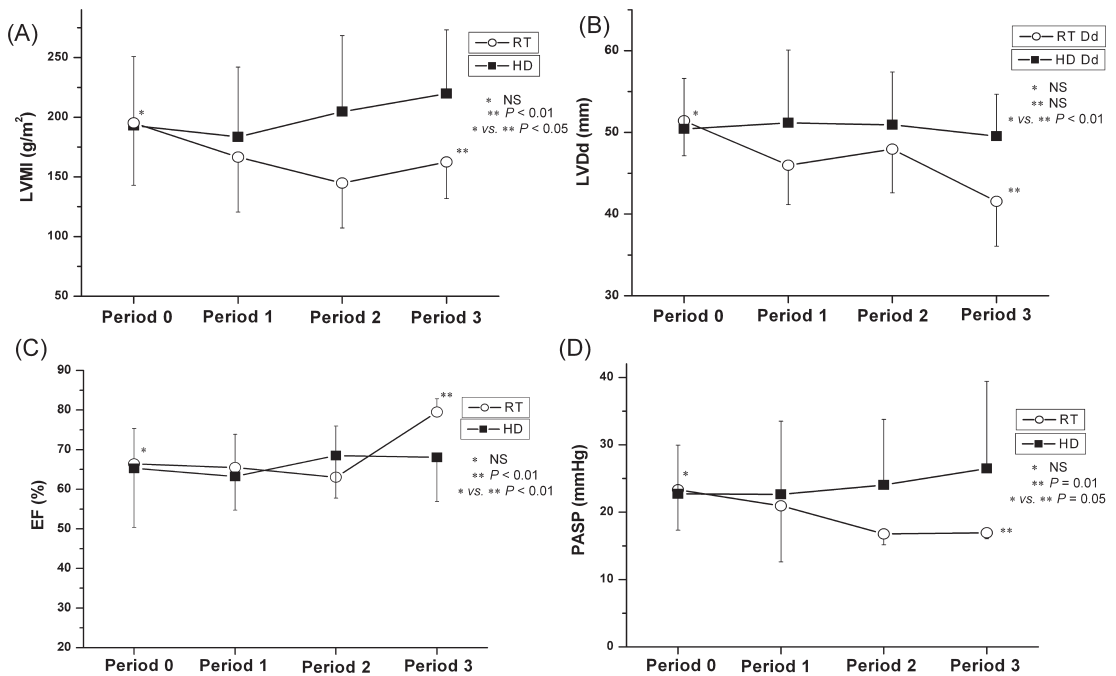

Fig. 1.　Comparison of echocardiographic parameters in the RT and HD groups.　Changes in LVMI (A), LVDd (B), EF (C) and PASP (D) during follow up.　Values are means ± SD.　NS, not significant at $p<0.05$.　＊ HD $vs.$ RT at period 0.　＊＊ HD $vs.$ RT at period 3.　＊ $vs.$ ＊＊ Period 0 $vs.$ period 3 in RT group.
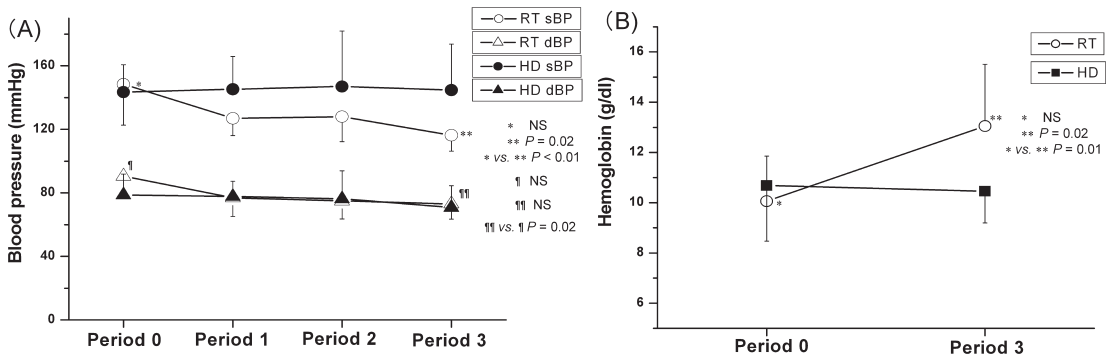
Fig. 2. Changes in blood pressure and hemoglobin after renal transplantation. Changes in blood pressure (A) and hemoglobin (B) after renal transplantation. Values are means ± SD. NS, not significant at $p<0.05$. *HD *vs*. RT at period 0. ** HD *vs*. RT at period 3. * *vs*. ** Period 0 *vs*. period 3 in RT group. ¶ HD *vs*. RT at period 0. ¶ ¶ HD *vs*. RT at period 3. ¶ *vs*. ¶ ¶ Period 0 *vs*. period 3 in RT group.
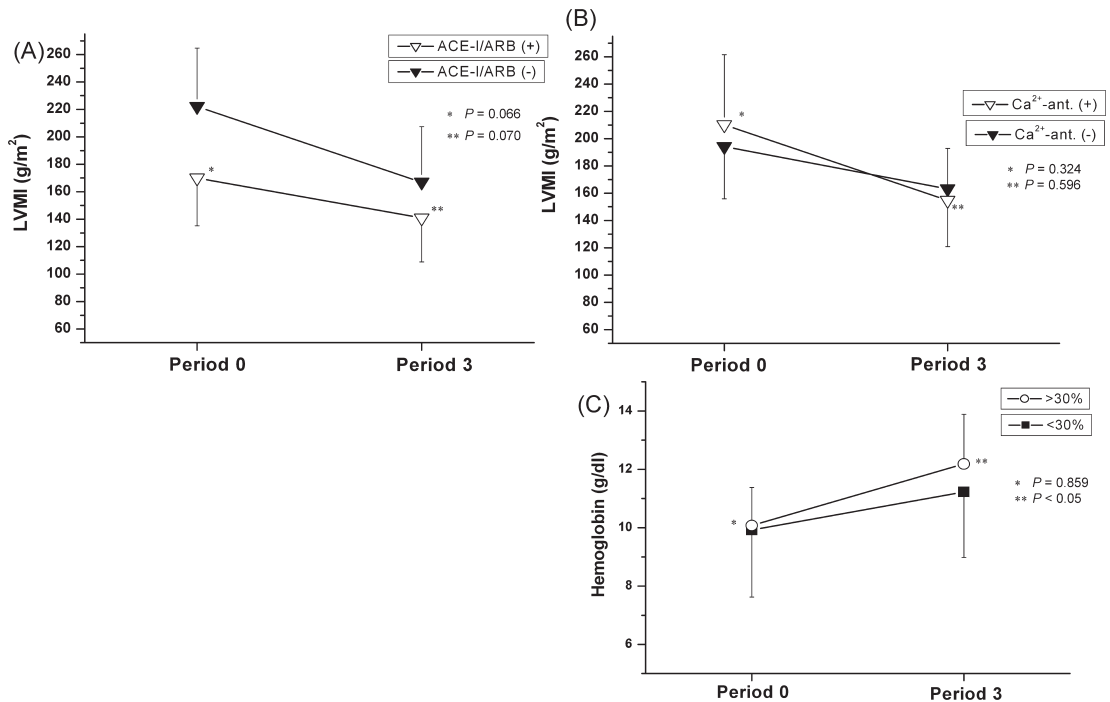

Fig. 3. Changes in LVMI in the RT patients subdivided based on antihypertensive drugs ; ACE–I/ ARB (A) and Ca^{2+}-antagonists (B). Comparison of the hemoglobin pre– and post–transplantation in RT patients subdivided based on the rate of reduction in LVMI (C). Values are means ± SD. NS, not significant at $p<0.05$. * HD *vs.* RT at period 0. ** HD *vs.* RT at period 3.

The LV wall thickness tended to decrease and the left ventricular diastolic diameter (LVDd) also decreased in the RT group (Fig. 1B). The changes in left atrial diameter (LAD) and left ventricular systolic diameter (LVDs) were not significant in either group.

Cardiac function

The baseline left ventricular ejection fraction (EF) was normal in both groups. In the HD group, LVEF did not change significantly during the follow-up period, while in the RT group, LVEF increased from 63.0±17.1% to 79.5 ± 3.3% ($p < 0.01$) (Fig. 1C). The E/A ratio during period 3 was normal in the RT group, whereas it showed an abnormal relaxation pattern in the HD group. The pulmonary artery systolic pressure estimated from the tricuspid regurgitation velocity using Doppler ultrasound was improved in the RT group compared with the HD group (Fig. 1D).

Biochemical and physiological parameters

After transplantation, the systolic blood pressure (BP) decreased from 148.4 ± 25.9 to 116.2 ± 10.0 mmHg ($p < 0.01$) (Fig. 2A). Similarly, the diastolic blood pressure decreased from 90.6 ± 12.2 to 73.1 ± 9.6 mmHg ($p = 0.02$). Anemia and HbA1c were also improved (Fig. 2B).

Figure 3 shows the changes in LVMI according to the antihypertensive drugs taken. The LVMI of the patients taking ARB was lower than that of the patients not taking ARB at period 0, and the difference was greater at period 3 (Fig. 3A). By contrast, there was not as great a difference between the patients taking or not taking Ca^{2+}-antagonists (Fig. 3B).

When the RT group was subdivided based on the reduction in LVMI, 62.5% of the patients had an LVMI reduction >30% (>30% group) at period 3. Comparing the post- and pre-transplant periods, the mean systolic BP, diastolic BP, blood urea nitrogen (BUN), and creatinine were improved in both the >30% and <30% groups. Hemoglobin and HbA1c were improved significantly in the >30% group compared with the <30% group (Fig. 3C).

Discussion

Cardiovascular disease is the second-leading cause of death in Japan. Recently, chronic kidney disease (CKD) has been a focus of attention as a risk factor for cardiovascular disease[5]. Analysis of more than 26,000 people in the Atherosclerosis Risk in Communities Study, Framingham Heart Study, Framingham Offspring Study, and Cardiovascular Health Study showed that a decreased glomerular filtration rate (GFR) is a potent risk factor for increased mortality and cardiovascular events[2]. Moreover, the reported mortality of cardiovascular disease was greater in CKD than the rate of progression to ESRD in a 5-year follow-up[18]. In Japan, more than 260,000 patients are on dialysis or one person in 500. This number is expected to continue to increase by 10,000 annually. Based on data from the Japanese Society for Dialysis Therapy, the cardiovascular mortality of dialysis patients is nearly 40% of all deaths.

The main cause of ESRD is diabetic nephropathy, although the nephrosclerosis caused by hypertension is increasing rapidly. Patients with ESRD have a high prevalence of hypertension. Furthermore, changes in blood pressure and preload during dialysis therapy are unavoidable. In this study, antihypertensive drugs were used by 95% and 76% of the patients in the HD and RT groups, respectively. Hypertension leads to pressure overload, which results in concentric hypertrophy of the heart[10]. In addition, 73.6% of the HD patients and 82.3% of the RT patients were found to have anemia at baseline. Anemia contributes to volume overload, which causes eccentric hypertrophy of the heart[10]. Dialysis is associated with a much higher incidence of left ventricular hypertrophy (LVH).

Left ventricular hypertrophy itself is a strong, independent predictor of death and cardiac failure that is present in about 42% of patients starting ESRD therapy[7]. In our study, LVH was present in about 50% of the patients in both groups. In the HD group, the echocardiograms showed that LVMI and wall thickness increased during the follow-up period, without changes in EF and LV volume. Patients in both groups, and particularly in the HD group, were being treated for hypertension with Ca^{2+} antagonists and ACE-I/ARB. ACE-I/ARB are effective for

cardioprotection and renoprotection[19,20]. These results suggest that it is difficult for patients on HD to control changes in blood pressure and preload during dialysis. By contrast, LVMI and wall thickness decreased significantly in the RT group, while EF and LV volume improved. Renal transplantation is an effective strategy for regression of LVH in patients with ESRD.

The number of renal transplants is increasing annually[15]. In Japan, more than 1,000 patients undergo renal transplantation each year. According to the Japan Society for Transplantation survey, the 5-year survival rate of living renal transplantation is 90%, and that of cadaveric renal transplantation is 84%. The graft survival rate has also improved since 1992, when tacrolimus was introduced. From 1992 to 2001, the 1-year graft survival of living RT (cadaveric RT) was 94.4% (85.7%) and the 5-year survival was 83.4% (69.2%). These results suggest that RT patients have a better prognosis than HD patients. Other advantages of renal transplantation are improved quality of life and restored physiological metabolism. In our study, blood pressure stabilized postoperatively, and anemia, BUN, creatinine, uremic acid, and HbA1c were improved. The echocardiograms showed significant improvements in cardiac condition, including an increased EF, normalized E/A ratio, and decreased LVMI, LV volume, and pulmonary artery systolic pressure (PASP). The biggest problem with RT is taking immunosuppressive drugs and steroids. The leading cause of death for RT patients is infection. In addition, immunosuppressive drugs increase the rate of carcinogenesis, and steroids have many side effects, including diabetes mellitus, hypertension, immunosuppression, thrombosis, gastric ulcers, and osteoporosis. Cardiovascular disease is the second most common cause of death for RT patients. However, these problems should be ameliorated with treatment that involves the close coordination and cooperation of the internist and urologist.

Our study also indicated the importance of antihypertensive therapy before RT. In the patients taking ACE-I/ARB before transplant, the LVMI was much lower than in the patients not taking ACE-I/ARB. By contrast, there was little difference in the LVMI before and after RT between the patients taking or not taking Ca^{2+}-antagonists. These results show the anti-hypertrophic effect of ACE-I/ARB that has been reported in some studies. ACE-I/ARB is recommended as first-line therapy for patients with ESRD.

When the RT group was subdivided based on the ratio of the reduction in LVMI, 20% of the patients had a high rate of reduction of LVMI at period 2 and 62.5% at period 3. The patients with a high rate of reduction in LVMI showed good control of blood pressure, hemoglobin, and HbA1c during follow-up. These results suggest that RT requires much time to reduce the LVMI, and strict treatment of hypertension and anemia after transplantation will improve RT patient outcome.

HbA1c was improved in RT patients compared with HD patients. HbA1c was also decreased in the patients with a high rate of reduction in LVMI. Why did the improvement of HbA1c correlate with reduction of LVMI? One possible explanation for the mechanism is that RT reduces insulin resistance with improved microcirculation.

In summary, our study demonstrated an improvement in LVH and cardiac condition after renal transplantation. These findings were correlated with controlling the risk factors of high blood pressure and anemia. We must be sure to treat these risk factors before and after RT. We conclude that renal transplantation is an effective treatment strategy for ESRD that improves LVH and cardiac function.

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