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

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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 ($\leq$6 months post implantation) and long term (>6 months).
Results: A total of 588 patients with mean age of 67 $\pm$ 12 yrs were included in the study. CRT responders (defined by increase in LVEF $\geq$ 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.

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

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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 $\pm$ 7 cc of contrast were given, whereas those with advanced CKD (Stage 4 and 5) were given mean 40 $\pm$ 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 $\pm$ 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 $\pm$ 559 days. The average short term follow up duration was 100 $\pm$ 67 days and the average long term follow up duration was 377 $\pm$ 164 days.

Table 1
Baseline clinical characteristics.

Baseline characteristics	
Age	67 $\pm$ 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 $\pm$ 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%)