ABSTRACT. The implementation of cardiac resynchronization therapy (CRT) to improve systolic heart failure symptoms and quality of life have been well established. Chronic kidney disease (CKD) independent of ejection fraction confers the worse prognosis. We examined the relationship between CRT and its impact on renal function. This is a retrospective chart analysis examining the improvement of serum creatinine (sCr) post CRT. All consecutive patients 18 years of age or older who were admitted to Providence Hospital and Medical Center in Southfield between January 2008 and March 2011 for CRT were analyzed. Serum creatinine, estimated glomerular filtration rate (GFR) using a Modification of the Diet in Renal Disease (MDRD) equation, and routine blood work were obtained before and after CRT implantation. The primary outcome of the study was the change in the serum creatinine levels after biventricular cardioverter-defibrillator implantation. There were 101 patients who met the study criteria. The mean baseline creatinine was 1.38 ± 0.8 prior to device implantation and 1.27 ± 0.6 (p = 0.01) after device placement. This correlated to an estimated glomerular filtration rate improvement using the MDRD equation from 62.7 ± 27.6 to 66.8 ± 27.6 (p = 0.03) in non-African American patients. In the African American population GFR was 56.8 ± 20 before device to 58.1 ± 19.6 after device implantation. We were able to demonstrate a significant improvement in baseline sCr and GFR levels after CRT.

KEYWORDS. biventricular implantable cardioverter-defibrillator, cardiac resynchronization therapy, chronic kidney disease, defibrillation, renal impairment.

Introduction

Heart failure (HF) incidence continues to grow, with more than 5 million cases in the United States and more than 23 million cases worldwide. The prevalence increases with age, further complicating treatment due to other comorbidities in the elderly population. HF with prolonged QRS duration (>120 ms) portends to worse prognosis due to more rapid structural and clinical progression related to mechanical dyssynchrony. Establishment of mechanical synchrony with biventricular (BiV) pacing has shown improvement in multiple clinical and structural parameters. It has been demonstrated from multiple previous trials that BiV pacing improves quality of life, patient performance on a 6-min walk test, oxygen delivery, and mitral regurgitation severity. The prevalence of HF in chronic kidney disease (CKD) is estimated to be 30-50%. One in 10 American adults has a variable degree of CKD, equating to about 20 million people in the United States alone (Kidney Disease Statistics for the United States, 2012). Progression of CKD is defined as a sustained decrease in glomerular filtration rate (GFR) of >5 mL/min/1.73 m²/year or sustained albuminuria. Despite improvements in HF management, the prevalence of HF-related CKD continues to increase. Cardiac renal syndrome (CRS) is defined as chronic disorder of one organ, heart, or kidney, resulting in progressive dysfunction in the other organ. CRS confers a worse prognosis independent of ejection fraction. Furthermore, mortality and morbidity is worse, irrespective of the different subtype of CRS. Appropriate management requires thorough evaluation of the temporal sequence of events to determine which organ is responsible for the other organ’s progressive failure. CRS subtype II indicates underlying chronic HF leading to progressive CKD.
Cardiac resynchronization therapy (CRT) has shown to be beneficial in achieving a multitude of clinical endpoints; thus it seems logical that improvement in renal function would also be expected. We therefore undertook this retrospective chart review to determine renal function improvement after implantation of a BiV defibrillator.

Methods

All patients that had a BiV pacemaker implanted between January 3, 2008 and March 18, 2011 were included in the study. The charts were reviewed and data collected. The study was approved by the institutional review board. Variables included patient demographics, pertinent past medical history, including but not limited to diabetes, tobacco use, coronary artery disease, alcohol use, and relevant laboratory values. The relevant laboratory values included but were not limited to electrolytes, leukocyte counts, coagulation values, and more importantly BUN and creatinine. Laboratory values were obtained for patients from before implantation of the BiV pacemaker and also after implantation. If a patient had more than one set of laboratory values from before implantation, then the laboratory values closest to the date of BiV implantation were used. Furthermore, if a patient had more than one set of values of data available from after implantation, then the values furthest from implantation were used.

We conducted a randomized retrospective chart review of 203 patients aged 18 years and older who had undergone biventricular pacemaker implantation between the dates of January 3, 2008 and March 18, 2011. The patient population ranged in age from 67 to 81 years of age, with a mean of 70.6 years. A sample of both male and female patients was obtained: 37% female and 63% male. Thirty-nine percent of the patients were tobacco users, while 60% had coronary artery disease. The baseline demographics and exclusion criteria are presented in Table 1 and Figure 1, respectively.

The patients’ pre- and post-BiV implantation glomerular filtration rate was recorded using the Modification of Diet in Renal Disease (MDRD) equation. The two data sets were analyzed for differences in the renal function post BiV ICD implantation.

Results

There were 101 patients who met the study criteria. The mean creatinine was $1.38 \pm 0.8$ prior to device implantation and $1.27 \pm 0.6$ ($p=0.01$) after device placement (Figure 3). This correlated to an estimated GFR improvement using the Modification of Diet in Renal Disease (MDRD) equation from $62.7 \pm 27.6$ to $66.8 \pm 27.6$ ($p=0.03$).
in the African American patients. In the Caucasian population GFR was 56.8 ± 20 before device implantation to 58.1 ± 19.6 after device implantation. Fisher’s exact test produced a p-value of 0.01, which was Figure 2 considered statistically significant.

Secondary laboratory values were calculated with noted significant changes between pre and post implantation for hemoglobin, platelet counts and other cell count parameters. See Table 2 for results.

### Discussion

Incidence of both HF and renal disease are on the rise. HF with reduced ejection fraction has poor prognosis and CKD adds to further increased morbidity and mortality. In the current study, CRT resulted in a significant improvement in the overall baseline serum creatinine (sCr) levels and GFR among African Americans. However, no significant GFR improvement was seen in the non-African Americans with CRT. In addition, hematopoietic lines that improved after CRT included RBC, HGB, HCT, and platelet count. Multiple factors have been associated with increased mortality and sudden cardiac death in patients with HF and CKD. Reduced cardiac output leads to renal hypoperfusion. Elevated filling pressures cause renal congestion, attenuation of outflow, and cellular injury culminating in renal injury. Renal disease accelerates vessel calcification and renal hypertension. Such changes result in rapid progression of ventricular hypertrophy, coronary artery disease and finally cardiomyopathy. Renal disease further complicates HF secondary to anemia, electrolyte disturbance, and conduction abnormalities. As a consequence, overall mortality and morbidity is increased in HF patients with CKD.

Our finding of renal function improvement after CRT replicates other studies. In the Multicenter Automatic Defibrillator Implantation Trial (MADIT-CRT) renal sub-analysis, patients with GFR >35% had mortality reduction. Renal improvements with CRT benefit have significant implications in the setting of severe to end-stage renal disease. Tura-khia et al. studied the mortality rate before and after ICD implantation. Failure to improve renal function or worsening of GFR resulted in increased mortality. Mortality was increased in end-stage renal disease and no significant mortality benefit was shown with severe renal disease. The Cardiac Resynchronization Therapy in Heart Failure (CARE-HF) study evaluated 813 patients with NYHA III or IV, QRS >120 ms with baseline GFR 61 mL/min/1.73 m² and found no benefit of CRT of mortality if GFR > 60 mL/min/1.73 m². The Multicenter InSync Randomized Clinical Evaluation Study (MIRACLE) study demonstrated improvement of GFR with CRT with GFR between <60 and >30 mL/min/1.73 m². The mechanism of renal dysfunction with CRT and poor outcome is not fully understood. Fung and colleagues evaluated 85 patients, mean baseline GFR of 56 mL/min/1.73 m² left ventricular function and renal function 3 months before and after CRT. Improvement in left ventricular remodeling (defined as >10% reduction in end systolic volume) resulted in a small but significant improvement in renal function. More importantly, failure of reverse LV remodeling at 3 months caused significant renal function deterioration. Thus, renal function improvement is a consequence of LV remodeling from CRT; absence of this remodeling indicates poor prognosis and potentially identifies higher risk patients.

More interestingly, certain bone marrow parameters also improved after implantation of CRT devices. To our knowledge, no prior study has shown these findings. Anemia and abnormal platelet function is well established in CKD patients. Abnormal renal function results in decreased erythropoietin (EPO) hormone with several resultant consequences. First, reduced levels of EPO suppress erythropoiesis in the bone marrow leading to reductions in hemoglobin levels. Secondly, red blood cell life span is reduced because of deficient EPO levels. Both physiologic events cause anemia of chronic disease resulting in further exacerbation of underlying HF and subsequent renal disease. Reduced red blood cell production causes reduced iron-carrying capacity and high output HF, cardiomyopathy, and myocyte death; the cycle of HF worsening renal function and vice versa accelerated the decline of both organ functions. Intervention to reduce or prevent one or both disease processes can have a potential benefit in both organs.

There are several limitations in our current study. First, it is a retrospective chart review; therefore, data were limited by electronic medical record. Second, laboratory values were not standardized pre- and post-CRT implantation. The improvement in renal and cardiac function with placement of a BiV ICD has important implications given the paucity of studies linking improved renal function to cardiac resynchronization therapy. Our study contributes to better define additional benefits of CRT and the role of CRT in cardio renal syndrome. To fully address these findings, a large randomized study may be warranted.

### Conclusion

We were able to demonstrate a significant improvement in baseline sCr and GFR levels after CRT. Moreover, several hematopoietic stem lines improved, suggesting additional benefits of CRT therapy not previously described.

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**Table 2: Clinical and Laboratory change before and after CRT implantation**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Pre-implant value</th>
<th>Post-implant value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>1.38 ± 0.8</td>
<td>1.27 ± 0.6</td>
<td>0.01</td>
</tr>
<tr>
<td>GFRF-CA</td>
<td>62.2 ± 27.6</td>
<td>66.8 ± 27.6</td>
<td>0.03</td>
</tr>
<tr>
<td>GFRF-C</td>
<td>56.8 ± 20.0</td>
<td>58.1 ± 19.6</td>
<td>0.5</td>
</tr>
<tr>
<td>SBP</td>
<td>129.5 ± 20.9</td>
<td>129.3 ± 21.2</td>
<td>0.9</td>
</tr>
<tr>
<td>DBP</td>
<td>70.3 ± 13.9</td>
<td>70.9 ± 13.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Pulse</td>
<td>75.3 ± 18.1</td>
<td>75.0 ± 14.6</td>
<td>0.6</td>
</tr>
<tr>
<td>RBC</td>
<td>4.0 ± 0.6</td>
<td>4.3 ± 0.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HGB</td>
<td>12.1 ± 1.8</td>
<td>12.6 ± 1.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HCT</td>
<td>36.3 ± 5.1</td>
<td>37.8 ± 5.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RDW</td>
<td>15.4 ± 2.2</td>
<td>15.1 ± 2.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Platelets</td>
<td>176.0 ± 57.9</td>
<td>195.6 ± 70.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

RBC: Red Blood Cell, HGB: Hemoglobin, HCT: Hematocrit, RDW: Red Cell Distribution Width
Figure 2: GFR levels before and after CRT implantation. Significant improvement of GFR in the AA but not Caucasian group pre- and post CRT. AA: African American; CRT: cardiac resynchronization therapy; GFR: glomerular filtration rate.

Creatinine improvement pre- and post CRT

$P = 0.01$

Figure 3: Change in serum creatinin before and after CRT implantation
References


