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Cardiac Resynchronization Therapy prevents progression of renal failure in heart failure patients

Vinodh Jeevanantham [a], Mohit Turagam [c], David Shanberg [a], Madhu Reddy [a], Moustapha Atoui [a], James P. Daubert [b], Buddhadeb Dawn [a], Dhanunjaya Lakkireddy [a, *]

[a] University of Kansas Medical Center, Kansas City, KS, USA
[b] Duke University, Durham, NC, USA
[c] University of Missouri, Columbia, MO, USA

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ABSTRACT

Background: The goal of this study is to assess the effect of cardiac resynchronization therapy (CRT) over time on renal function and its impact on mortality. The effect of CRT on renal function in patients with heart failure is not well understood.

Methods: All patients who underwent CRT implantation at University of Kansas between year 2000 and 2009 were reviewed and patients who had pre and post CRT renal function studied were included in our study. Stages of chronic kidney disease (CKD) were defined based on Kidney Disease Outcome Quality Initiative (KDOQI) guidelines. The effect of CRT on renal and cardiac function were studied at short term (≤6 months post implantation) and long term (>6 months).

Results: A total of 588 patients with mean age of 67 ± 12 yrs were included in the study. CRT responders (defined by increase in LVEF ≥ 5%) were 54% during short term follow-up and 65% on long term follow-up. When compared to baseline, there was no significant deterioration in mean Glomerular Filtration Rate (GFR) during follow up. When analyzed based on the stages of CKD, there was significant improvement of renal function in patients with advanced kidney disease. Multivariate logistic regression analysis showed that stable GFR or an improvement in GFR independently predicted mortality after adjusting for co-morbidities.

Conclusions: CRT was associated with stabilization of renal function in patients with severe LV dysfunction and improvement in stage 4 and 5 CKD. Improved renal function was associated with a lower mortality.

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1. Introduction

Chronic kidney disease (CKD) is a very common co-morbidity associated with congestive heart failure [1]. Often times, a large proportion of these patients have co-morbidities that can cause kidney dysfunction in addition to the pre renal effects of the poor systemic perfusion related to low cardiac output status. Cardiac Resynchronization Therapy (CRT) has been shown to improve cardiac function in heart failure patients who have New York Heart Association (NYHA) class II, class III and ambulatory class IV symptoms, females, and patients with wider QRS duration (the longer the QRS duration, the greater the benefit) despite optimal medical management [2–10]. Furthermore COMPANION and CARE-HF studies have shown that CRT improves survival and decrease morbidity in patients with heart failure and wide QRS [7,8].

Renal function is one of the important factors that predicts prognosis in heart failure patients [11]. Cardiovascular disease mortality rates are up to 15 times higher in patients with end-stage renal disease compared to general population [1]. Among implantable cardioverter defibrillator (ICD) recipients, those with renal failure had a significantly higher mortality than those with normal renal function [12,13]. However there is limited data on the effect of CRT on renal function in patients with heart failure. Mathew J et al. performed a posthoc analysis of REVERSE trial and found that patients with underlying CKD had more LV dysfunction

* Corresponding author. Center for Excellence in Atrial Fibrillation/Complex Arrhythmia Management, Bloch Heart Rhythm Center @ University of Kansas Hospital, USA.
E-mail address: dlakkireddy@kumc.edu (D. Lakkireddy).
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and CRT improved LV structure and function to a lesser extent in these patients compared to those with normal renal function [14]. Posthoc analysis of MIRACLE trial showed that renal function improved in patients with stage III CKD compared to controls, whereas patients with stage II had no significant differences in renal function improvement compared to controls [11].

In Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy (MADIT-CRT), heart failure patients with EF <30% and NYHA class I or II who had an elevated ratio of BUN to serum Creatinine (SCr) experienced a significantly greater reduction in the risk of heart failure or death with CRT-D therapy as compared with patients with a low ratio of BUN to SCr. These findings suggest an association between prerenal function and response to CRT [15].

Recently Adelstein et al. have shown that heart failure patients who received CRT-D and who had moderate renal insufficiency showed higher survival benefit compared to patients who received standard defibrillators [16]. However this study did not examine or differentiate the outcomes based on cardiovascular response to CRT.

In the current study we attempt to assess if improvement in left ventricular ejection fraction (>5% defined as CRT response for the purposes of this study) has any effect on renal function in patients with congestive heart failure and renal dysfunction. We hypothesized that (i) patients who respond to CRT might have an improvement in renal function (ii) An improvement in renal function after CRT therapy might improve overall survival.

2. Materials and methods

All patients who underwent CRT implantation at University of Kansas between 2000 and 2009 were reviewed from a prospective CRT registry and patients who had pre and post CRT renal function studied were included in our study. The study was approved by institutional review board at University of Kansas Medical Center. Baseline clinical characteristics were collected. Renal function was determined using glomerular filtration rate (GFR) and classified into 5 stages of chronic kidney disease before and after CRT. Estimated GFR was assessed using the four-component Modification of Diet in Renal Disease (MDRD) equation incorporating age, race, sex, and SCr level [17]. The CKD classification was done based on GFR (ml/min): Stage 1 (>90), stage 2 (60–90), stage 3 (30–59), stage 4 (15–29) and stage 5 (<15) [18]. Due to small sample size in advanced stages of kidney disease, for the purposes of this study we merged stages IV and V. LVEF was determined by standard 2-D echocardiogram. Both the pre and post LVEF measurements were interpreted by same cardiologist who were not aware of the clinical data. For those with stage 1–3 CKD, a mean 45 ± 7 cc of contrast were given, whereas those with advanced CKD (Stage 4 and 5) were given mean 40 ± 4 cc of contrast. All patients with CKD stage 4 and 5 were given IV normal saline with sodium bicarbonate at 1 cc/kg/hr starting in the morning of the procedure for a total of 24 h.

2.1. CRT implantation

CRT was implanted using standard technique by placing a pacing lead through the coronary sinus (CS) targeting the mid to basal posterolateral aspect of the left ventricle. The use of contrast is minimized as much as possible. All patients were appropriately pre-treated for renal protection. No significant post implantation fluctuation was seen in the study cohort. Post implantation all CRTs were appropriately optimized for A-V and V-V timing. Triggered biventricular pacing response was activated whenever relevant to maximize biventricular pacing in patients with atrial arrhythmias and frequent PVCs.

The effect of CRT on renal and cardiac function was studied after short term (≤6 months post implantation) and long term (>6 months) follow up. Mortality data was obtained from social security death index and review of electronic records.

We studied the differences in mortality between those who had improved GFR vs. those who did not post CRT. We also assessed the degree of improvement in renal function between patients with various stages of CKD who received CRT. Any patient without baseline laboratory parameters within prior 6 months was excluded.

2.2. Statistical analysis

Statistical analyses were performed using SPSS. Data was plotted (e.g., histograms and spaghetti plots linking before/after CRT-D measurements) to examine for potential outliers and for the necessity of transformation prior to analysis. Summary statistics (e.g., mean, standard deviation, minimum, maximum, proportions) were calculated for all variables. The primary comparison between participants before and after CRT-D was made using a paired *t*-test for primary and secondary outcomes. Pearson's correlation was used to describe the relationship between eGFR and improvement in LVEF. These relationships were also examined graphically using a scatterplot and, if the relationship was nonlinear, the Spearman correlation coefficient was used instead of the Pearson. We used a multivariable regression analyses to find independent predictors of mortality. A p value of <0.05 was considered to be statistically significant.

3. Results

A total of 558 patients with mean age of 67 ± 12 yrs were included in the study (See Table 1). The entire study cohort was distributed into the following stages of CKD: Stage 1 was 47 patients (8.4%), stage 2 was 217 patients (39%), stage 3 was 232 patients (41.5%), stage 4 was 45 patients (8.1%) and stage 5 was 17 patients (3%) (Table 1). Table 2 also shows baseline medication use. About 9% of those who received CRT were African Americans and the remaining patients were Caucasians (91%). One percent of the devices were CRT-P and the rest were CRT-D. Twenty one percent had prior ICD, 15% had prior PPM, 0.4% had prior CRT-P and 63% had no prior device.

Twenty nine percent died during a mean follow up of 852 ± 559 days. The average short term follow up duration was 100 ± 67 days and the average long term follow up duration was 377 ± 164 days.

Table 1
Baseline clinical characteristics.

Baseline characteristics	
Age	67 ± 12
Non Ischemic Cardiomyopathy	230 (41%)
Women	151 (27%)
Diabetes	188 (34%)
Atrial Fibrillation	194 (35%)
Hypertension	378 (68%)
Coronary Artery Disease	357 (64%)
Coronary Artery Bypass Graft	192 (34.5%)
Smoking	206 (37%)
Hyperlipidemia	341 (61%)
NYHA Class	3 ± 0.3
Stages of CKD	
Stage I	47 (8.4%)
Stage II	217 (38.9%)
Stage III	232 (41.6%)
Stage IV	45 (8.1%)
Stage V	17 (3%)

Table 2
Medication use at baseline and follow up.

Medications	At Baseline	During short term follow-up	During long term follow-up
Beta-Blockers	90%	93%	93%
ACE inhibitors	65%	64%	61%
ARB's	20%	20%	21%
Lasix	68%	67%	71%
Spironolactone	36%	46%	46%
Digoxin	33%	36%	34%
Antiarrhythmics	21%	22%	24%
Metformin	8%	7%	6%
Statins	62%	65%	68%

GFR stayed the same or improved in 210 patients during short term follow up and in 207 patients during long term follow-up. LVEF stayed the same or improved in 77% during short term follow-up and 79% during long term follow-up. CRT responders (defined by increase in LVEF $\geq$ 5%) were 54% during short term follow-up and 65% during long term follow-up. LVEF significantly improved from baseline to short term follow up (24 ± 9 vs. 28.6 ± 11, $p < 0.001$) and during long term follow up (24 ± 9 vs. 33 ± 13, $p < 0.001$).

Table 2 shows the use of medications such as beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, furosemide, spironolactone, digoxin, anti-arrhythmic and statins. There was no significant differences in the use of these medications between baseline and follow up (Table 2).

Table 3 shows the effect of CRT on cardiovascular and renal parameters before and after CRT. When compared to baseline, there was no significant deterioration in mean GFR during follow up (short term: 57 ± 23 vs. 57 ± 23, p 0.9 and long term: 58 ± 22 vs. 57 ± 24, $p = 0.1$) for the total study cohort. In the subgroup analysis based on the stages of CKD, there was significant improvement of renal function in patients advanced kidney disease during short term and long term follow up (Table 4). Stage 4 CKD had the most clinical improvement in renal function both in the short and long term follow ups (Fig. 1).

3.1. Mortality response to CRT therapy and improvement in GFR

Differences in mortality among those who had improvement in GFR vs. those who did not during long term follow up, showed a trend toward significance (25% vs. 33%, $p = 0.08$) but did not reach statistical significance (Fig. 2). Similarly during short term follow up there was a decrease in mortality in patients who had improvement in GFR compared to those who did not but this was not statistically significant (33% vs. 35%, $p = 0.6$).

An improvement in EF of at least 5% showed decreased mortality compared to those who did not during short term follow up (24% vs 35%, $p = 0.03$) and did not reach statistical significance during long term follow up (25% vs. 34.5%, $p = 0.1$) Mean BUN/Cr ratio was 18.2 ± 7.4 and median was 17.8. Based on pre-CRT azotemia defined by BUN/Cr ratio there was no differences in mortality during follow up.

Multivariate logistic regression analysis showed that an improvement in GFR after CRT independently predicted mortality after adjusting for age, gender, diabetes, hypertension, coronary artery disease, smoking, change in LVEF by 5%, atrial fibrillation and hyperlipidemia (Table 5).

4. Discussion

4.1. Main findings

Our study showed that 1. CRT stabilizes renal function with no significant deterioration in mean GFR during follow up. 2. Patients with advanced stages of CKD seem to benefit the most while other stages seem to be stable or show a trend for improvement. 3. Importantly, improvement in GFR showed a trend towards decreased mortality during long term follow up. The mechanism of improvement in LV function, symptoms and survival is probably due to synchronized stimulation of both right and left ventricles to contract simultaneously and thereby correcting atrioventricular mechanical dyssynchrony, atrioventricular interval, interventricular conduction delay and improving left ventricular (LV) contractility [19–23]. Recent studies have shown that patients who have pre-renal azotemia (probably reflecting patients with cardio-renal syndrome) showed decreased risk of death or heart failure compared to patients with a low BUN/Cr ratio [15].

4.2. Renal function and heart failure

Our study showed that the renal function stays the same for most patients and improves in patients with stage 4 & 5 CKD. CKD patients were either totally excluded or grossly underrepresented in various CRT trials. Even in the most recent MADIT-CRT had only 5% of patients with stage 4 and 5 CKD. While our study showed benefit of CRT in advanced stages of CKD, Boerringter et al. showed

Table 3
Effect of CRT on cardiovascular and renal parameters before and after CR.

Clinical parameter	Baseline	Short term follow-up (n = 317)	Long term follow-up (n = 382)
Mean follow up in days	0	100 ± 67	377 ± 164
Cardiovascular parameters			
LVEF in %	24 ± 9	28.6 ± 11 ($p < 0.001$)	33 ± 13 ($p < 0.001$)
LVEDD (cm)	6 ± 0.9	5.9 ± 0.9 ($p < 0.001$)	5.8 ± 1 ($p < 0.001$)
LVESD (cm)	5 ± 1.3	4.8 ± 1 ($p < 0.001$)	4.7 ± 1.3 ($p < 0.001$)
Mean NYHA class	3 ± 0.3	2.5 ± 0.6 ($p < 0.001$)	2.4 ± 0.6 ($p < 0.001$)
Renal parameters			
Cr (mg/dl)	1.5 ± 1.5	1.6 ± 1.5 ($p = 0.43$)	1.6 ± 1.8 ($p = 0.17$)
BUN	26 ± 18	29 ± 36 ($p = 0.35$)	27 ± 16 ($p = 0.31$)
Hb (gm/dl)	13 ± 1.8	12 ± 2($p = 0.046$)	12.6 ± 2 ($p = 0.001$)
eGFR (ml/min)	59 ± 22	57 ± 24 ($p = 0.97$)	57 ± 25 ($p = 0.11$)

Table 4
Mean GFR before and after CRT implantation during short and long term follow up.

Clinical parameter	Baseline Pre CRT GFR	Short term F-up Post CRT GFR	Long term F-up Post CRT GFR
Stage 1 (N = 34)	104 ± 13	95 ± 18 (p = 0.003)	94 ± 21 (p = 0.03)
Stage 2 (N = 157)	71 ± 8	69 ± 17 (p = 0.12)	68 ± 20 (p = 0.01)
Stage 3 (N = 185)	47 ± 8	48 ± 13 (p = 0.18)	48 ± 15 (p = 0.7)
Stage 4&5 (N = 50)	20 ± 7	27 ± 16 (p = 0.003)	28 ± 18 (p = 0.002)

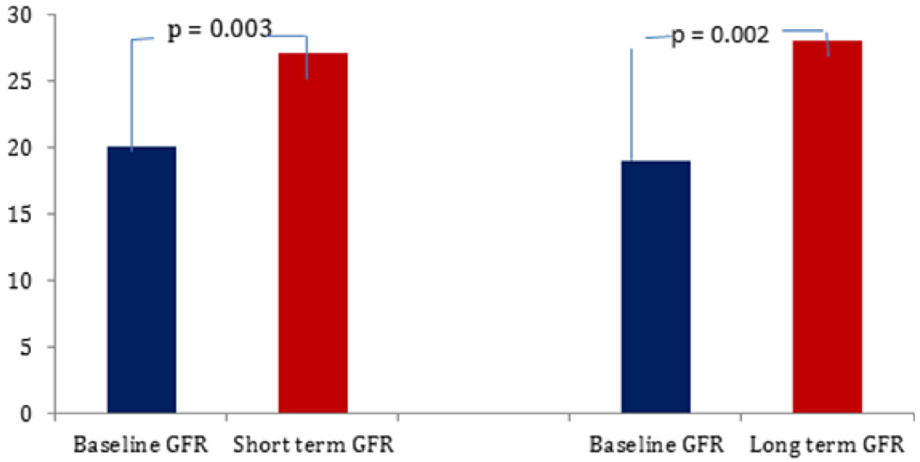

Fig. 1. Mean change in GFR during short term and long term follow up in patients with advanced stages (stage 4 and 5) CK.

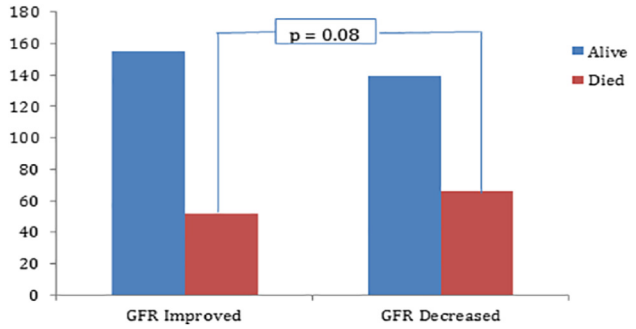

Fig. 2. Differences in mortality between patients with improved GFR vs. not.

Table 5
Predictors of long term mortality.

Variable	Odd's ratio	95% Conf interval	P value
Age	1.02	0.99–1.05	0.13
Female Gender	0.6	0.33–1.32	0.24
Diabetes	0.8	0.44–1.7	0.7
Hypertension	1.2	0.6–2.5	0.5
Coronary Artery Disease	1.04	0.52–2.1	0.9
Smoking	0.9	0.47–1.77	0.78
Atrial Fibrillation	2.6	1.4–5	0.002[a]
Hyperlipidemia	2.4	1.2–4.8	0.009[a]
LVEF inc by 5%	0.7	0.34–1.4	0.3
GFR same or inc during follow up	0.51	0.27–0.95	0.03[a]

[a] Final independent predictors of mortality after adjusting for age, gender, diabetes, hypertension, coronary artery disease, smoking, change in LVEF by 5%, atrial fibrillation and hyperlipidemia. OR-Odds ratio, CI-Confidence interval.

improvement in stage 3 CKD [11]. Overall these are very important findings that there may be a potential role of CRT in patients with cardio-renal syndrome. This shows that even patients with end stage renal disease may derive significant benefit in their LV function, renal function and mortality with CRT.

Progressive renal dysfunction could be due to several factors such as hypertension, diabetes, increasing age, and activation of renin angiotensin aldosterone system in patients with heart failure. Management of patients with heart failure and CKD often poses challenge including use of ACE inhibitors which are often discontinued by other providers due to modest increases in serum creatinine. Renal perfusion is decreased in patients with low cardiac output and this independently predicts poor outcomes [24]. In patients with decompensated heart failure, a rise in serum creatinine often leads to use of inotropic agents [25]. Reduced renal perfusion leads to reduced water excretion by nephrons and stimulates secretion of anti-diuretic hormone leading to water retention [25]. Therefore any therapy which slows down renal dysfunction or improves renal function in patients with heart failure would favor long term outcomes. Our data suggests that CRT therapy has modest impact on renal dysfunction across most stages of CKD.

Prior studies have shown that worsening renal function in heart failure patients predicts poor survival [24]. In our study we showed that an improvement in GFR shows a trend towards improved survival and is an independent predictor of survival. These effects on mortality may be due to an indirect effect of improved renal perfusion and thereby decreasing the adverse effects of abnormal neuro-hormonal activation seen in heart failure patients.

4.3. Study limitations

This is a smaller single institutional observational study. Obviously, the lack of a control group limits the systematic assessment of the progression of CKD and changes in GFR without CRT therapy. Due to smaller numbers mortality and subgroup analysis based on stages of CKD are inherently limited. The benefits of CRT were also primarily seen in patients with advanced CKD (Stage 4 and 5) which comprised of only 10% of study population. Other limitations include lack of biventricular pacing percentage data in the

responders vs non responders. Finally, the long term follow up was limited to one year due to loss of follow up. However, attempts have been made to maximize Biventricular pacing in every patient irrespective of their renal function. Larger studies are needed to further understand the role of CRT in patients with CKD and its role in preventing the progression of cardio-renal syndrome.

5. Conclusions

CRT was associated with stabilization of renal function in patients with severe LV dysfunction and improvement in stage 4 and 5 CKD. Improved renal function was associated with a lower mortality.

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Conflict of interest

No specific conflict of interest to the current study for any of the authors.

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