Chapter 5

Cardiac Resynchronization Therapy in CKD Stage 4 Patients

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Renal dysfunction is a common comorbidity in heart failure patients associated with poor prognosis.[1-3] Cardiac resynchronization therapy (CRT) is a well-established heart failure treatment for patients with broad QRS duration, improving left ventricular (LV) function, reducing heart failure symptoms and improving long-term prognosis.[4] In addition, CRT has demonstrated to be associated with improvement of renal function.[5-11] However, landmark trials excluded patients with severe renal dysfunction and only few data are available on the effect of CRT in this particular population.[10] Therefore, the beneficial effect of CRT in patients with severe renal dysfunction remains still to be demonstrated. Accordingly, the present study aimed to investigate in this specific subgroup of patients the impact of CRT on renal function, cardiac performance and long-term outcome.

METHODS

Patient population

A total of 73 patients with severe renal dysfunction (defined by an estimated glomerular filtration rate [eGFR] of 15-29 ml/min/1.73m²) undergoing CRT at the Leiden University Medical Center between 2000 and 2012 were selected. All patients in hemodialysis, peritoneal dialysis or previous kidney transplantation before device implantation were excluded. Patients received CRT devices (with a defibrillator function) according to the current guidelines based on the presence of LV ejection fraction (LVEF) ≤35%, heart failure symptoms as New York Heart Association (NYHA) class II, III and ambulatory IV despite optimal medical therapy and a QRS duration ≥120 ms.4 In addition, 18 patients with severe renal dysfunction undergoing implantable cardioverter defibrillator (ICD) implantation, matched for age, sex and LVEF, were selected as control group. All devices were conventionally implanted in the pectoral region as described earlier.[12,13]

The etiology of heart failure was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or a history of myocardial infarction or previous revascularization. Patients with recent myocardial infarction (<3 months) or decompensated heart failure were excluded from analysis. Clinical data and all follow-up visits were prospectively collected in the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Centre, Leiden, the Netherlands) and retrospectively analyzed.

Clinical evaluation

Before device implantation, NYHA functional class was evaluated. Serum creatinine levels were routinely assessed before implantation and were used to calculate eGFR according to the Modification of Diet in Renal Disease (MDRD) equation.[14] An eGFR between 15-29 ml/min/1.73 m² corresponding with chronic kidney disease (CKD) stage 4 according to National Kidney Foundation classification was considered as severe renal dysfunction.[15] The change in renal function with an improvement to stage 3 CKD (eGFR between 30-59 ml/min/1.73 m²) or a further deterioration of renal function (stage 5 CKD defined by eGFR <15 ml/min/1.73m²) was also evaluated.

Echocardiographic evaluation

All patients were evaluated with 2-dimensional (2D) transthoracic echocardiography using a commercially available system (Vivid 7 and E9, General Electric Vingmed Ultrasound, Horton, Norway). Standard 2D and Doppler images were recorded and saved in cine-loop format for off-line analysis (EchoPac, version 110.0.0, GE-Vingmed, Horton, Norway). Echocardiographic analysis was performed according to the current recommendations and included quantification of LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVEF by biplane Simpson's method.[16] The severity of mitral regurgitation (MR) was graded according the most recent recommendations based on a multiparametric approach.[17] Right ventricular (RV) function was evaluated measuring the tricuspid annular plane systolic excursion (TAPSE) and the central venous pressure was evaluated by estimating the right atrial pressure using the inferior vena cava diameter and percentage of collapse during inspiration.[18] LV dyssynchrony was assessed by the septal-to-lateral wall delay using color-coded tissue Doppler imaging (TDI) in the apical 4-chamber view as described previously.[19]

Patients alive at the 6-month follow-up visit were re-evaluated and changes in clinical (including renal function) and echocardiographic variables during follow-up were recorded. Reduction of ≥15% in LVESV at 6-month follow-up echocardiography among CRT patients defined CRT-response.[20]

Long-term follow-up outcome

After 6-month follow-up, regular outpatient visits (every 3-6 months) were scheduled for all patients. Long-term follow-up was performed by medical chart review, telephone contact or correspondence with the general practitioner, and by retrieval of survival status through the municipal civil registries. A combined end point was used including appropriate defibrillator therapy (antitachycardia pacing and defibrillator shocks), heart failure (HF) hospitalization and all-cause mortality (whichever came first).[21] HF hospitalizations were adjudicated by the cardiologist responsible for

the management of the patient during admission, while the appropriate defibrillator therapy was adjudicated by trained pacemaker technicians (and confirmed by a cardiologist) after device interrogation.

Statistical analysis

Continuous variables are presented as mean±standard deviation and categorical data as numbers and percentages. Unpaired Student t–tests was used to compare continuous variables and $\chi 2$ tests to compare categorical variables. Differences in magnitude of change over time between ICD and CRT patients were compared; repeated-measures ANOVA was used for normally distributed continuous variables and generalized estimating equations (GEE) for ordinal/categorical variables. Wilcoxon matched-pairs signed-rank test was used to test the significance of the change in CKD stage and in NYHA class at follow-up compared to the baseline. Bivariate logistic analysis with Pearson's test was used to evaluate the correlation between decrease in LVESV and increase in eGFR. The log-rank tests were utilized to compare the difference in Kaplan-Meier curves for the survival free from the combined endpoint between the groups. Furthermore, the predictors of the combined endpoint were evaluated with the Cox proportional hazards model; all clinically relevant variables or significant predictors ($p<0.20$) at the univariate analysis were introduced in the multivariate model. In case of collinearity, only one of these variables was entered in the multivariate model. Considering the limited number of events, backward stepwise elimination was used and the least significant parameter was discarded from the model until appropriate number parameters remained (1 parameter per 12-15 events). All statistics were two-tailed. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed by using IBM PASW Statistics, version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient population

The baseline clinical and echocardiographic characteristics of the 73 CRT and 18 ICD recipients with stage 4 CKD are summarized in Table 1. Despite similar age, sex and LVEF, CRT patients had a worse NYHA functional class, more prolonged QRS duration and more LV dyssynchrony as assessed by septal-to-lateral delay.

Table 1. Baseline clinical and echocardiographic characteristics of the patient population

	ICD (n=18)	CRT (n=73)	p-value
Age, years	74±10	71±10	0.24
Male, n (%)	12(67)	48(66)	0.94
Ischemic etiology, n (%)	14(78)	48(66)	0.33
QRS duration, ms	130±21	168±28	<0.001
Atrial fibrillation, n (%)	6(33)	14(19)	0.19
Diabetes, n (%)	7(41)	26(36)	0.67
eGFR, ml/min/1.73 m²	24±4	25±4	0.66
Creatinine, mg/dl	2.9±2.1	2.5±0.5	0.44
Hemoglobin, g/dl	12±1	12±2	0.21
NYHA functional class	1.5[2-3]	3[3-3]	<0.001
β-blockers, n (%)	10(56)	40(55)	0.95
ACE-I/ ARB-II	11(61)	61(84)	0.04
Diuretics, n (%)	16(89)	70(96)	0.24
Amiodaron, n (%)	10(56)	24(47)	0.54
LVEDV, ml	172±60	205±87	0.13
LVESV, ml	126±54	159±78	0.09
LVEF, %	28±12	24±8	0.10
Mitral regurgitation >2, n(%)	7(39)	35(48)	0.49
LV dyssynchrony, ms	21±24	67±49	< 0.001
TAPSE, mm	14±4	16±6	0.31
Right atrial pressure, mmHg	7±5	6±4	0.42

Mean ± SD and median with [IQR]. The ACE-I/ ARB-II=angiotensin-converting enzyme inhibitor/angiotensin II type I receptor blocker; eGFR=estimated glomerular filtration rate; IQR=interquartile range; LV = left ventricular; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end-systolic volume; NYHA=New York Heart Association; TAPSE=tricuspid annular plane systolic excursion

Clinical and echocardiographic evaluation at 6 months

As shown in Table 2, at 6 months follow-up, NYHA functional class improved from 3 [3-3] to 2 [2-3], (Wilcoxon p<0.001) in CRT patients whereas the ICD recipients showed a significant deterioration from 1.5 [2-3] to 3[3-4], (Wilcoxon p=0.02). The magnitude of change over time in NYHA functional class between the two groups was significantly different (interaction time and group p<0.001).

Similarly, renal function improved from 25±4 to 30±9 ml/min/1.73 m² (p<0.001) in CRT recipients while the ICD patients showed no improvement (24±4 to 24±13 ml/min/1.73 m², p=0.84) after 6 months (Figure 1). The magnitude of change over time in eGFR between the two groups was significantly different (interaction time and group p=0.04). Furthermore, the change in renal dysfunction stage according to

Table 2. Clinical and echocardiographic changes compared between device groups (CRT versus ICD) at 6-month follow-up

	ICD (n=18)		CRT (n=73)		Time and group interaction p-value
	Baseline	Follow-up	Baseline	Follow-up	
NYHA functional class	1.5[2-3]	3[3-4]	3[3-3]	2[2-3]†	<**0.001**
eGFR, ml/min/1.73 m²	24±4	24±13	25±4	30±9*	**0.04**
LVEDV, ml	172±60	164±55	205±87	196±85*	0.06
LVESV, ml	126±54	119±49	159±78	145±78*	**0.048**
LVEF, %	28±12	29±11	24±8	28±11*	0.30
Mitral regurgitation > 2, n(%)	7(39)	2(11)	35(48)	23(32)†	0.20
TAPSE, mm	14±4	15±3	16±6	17±3	0.91
Right atrial pressure, mmHg	7±5	8±4	6±4	5±4	0.37

Mean ± SD or median [IQR]. eGFR=estimated glomerular filtration rate; IQR= interquartile range; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end-systolic volume; NYHA=New York Heart Association; TAPSE=tricuspid annular plane systolic excursion. † Wilcoxon p-value comparing baseline versus follow-up within the group is significant. * p-value comparing baseline versus follow-up within the group is significant.

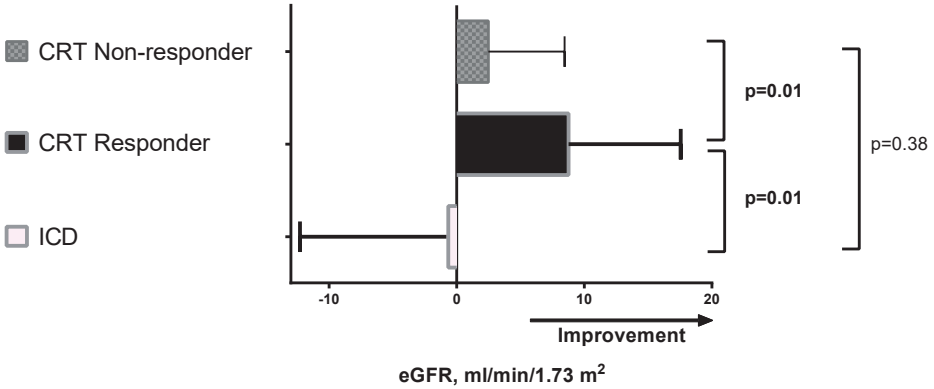

Figure 1. Comparison of mean changes (± SD) in eGFR six months after device implantation among ICD and CRT recipients with further stratification for response to CRT. As compared to baseline, eGFR improved significantly in CRT responders (p<0.001) while no significant changes were observed in CRT non-responders (p=0.053) and ICD patients (p=0.84).

the National Kidney Foundation CKD classification was also evaluated. At 6 months after implantation, the majority of the ICD patients remained in stage 4 CKD (54%), while 23% improved to stage 3 CKD and 23% deteriorated to stage 5 CKD (Wilcoxon p>0.99, Figure 2). In the CRT group, a small group deteriorated further to CKD stage 5 CKD (2%). More importantly, 58% remained in stage 4 CKD while a relatively large group of patients improved to stage 3 CKD (40%), (Wilcoxon p<0.001). At 6 months follow-up, LVEDV and LVESV decreased and LVEF increased among CRT

recipients whereas no significant changes were noticed in LV volumes or LV function among ICD recipients (Table 2). At 6 months follow-up, the reduction in LVESV was significantly different between CRT and ICD recipients (interaction group and time p=0.048, Table 2).

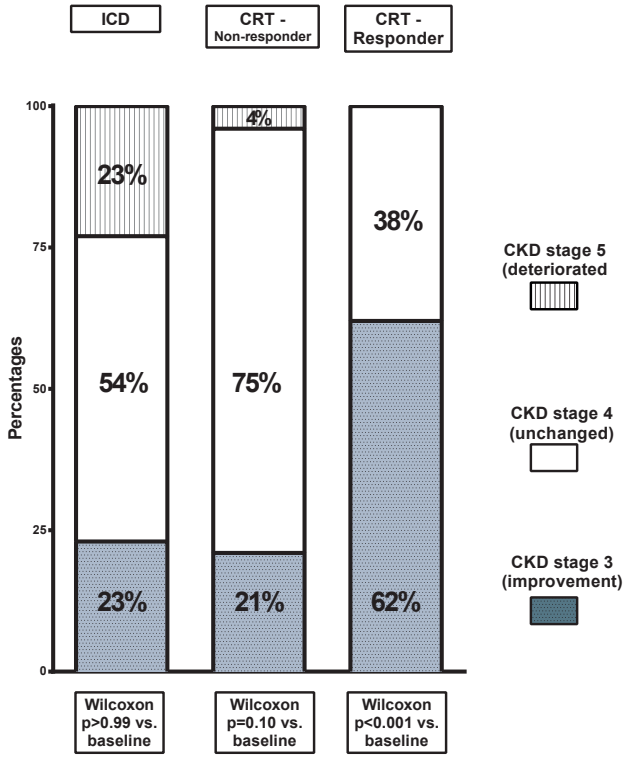

Figure 2. Distribution of chronic kidney disease stage at 6-months follow-up among ICD patients, CRT-responders and CRT non-responders.

Response to CRT and renal function

According to the definition of response to CRT, 22 (30%) CRT patients were classified as responders at 6 months follow-up. As showed in Figure 1, improvement in renal function was statistically significant only among CRT responders (25±3 to 34±9 ml/min/1.73 m², p<0.001 vs. 25±4 to 27±7 ml/min/1.73 m², p=0.053 in CRT non-responders) and as a result 62% of responders to CRT improved in CKD stage (from 4 to 3). The specific distribution of CKD stage at 6 months follow-up in CRT responders and non-responders is displayed in Figure 2. Furthermore, a significant difference in the changes (delta) of eGFR was observed only between ICD patients and CRT responders (1±12 ml/min/1.73 m² versus -9±9 ml/min/1.73 m², p=0.01) as shown in Figure 1. A correlation between reduction in LVESV and increase in eGFR

was observed but did not reach statistical significance (Pearson correlation 0.26, p=0.09, 2-tailed).

Long-term prognosis after CRT

During a median follow-up of 33 months (interquartile range: 14-52 months) 74 patients (81%) died (59 CRT and 15 ICD patients). Five CRT (7%) and two ICD (11%) patients died before 6 months follow-up (χ^2=0.19, log-rank p=0.89). During long-term follow-up a total of 29 appropriate defibrillator therapy (32%) and 24 HF hospitalizations (26%) occurred together with 35 deaths. The majority of the patients died due to heart failure progression (53%) and infections (14%). The other causes of death were sudden cardiac death (3%), malignancies (4%), major bleeding (1%), renal failure progression (1%) and unknown (4%). Specifically, the combined endpoint was observed in 17 ICD and 62 CRT patients. As compared to ICD patients, a superior survival free from the combined endpoint was observed among CRT patients (Figure 3A; χ^2=4.55, log rank p=0.03). Furthermore, the cumulative incidence of the combined end point was significantly lower among CRT responders (Figure 3B; χ^2=8.55, log rank p=0.01 for the comparison between CRT responders, CRT non-responders and ICD patients). More specifically, response to CRT was associated with a better long-term outcome as compared to CRT non-response (χ^2=4.56, log rank p=0.03) and ICD patients (χ^2=7.49, log rank p=0.006).

Predictors of long-term outcome

Univariate analysis performed in the CKD stage 4 patients indicated that CRT response was significantly related to combined end point (Table 3). In multivariate Cox analysis, CRT response was independently associated with better survival free from the combined end point after adjustment for relevant clinical and echocardiographic characteristics (sex, ischemic etiology, ACE-I/ARB-II use and LVEF; Table 3) age, atrial fibrillation, diabetes, β-blockers use and hemoglobin were dispensed by the predefined backward stepwise elimination.

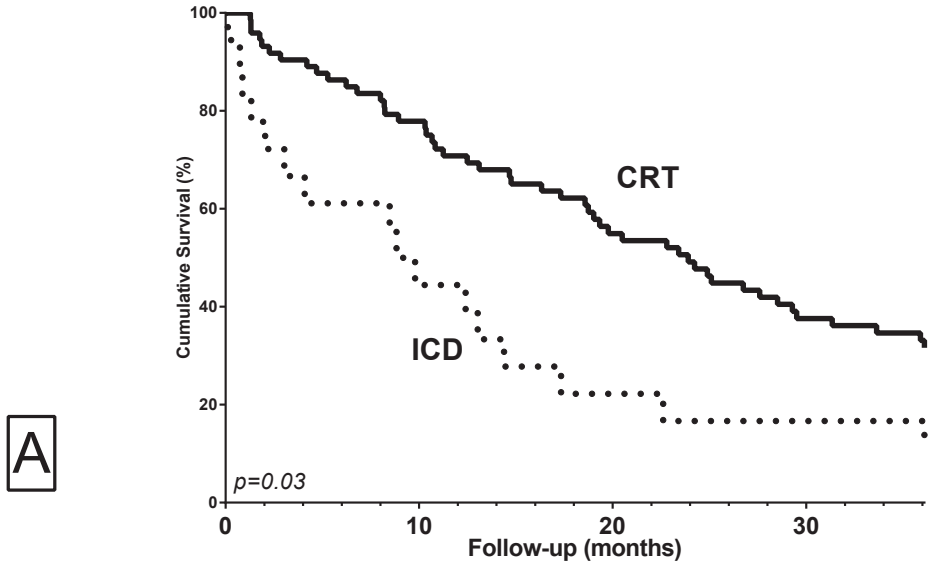

Figure 3. Panel A. Kaplan Meier curves comparing the survival free from defibrillator therapy, heart failure hospitalization and all-cause mortality between ICD and CRT patients.

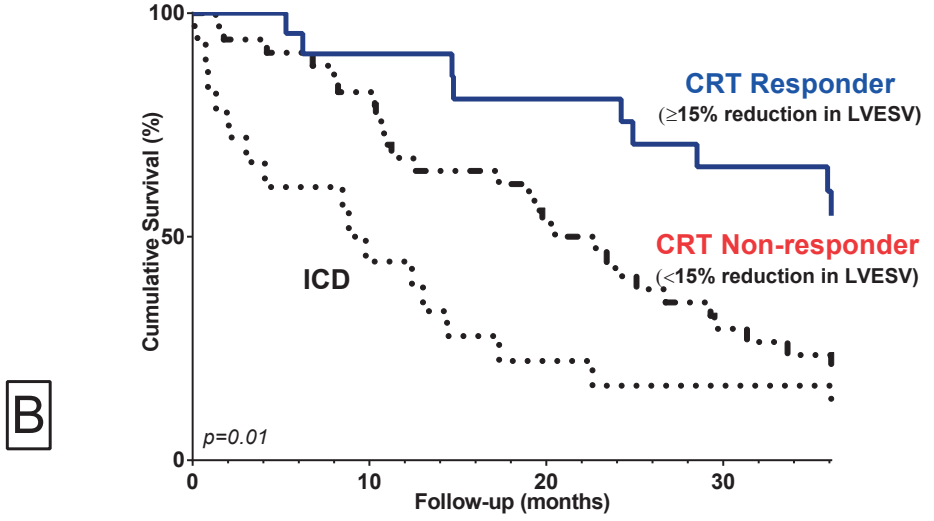

Figure 3. Panel B. Kaplan Meier curves comparing the survival free from defibrillator therapy, heart failure hospitalization and all-cause mortality between ICD patients, CRT responders and CRT non-responders.*In 56 patients, response to CRT (LV reverse remodeling at 6-month follow-up) could be assessed. In 17 patients, response to CRT could not be defined due to death before 6-month follow-up or technical issues.

Table 3. Cox regression analysis for the combined endpoint (of heart failure hospitalization, defibrillator therapy and all-cause mortality) in CKD stage 4 patients who underwent ICD or CRT implantation.

	Univariate			Multivariate		
	HR	**95%- CI**	***P value***	**HR**	**95%- CI**	***P value***
Age, per year	1.02	0.99 - 1.04	0.14			
Male	1.29	0.80 - 2.07	0.30	1.20	0.68- 2.08	0.55
Ischemic etiology	1.29	0.80 - 2.10	0.30	1.34	0.71- 2.46	0.38
Diabetes	0.85	0.53 - 1.36	0.50			
Atrial fibrillation	1.74	1.01 - 2.99	0.05			
QRS duration, pre ms	1.00	0.99 - 1.01	0.42			
eGFR, per ml/min/1.73 m²	0.96	0.91 - 1.02	0.19			
Hemoglobin, per g/dl	0.81	0.64 - 1.02	**0.07**			
ACE-I/ ARB-II	0.47	0.28 - 0.79	**0.005**	0.53	0.27- 1.03	0.06
β-blockers	0.81	0.52 - 1.26	0.35			
LVEDV, per ml	1.00	1.00 - 1.00	0.71			
LVESV, per ml	1.00	1.00 - 1.00	0.69			
LVEF, per %	1.00	0.97 - 1.02	0.71	1.01	0.98- 1.04	0.47
Mitral regurgitation >2	1.16	0.73 - 1.82	0.53			
LV dyssynchrony, per ms	1.00	0.99 - 1.00	0.40			
CRT- Non Response (reference)			**0.02***			**0.04***
CRT- Response (versus reference)	0.55	0.30 - 1.01	**0.06**	0.51	0.27- 0.98	**0.04**
ICD (versus reference)	1.50	0.82 - 2.75	**0.19**	1.18	0.60- 2.23	0.64

DISCUSSION

The main findings of the present study can be summarized as follows: CRT implantation in patients in stage 4 CKD was associated overall with an improvement in symptoms, in LV systolic performance and in eGFR as compared to ICD patients. The beneficial effect on renal function particularly was more pronounced among CRT responders as compared to non-responders and ICD patients. However, the response rate to CRT was relatively low in this category of very ill patients; nevertheless, when response to CRT occurred, it was associated with a better long-term outcome (including survival, HF hospitalization and defibrillator therapy) as compared to CRT non-response or ICD.

Impact of CRT on renal function in patients with severe renal dysfunction

Heart failure and renal dysfunction often coexist.[1] Treatment of heart failure with CRT has been associated with improved renal function potentially through several mechanisms.[6-9] CRT often results in a significant improvement in LV systolic function

which therefore improves systemic hemodynamic status and pre-renal circulation.[6,22-29] In addition, CRT decreases central venous pressure, which is described to play an important role in the progression of renal failure.[3,29,30] Finally, reduced sympathetic nerve and renin-angiotensin-aldosterone system activity and improved NT-proBNP levels are described after CRT.[6,31,32] This favorable neurohormonal modulation further contributes to the CRT derived improvement of renal function.

However, data on the effect of CRT in patients with severe renal dysfunction is scarce.[5] Major CRT clinical trials excluded patients with severe renal dysfunction and only 2 small retrospective studies described the impact of CRT in this group of patients.[5,10,11] Adelstein and co-workers evaluated the impact of CRT in severe renal dysfunction patients (mixed group including stage 4 and 5 CKD) in comparison with other CKD stages (<3) and ICD implantation alone.[10] This study showed a larger improvement in renal function in CKD stage 4 patients after CRT as compared to other CKD stages (<3) but without significant improvement in LV function (LV reverse remodeling) as compared to ICD alone.[10] Similarly, our study showed an overall significant improvement in renal function (and CKD stage) in patients with stage 4 CKD, suggesting a favorable effect of CRT in these patients. However, the current study also showed that the effect on renal function was significantly different between CRT responders and non-responders. CRT responders showed a better improvement in eGFR as compared with CRT non-responders and ICD patients, suggesting that an increase in LV function (and overall in cardiac performance) is probably a key step for the improvement in renal function.

However, it is important to note that the rate of response to CRT in stage 4 CKD patients was relatively low (30%) as compared to that reported in a general heart failure population referred for CRT.[7,10] Particularly, van Bommel et al reported a CRT response rate of 43% in patients with eGFR <60 ml/min/1.73 m², of 62% in patients with eGFR between 60 and 90 ml/min/1.73 m² and of 58% in patients with eGFR >90 ml/min/1.73 m².[7] Unfortunately, there are no data regarding CRT response among CKD stage 4 patients to compare with. The limited reverse remodeling capacity of the myocardium after CRT in these patients may be due to a chronic damage based on uremic toxins, calcium/phosphate abnormalities and the hypervolemic damage (water and sodium retention) that could lead to myocardial fibrosis, capillary rarefraction and endothelial cell dysfunction.[5,7,13,33-35] Probably concomitant conditions such as anemia, increased levels of catecholamines, activated renin-angiotensin-aldosterone system resulting in increased myocardial fibrosis, fluid retention and increased afterload might represent other important factors to limit the favorable effect of CRT in cardiac function.[35]

Impact of CRT on clinical outcome among patients with severe renal dysfunction

Severe renal dysfunction in heart failure patients is well known to be associated with poor survival.[1-3] Data on long-term outcome in CRT patients with severe renal dysfunction is scarce and warranted.5 Adelstein and co-workers showed no additional benefit of CRT on long-term outcome as compared to ICD in patients with severe renal dysfunction.[10] However, the patient cohort evaluated by Adelstein et al also included stage 5 CKD patients, which were older as compared to the ICD control group (median 74 versus 65 years, $p<0.05$), and the authors did not distinguish between CRT response and non-response.[10]

In line with the findings of Adelstein et al, we observed a high mortality rate in our cohort (55% at 3 years), emphasizing again the important prognostic value of significantly impaired renal function. The current study showed improved long-term outcome among CRT patients in comparison to ICD patients. However, this result was mainly driven by a superior clinical outcome in CRT responders. As shown by the difference in some baseline characteristics with ICD patients, CRT patients are in general more fragile patients with relatively more advanced heart failure, severely dilated LV volumes and higher grades of mitral valve regurgitation and a head-to-head comparison could lead to an underestimation of the positive effect of CRT as compared to ICD. Furthermore, in this specific group of patients at high risk an advantage in terms of symptoms/quality of life, an improvement in LV performance and a reduction of the progression of renal dysfunction could represent an important end point on top of the advantage in terms of survival. Importantly, improvement in LV function (CRT response) seems a key step to a better long-term prognosis,emphasizing the need for a good selection of candidates referred to CRT.[4]

Limitations

Several limitations of the current study should be mentioned. A rather small population and a retrospective design are the main limitations. However, the majority of the landmark trials on CRT and ICD have excluded patients with severe renal dysfunction and the present study represents one of the largest series so far. Therefore, the present study should be considered hypothesis generating and further studies with a larger patient population and longer follow-up are needed. Indication for cardiac device therapy was based on the available guidelines at the moment of implantation. Therefore, characteristics of patients qualifying for ICD or CRT implantation represent a potential selection bias, which we tried to minimize matching for age, sex and LVEF, but which should be taken into account in the interpretation of the result. Furthermore, the preexistent pathology of renal dysfunction preceding heart failure and the effect of heart failure medications on renal function in the follow-up

could not be evaluated. Nonetheless, heart failure medication was optimized before device implantation in all patients. After 6 months follow-up measure of eGFR was also not systematically available and therefore analysis on the effect on CRT on clinical outcome could not be corrected for this factor. Also, longer-term changes in renal function and in relation to cardiac function could not be evaluated. Between device implantation and 6 months follow-up, three hospitalizations occurred; the worsening of renal function due to these hospitalizations could not be systematically assessed but was taken into account when measuring the renal function at 6 months follow-up and including heart failure hospitalization in the endpoint. Finally in a total of eight patients renal replacement therapy was intended (RRT, median time to dialysis was 28 months [IQR 13-45 months]); however, the prognostic implications of RRT could not be tested considering the low number of patients.

CONCLUSIONS

Patients with severe renal dysfunction undergoing CRT showed an improved eGFR and CKD stage at 6 months follow-up as compared to ICD patients. Improvement in renal function was more pronounced among CRT responders as compared to CRT non-responders, although CRT response rate was relatively low (30%). More importantly, CRT response was independently associated better long-term prognosis after adjustment for sex, etiology, ACE-I/ARB-II use and LV ejection fraction.

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