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Original article

Impact of renal insufficiency on long-term clinical outcome in patients with heart failure treated by cardiac resynchronization therapy

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ABSTRACT

Background: Renal insufficiency is recognized as a predictor of mortality and adverse outcome in heart failure (HF) patients. However, the long-term clinical outcome of cardiac resynchronization therapy (CRT) in Japanese HF patients with renal insufficiency remains uncertain.
Methods: We evaluated 67 consecutive patients who underwent CRT at our hospital. The patients were divided into two groups according to a baseline estimated glomerular filtration rate (e-GFR) cut-off value of 50 ml/min, which is defined as the time at which patients should be referred to a nephrologist, by the Japanese Society of Nephrology. Follow-up echocardiographic findings and renal function were examined at 3–6 months after CRT. Then, we compared long-term clinical outcomes between the two groups, and analyzed the effect of CRT on renal function, echocardiographic parameters and cardiac survival.
Results: During a mean follow-up period of 30.3 months, patients with advanced renal insufficiency (e-GFR < 50 ml/min) had significant higher all-cause mortality (log-rank $p = 0.033$) and higher cardiac mortality combined with HF hospitalization (log-rank $p = 0.017$) than patients with e-GFR ≥ 50 ml/min. Multivariate analysis revealed that advanced renal insufficiency was an independent predictor of cardiac mortality combined with HF hospitalization (odds ratio = 3.01, $p = 0.008$). Subgroup analysis in the baseline advanced renal insufficiency group revealed that patients with preserved renal function by CRT (<10% reduction in e-GFR) had a higher rate of decrease of left ventricular end-systolic diameter (−14.0% vs. −0.8%, $p = 0.023$) and lower cardiac mortality combined with HF hospitalization (log-rank $p = 0.029$) compared with patients with deterioration of renal function (≥10% reduction in e-GFR).
Conclusions: The present study suggests that advanced renal insufficiency is quite useful for the prediction of worsening clinical outcomes in HF patients treated by CRT. Preservation of renal function by CRT brings about better cardiac survival through prevention of adverse cardiac events, even in HF patients with advanced renal insufficiency.

Introduction

Cardiac resynchronization therapy (CRT) improves left ventricular function, symptoms, exercise capacity as well as endothelial function and reduces both morbidity and mortality in patients with advanced heart failure [1–4]. In the Comparison of Medical Therapy, Pacing, and Defibrillation Heart Failure (COMPANION) trial, all-cause mortality was reduced in patients on optimal medical therapy together with CRT, compared with optimal medical therapy alone [5]. About two-thirds of hospitalized heart failure patients have renal insufficiency [6]. Heart failure and renal insufficiency actively interact pathophysiologically with each other, and renal insufficiency is recognized as an independent predictor of mortality and adverse outcome in heart failure patients [7,8]. Estimated glomerular filtration rate (e-GFR) is used as the best value for estimating renal function, and recently, the Japanese GFR estimated equation for the evaluation of Japanese renal function was defined by the Japanese Society of Nephrology in 2008. The relationship between renal insufficiency and clinical outcomes in patients with CRT and the effect of CRT on renal function have not been fully studied [9–13]. Especially, these evaluations still have not been carried out in Japanese heart failure patients,

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using the Japanese GFR estimated equation as an index of renal function. We sought to analyze the impact of renal insufficiency on long-term clinical outcomes in heart failure patients treated with CRT. Furthermore, we determined the effect of CRT on renal function, especially focusing on heart failure patients with renal insufficiency by analyzing cardiac survival.

Materials and methods

Study population

We evaluated heart failure patients who underwent CRT at our hospital between 2004 and 2008. The selection criteria for CRT included advanced symptomatic heart failure despite optimal medical therapy, which was applied to the patients according to the current guidelines and clinical standards. A CRT-P (pacemaker) or CRT-D (defibrillator) was implanted transvenously, and a left ventricular (LV) pacing lead was inserted through the coronary sinus and positioned as far as possible in the venous system, preferably in a posterolateral vein. Optimization of the devices, such as atrioventricular delay, was performed by echocardiography. Patients who had no data on baseline e-GFR just before CRT implantation were excluded. Accordingly, a total of 67 patients with baseline data undergoing transvenous pectoral implantation of a CRT-P or CRT-D were included in the present analysis. e-GFR was calculated using the Japanese GFR estimated equation: e-GFR (in ml/min/1.73 m^2) = 194 × (serum creatinine in mg/dl)$^{-1.094}$ × (age in years)$^{-0.287}$ × (0.739 if female). The patients were divided into two groups by baseline e-GFR; no or mild renal insufficiency group (e-GFR ≥ 50 ml/min, $n = 35$) and advanced renal insufficiency group (e-GFR < 50 ml/min, $n = 32$). This e-GFR cut off value of 50 ml/min was defined as the time that patients with chronic kidney disease (CKD) should be referred to a nephrologist, according to the clinical practice guidelines on CKD of the Japanese Society of Nephrology. Echocardiographic evaluation was performed before CRT implantation and at 3–6 months' follow-up. LV dimensions and ejection fraction were assessed by M-mode echocardiography. The primary endpoint of this study was hospitalization due to heart failure or all-cause death during long-term follow up after implantation. This study was approved by the ethical committee of our hospital (approval number B080703013).

Statistical analysis

Comparisons of quantitative and categorical variables between groups were made using Pearson chi-squared (χ^2) test or Student's *t*-test. All continuous data were expressed as mean ± standard deviation (SD). Kaplan–Meier analysis was used to assess time-related outcomes, and statistically significant differences were tested using the log-rank test. Separate univariate and multivariate Cox regression models with a forward stepwise approach were run to assess the crude and multivariate adjusted odds ratios (ORs), which are presented with 95% confidence intervals (CIs). For all tests, a *p*-value < 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS.

Results

Baseline characteristics

The mean age of the study population was 64.8 ± 15.1 years, and 70.1% were men. The etiology of heart failure was ischemic in 17.9%, dilated cardiomyopathic in 65.7%, and other causes in 16.4%. These patients had advanced heart failure with mean New York Heart Association of 2.78 ± 0.69, LV ejection fraction (LVEF) of 29.4 ± 9.9%, and QRS duration of 149.6 ± 36.8 ms. The proportion of patients receiving an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) was 73.1%, and a β-blocker was 55.0%. Mean baseline e-GFR was 50.7 ± 21.8 ml/min. Baseline clinical characteristics, classified according to e-GFR, are listed in Table 1. Compared to those in the no or mild renal insufficiency group, patients in the advanced renal insufficiency group were older ($p = 0.009$), had lower usage of β-blockers ($p = 0.005$), and had a higher prevalence of atrial fibrillation ($p = 0.036$) and CRT-D implantation ($p = 0.039$). Echocardiographic left ventricular dimensions and LVEF did not differ between the two groups.

Table 1
Baseline clinical characteristics according to e-GFR.

	e-GFR < 50 ($n = 32$)	e-GFR ≥ 50 ($n = 35$)	*p*-Value
Age (years)	69.8 ± 9.6	60.2 ± 17.8	0.009
Male	22 (68.8%)	25 (71.4%)	0.811
e-GFR (ml/min)	33.9 ± 13.0	66.1 ± 16.0	<0.001
NYHA	2.75 ± 0.67	2.80 ± 0.72	0.770
Ischemic HF	6 (18.8%)	6 (17.1%)	0.864
Hypertension	13 (40.6%)	7 (20.0%)	0.065
Diabetes mellitus	8 (25.0%)	11 (31.4%)	0.560
Atrial fibrillation	14 (43.8%)	7 (20.0%)	0.036
Ventricular arrhythmia	8 (25.0%)	14 (40.0%)	0.192
QRS duration (ms)	156.1 ± 36.7	143.6 ± 36.4	0.166
LBBB	16 (50.0%)	15 (42.9%)	0.558
RBBB	3 (9.4%)	4 (11.4%)	0.784
Serum BNP (pg/ml)	849.9 ± 744.2	517.2 ± 838.5	0.096
LVEDd (mm)	63.9 ± 9.5	66.9 ± 11.5	0.256
LVESd (mm)	54.4 ± 10.4	56.4 ± 12.5	0.491
EF (%)	27.8 ± 10.1	30.8 ± 10.4	0.212
ACE-I or ARB	22 (68.8%)	27 (77.1%)	0.439
β-Blocker	12 (37.5%)	25 (71.4%)	0.005
Spironolactone	13 (40.6%)	26 (74.3%)	0.193
Diuretic	28 (87.5%)	31 (88.6%)	0.893
Inotropic agent	4 (12.5%)	5 (14.3%)	0.830
CRT-D implantation	17 (53.1%)	27 (77.1%)	0.039

e-GFR, estimated glomerular filtration rate; NYHA, New York Heart Association; HF, heart failure; LBBB, left branch bundle block; RBBB, right branch bundle block; BNP, B-type natriuretic peptide; LVEDd, left ventricular end-diastolic diameter; LVESd, left ventricular end-systolic diameter; EF, ejection fraction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT-D, cardiac resynchronization therapy defibrillator.

Impact of baseline renal function on clinical outcomes

During a mean follow-up period of 30.3 ± 22.0 months, 25 (37.3%) of 67 patients died of any cause, including 12 (17.9%) cardiac deaths, and 21 (31.3%) patients were hospitalized for heart failure.

In Kaplan–Meyer analysis, survival free from all-cause death was significantly lower in the advanced than in the no or mild renal insufficiency group (62.5% vs. 82.9% at 2 years, log-rank $p = 0.033$) (Fig. 1). Survival free from cardiac death combined with heart failure hospitalization was also significantly lower in the advanced than in the no or mild renal insufficiency group (53.1% vs. 74.3% at 2 years, log-rank $p = 0.017$) (Fig. 2).

In univariate Cox regression analysis, advanced renal insufficiency (e-GFR < 50 ml/min) was associated with a higher risk of cardiac mortality combined with heart failure hospitalization (OR = 2.46, 95% CI 1.14–5.29, $p = 0.022$). Other clinical variables, including B-type natriuretic peptide (BNP) and LV end-systolic diameter (LVESd), were associated with higher risk of cardiac mortality combined with heart failure hospitalization (Table 2).

Multivariate Cox regression analysis controlling for age, sex, BNP, and LVESd revealed that advanced renal insufficiency (e-GFR < 50 ml/min) was an independent predictor of cardiac mortality combined with heart failure hospitalization (OR = 3.01, 95% CI

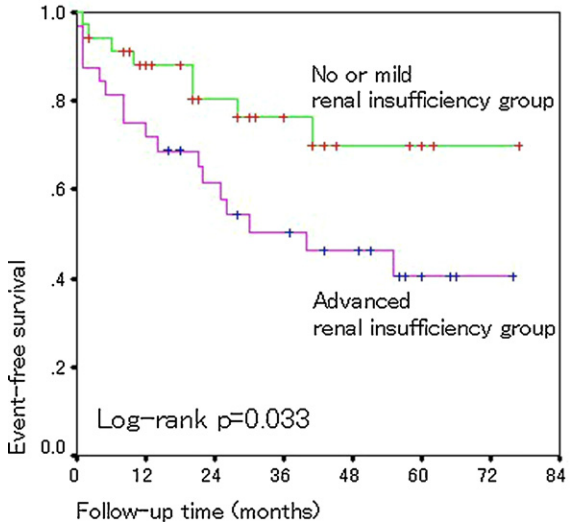

Fig. 1. Kaplan–Meier curves of survival free from all-cause death of no or mild renal insufficiency group [estimated glomerular filtration rate (e-GFR) ≥ 50 ml/min] and advanced renal insufficiency group (e-GFR < 50 ml/min).

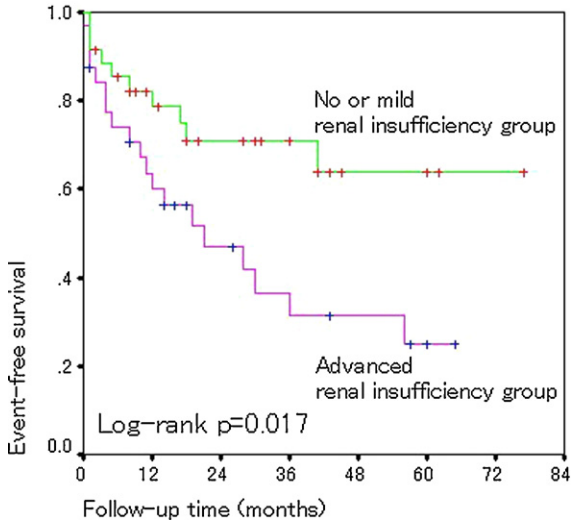

Fig. 2. Kaplan–Meier curves of survival free from cardiac death combined with heart failure hospitalization of no or mild renal insufficiency group [estimated glomerular filtration rate (e-GFR) ≥ 50 ml/min] and advanced renal insufficiency group (e-GFR < 50 ml/min).

Table 2
Univariate predictors of cardiac death combined with heart failure hospitalization by Cox proportional hazard models.

Variable	Odds ratio	95% CI	*p*-Value
e-GFR < 50 ml/min	2.455	1.139–5.291	0.022
LVESd (per 1 mm increase)	1.042	1.008–1.077	0.016
BNP (per 100 pg/ml increase)	1.030	1.000–1.061	0.049
Defibrillator	0.615	0.290–1.302	0.204
NYHA (per 1 increase)	1.357	0.815–2.262	0.241
ACE-I or ARB	0.719	0.290–1.781	0.476
Male	1.351	0.574–3.183	0.491
Age (per 1 year increase)	1.009	0.982–1.037	0.515
Atrial fibrillation	1.255	0.567–2.778	0.575
β-Blocker	0.821	0.391–1.722	0.601
Diabetes mellitus	1.005	0.442–2.285	0.990

e-GFR, estimated glomerular filtration rate; LVESd, left ventricular end-systolic diameter; BNP, B-type natriuretic peptide; NYHA, New York Heart Association; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 3
Multivariate predictors of cardiac death combined with heart failure hospitalization by Cox proportional hazard models.

Variable	Odds ratio	95% CI	*p*-Value
e-GFR < 50 ml/min	3.009	1.329–6.813	0.008
LVESd (per 1 mm increase)	1.049	1.014–1.085	0.005
BNP (per 100 pg/ml increase)	1.028	0.991–1.067	0.136

e-GFR, estimated glomerular filtration rate; LVESd, left ventricular end-systolic diameter; BNP, B-type natriuretic peptide.

1.33–6.81, $p = 0.008$) (Table 3). Therefore, long-term adverse cardiac events were significantly associated with e-GFR, even after adjustment for all other covariates.

Effects of CRT on renal function and clinical outcomes

Follow-up e-GFR was calculated from the last value of serum creatinine determined 3–6 months after implantation. Patients who had no follow-up e-GFR data or had died less than 3 months after CRT implantation were excluded. Therefore, among patients included in the present study, 51 (76.1%) had follow-up data of e-GFR. There was no significant difference in mean e-GFR change from baseline to follow-up between the advanced renal insufficiency group and the no or mild renal insufficiency group (+0.02 ± 8.57 ml/min vs. −2.64 ± 17.02 ml/min, $p = 0.48$).

Preserved renal function was defined as a <10% reduction in e-GFR, and deteriorated renal function was defined as a ≥10% reduction in e-GFR at follow-up when compared to baseline. A total of 51 patients were subdivided into four groups: no or mild renal insufficiency with preserved renal function subgroup (subgroup A; $n = 16$), no or mild renal insufficiency with deteriorated renal function subgroup (subgroup B; $n = 9$), advanced renal insufficiency with preserved renal function subgroup (subgroup C; $n = 13$), and advanced renal insufficiency with deteriorated renal function subgroup (subgroup D; $n = 13$). There was no significant difference in mean baseline e-GFR between subgroup C and subgroup D (35.2 ± 11.1 ml/min vs. 35.5 ± 11.5 ml/min, $p = 0.95$). The echocardiographic parameters and BNP at baseline and follow-up were compared between subgroup C and subgroup D, and the relationship between the change in renal function and the CRT response was examined (Table 4). There was no significant difference in baseline characteristics between subgroup C and subgroup D. In subgroup C, the mean LVESd decreased significantly from 51.2 ± 10.5 mm to 43.8 ± 13.3 mm ($p = 0.009$), and the mean LVEF increased significantly from 27.2 ± 12.0% to 41.1 ± 15.1% ($p = 0.007$). In subgroup D, there was no significant difference in echocardiographic parameters and BNP from baseline to follow-up. The mean rate of decrease of LVESd from baseline to follow-up in subgroup C was significantly higher than that in subgroup D (−14.0 ± 13.4% vs. −0.8 ± 11.1%, $p = 0.023$). The mean rate of increase of LVEF in subgroup C was also significantly higher than that in subgroup D (+72.1 ± 87.0% vs. +5.0 ± 54.4%, $p = 0.032$). These results showed that subgroup C was equal to CRT responder, even in the advanced renal insufficiency group. In Kaplan–Meyer analysis, survival free from cardiac death combined with heart failure hospitalization in subgroup C was significantly higher than that in subgroup D (log-rank $p = 0.029$). There was no difference in survival free from cardiac death combined with heart failure hospitalization between subgroup A, subgroup B, and subgroup C (Fig. 3). These results suggested that preservation of renal function by CRT brought about better cardiac survival through prevention of adverse cardiac events, even in patients with advanced renal insufficiency (e-GFR < 50 ml/min).

Table 4
Baseline clinical characteristics and mean changes of echocardiographic parameters and BNP from baseline to follow-up between subgroup C and subgroup D.

	Subgroup C ($n=13$)			Subgroup D ($n=13$)		
	Baseline	Follow-up	p-Value	Baseline	Follow-up	p-Value
Age (years)	67.7 ± 12.7			71.8 ± 6.7		
Male	10 (76.9%)			11 (84.6%)		
e-GFR (ml/min)	35.2 ± 11.1			35.5 ± 11.5		
Hypertension	5 (38.4%)			6 (46.2%)		
Diabetes mellitus	2 (15.4%)			5 (38.4%)		
Atrial fibrillation	4 (30.8%)			6 (46.2%)		
LVEDd (mm)	59.3 ± 8.9	55.0 ± 11.5	0.065	66.1 ± 10.2	67.5 ± 7.8	0.656
LVESd (mm)	51.2 ± 10.5	43.8 ± 13.3*	0.009	55.6 ± 11.4	57.6 ± 10.0	0.747
EF (%)	27.2 ± 12.0	41.1 ± 15.1*	0.007	27.8 ± 7.6	30.6 ± 12.5	0.329
Serum BNP (pg/ml)	787.0 ± 801.4	510.7 ± 430.6	0.095	633.9 ± 663.6	699.3 ± 679.2	0.811

e-GFR, estimated glomerular filtration rate; LVEDd, left ventricular end-diastolic diameter; LVESd, left ventricular end-systolic diameter; EF, ejection fraction; BNP, B-type natriuretic peptide.
* $p < 0.05$ compared between group C and group D at follow-up.

Discussion

There are some previous reports about the clinical outcome of CRT in heart failure patients with the complication of renal insufficiency. Fung et al. analyzed 85 patients treated by CRT, and reported significantly higher all-cause mortality in patients with deterioration of renal function after 3 months of CRT [9]. Shalaby et al. suggested high serum creatinine to be an independent predictor of mortality in patients undergoing CRT [10]. Recently, Lin et al. evaluated a large sample of 482 patients treated by CRT at Mayo Clinic and reported that survival was higher in patients with normal or mild renal dysfunction than in those with CKD (72% vs. 57% at 3 years, $p < 0.01$) [11]. There is only one report on the relationship between the effect of CRT and renal function in the Japanese population [12]. However, in that report, e-GFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation [14]. We used e-GFR calculated by the Japanese GFR estimated equation as a marker of renal insufficiency. The mean baseline e-GFR of this study population was 50.7 ± 21.8 ml/min, and 32 patients were included in the advanced renal insufficiency group (e-GFR < 50 ml/min). Patients with advanced renal insufficiency had significant higher all-cause mortality (log-rank $p = 0.033$) and higher cardiac mortality combined with heart failure hospitalization (log-rank $p = 0.017$) than patients with e-GFR ≥ 50 ml/min. If using the MDRD equation for calculation of e-GFR in this study, however, the mean baseline e-GFR was increased to 68.7 ± 29.4 ml/min, and 15 patients would be included in the advanced renal insufficiency group, which were much fewer than those in the case using the Japanese equation. Moreover, there was no significant difference in all-cause mortality or cardiac mortality combined with heart failure hospitalization between the two groups (log-rank $p = 0.696$, log-rank $p = 0.841$). These results suggested that the MDRD equation overestimated renal function in the Japanese population, and on the other hand, the Japanese GFR estimated equation was a precise evaluation of renal function and this equation could be more suitable to estimate clinical outcomes in the Japanese CRT patients.

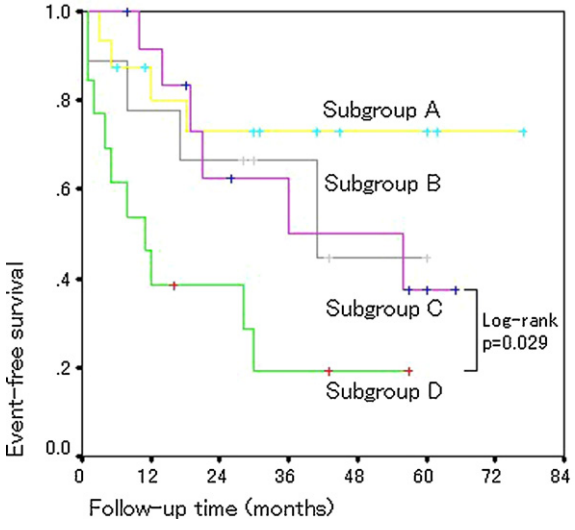

Fig. 3. Kaplan–Meier curves of survival free from cardiac death combined with heart failure hospitalization based on baseline estimated glomerular filtration rate and change in renal function by cardiac resynchronization therapy. Subgroup A: no or mild renal insufficiency with preserved renal function subgroup; Subgroup B: no or mild renal insufficiency with deteriorated renal function subgroup; Subgroup C: advanced renal insufficiency with preserved renal function subgroup; Subgroup D: advanced renal insufficiency with deteriorated renal function subgroup.

We decided the cut off value of e-GFR for dividing the patients into two groups to be 50 ml/min. In the clinical practice guidelines on CKD of the Japanese Society of Nephrology, e-GFR < 50 ml/min is defined as the time at which patients with CKD should be referred to a nephrologist. According to the guidelines, the e-GFR cut off value is quite important, because the rate of decline of renal function in the general population with e-GFR < 50 ml/min is more than twice in comparison to that in those with e-GFR between 60 and 70 ml/min [15].

Bai et al. suggested that in heart failure patients treated with a biventricular device, chronic renal failure, diabetes mellitus (DM), and history of atrial fibrillation (AF) appeared to be associated with a higher risk of death [16]. The present study revealed advanced renal insufficiency (e-GFR < 50 ml/min) to be an independent predictor of cardiac mortality combined with heart failure hospitalization. However, DM did not affect clinical outcomes. It is well known that DM is responsible for a high cardiac mortality in patients with ischemic heart disease [17]. One possible explanation for the results is that the proportion of ischemic etiology in our study was much smaller than that in Bai's study (17.9% vs. 66.6%). As for AF, it was not also associated with a higher risk of the adverse cardiac events in our study. Twenty-one patients had a history of AF, of which 4 patients had permanent AF and 17 patients had paroxysmal AF. A recent study concerning prognostic importance of AF patients with CRT suggested that paroxysmal AF was not associated with increased mortality, although permanent AF was an independent predictor of mortality [18]. The possible explanation for our results concerning AF may be due to the low proportion of the permanent AF patients.

Previous studies revealed that renal insufficiency is a strong predictor of mortality in heart failure patients in general. A meta-analysis of 16 studies with 80,098 heart failure patients showed that adjusted overall mortality is more than double in patients with

advanced renal insufficiency compared to those without insufficiency (HR 2.31 $p < 0.001$) [6]. Heart failure and renal insufficiency actively interact pathophysiologically with each other. A decrease in LV systolic function and cardiac output has an adverse effect on renal function due to decreased renal blood flow. In turn, renal insufficiency causes volume expansion secondary to sodium retention, hypertension, and atherosclerosis, and leads to severe heart failure [19]. Through such mechanisms, renal function is gradually impaired in the natural course of severe heart failure.

In the present study, concerning the baseline advanced renal insufficiency group (e-GFR < 50 ml/min), cardiac mortality combined with heart failure hospitalization was significantly lower in the preserved renal function subgroup (subgroup C described in the results) than in the deteriorated renal function subgroup (subgroup D). This means that preservation of renal function by CRT in patients with advanced renal insufficiency (e-GFR < 50 ml/min) was shown to bring about good efficacy to prevent adverse cardiac events and consequently improve the cardiac survival rate, whose mean value and standard deviation was almost equivalent to that in the no or mild renal insufficiency group. We focused on the effect of CRT in subgroup C, and found that the mean rate of decrease in LVESd from baseline to follow-up with CRT treatment in subgroup C was significantly higher than that in subgroup D ($-14.0 \pm 13.4\%$ vs. $-0.8 \pm 11.1\%$, $p = 0.023$). The mean rate of increase in LVEF in subgroup C was also significantly higher than that in subgroup D ($+72.1 \pm 87.0\%$ vs. $+5.0 \pm 54.4\%$, $p = 0.032$). This result directly showed that CRT had good effect on the better cardiac survival rate through improving heart function and preserving renal function even in the advanced renal insufficiency group (e-GFR < 50 ml/min). Consequently, the advanced renal insufficiency with deteriorated renal function subgroup had worst clinical outcomes. Compared to that in subgroup C, the prevalence of hypertension or DM tended to be higher in subgroup D (Table 4). This observation suggested that renal parenchymal damage caused by hypertension or DM might be a major cause of deteriorated renal function in subgroup D.

Based on these results, we conclude that the mechanism was as follows: CRT reduces LV dyssynchrony and improves LV systolic function. Improvement in LV systolic function, which correlates with reversal of LV remodeling, provides an increase in renal blood flow and leads to preservation of renal function, which is one of the mechanisms of the improved clinical outcome in renal insufficiency patients treated by CRT.

However, in order to confirm the above mechanism, we have to consider the following study limitations. One possible limitation is that this study was a non-randomized, retrospective analysis. Another possible limitation is that the total sample size was small, and follow-up echocardiographic assessment was available in only 73% of the study population. Further study with a larger sample size is needed to confirm the results of this study.

Conclusions

Advanced renal insufficiency, defined as e-GFR < 50 ml/min, predicts a poor clinical outcome in heart failure patients treated by CRT. Once renal function is preserved, however, CRT brings about a good clinical outcome, even in heart failure patients with advanced renal insufficiency. CRT can become one of the most effective therapeutic options for quite high-risk patients with both severe heart failure and renal insufficiency.

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