Cardiac Resynchronization Therapy in Patients with and without Atrial Fibrillation

Hung-Ta Wo, Po-Cheng Chang, Tien-Hsing Chen and Chun-Chieh Wang

Background: Cardiac resynchronization therapy (CRT) has emerged as an effective option in selected heart failure (HF) patients with electro-mechanical dyssynchrony. Several prospective, randomized controlled trials have proven its safety and clinical efficacy. However, most of these trials only enrolled patients in sinus rhythm (SR). The benefits of CRT in patients with atrial fibrillation (AF) are not yet well evaluated.

Methods: Fifty-six patients who received CRT between 2002 and 2008 were divided into two groups, SR and AF. Baseline characteristics were collected at the time of implantation. Echocardiographic examinations were performed in every patient within 2 days before and 6 months after device implantation. Echocardiographic parameters, tissue velocity, and strain images were analyzed.

Results: Forty patients were in SR and 16 had either persistent or permanent AF at the time of CRT implantation. Pre-CRT parameters showed no statistical difference between the two groups. Both groups had similar rates of clinical and echocardiographic responders. Six months after CRT, left ventricular ejection fraction of both groups had improved (26 ± 7% to 38 ± 15% in SR, p < 0.001; 27 ± 7% to 34 ± 11% in AF, p < 0.004). Indices of synchronicity (QRS duration, septal-posterior wall motion delay, standard deviation of time to peak tissue velocity, all p < 0.001) were improved in both groups.

Conclusion: Both patients in SR and AF showed similar responses to CRT. CRT therapy should be considered in AF patients with persistent HF symptoms and electro-mechanical dyssynchrony after optimal medical therapy.

Key Words: Atrial fibrillation • Cardiac resynchronization therapy • Sinus rhythm

INTRODUCTION

Despite advances in medical therapy, heart failure continues to be a major health issue, with high rates of morbidity and mortality. Advanced heart failure patients frequently have severe persistent symptoms leading to a poor quality of life. Heart failure and atrial fibrillation (AF) are two increasingly prevalent conditions that predispose to each other and frequently coexist.1 Cardiac resynchronization therapy (CRT) has been established as a therapeutic modality for patients with drug-refractory heart failure and left bundle branch block. CRT is indicated in sinus rhythm (SR) patients with symptomatic advanced heart failure (New York Heart Association [NYHA] functional class III or ambulatory class IV) despite optimal medical therapy, reduced left ventricular systolic function (left ventricular ejection fraction ≤ 35%), and evidence of electrical dyssynchrony (QRS duration ≥ 120 ms).2

Despite the high prevalence of AF observed among patients with moderate to severe heart failure, CRT has not been evaluated in a large, randomized clinical trial in patients with AF. In the most recent European Society of Cardiology (ESC) recommendations3 and American Col-
College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines, impaired left ventricular systolic function and intraventricular conduction delay (either de novo or paced) in the setting of AF were listed as class II indications to receive CRT.

In the present study, we retrospectively compared the baseline characteristics and analyzed the results after CRT in patients with either SR or AF. We also assessed the improvement in synchronicity indices in both groups.

MATERIALS AND METHODS

A retrospective study was performed in 56 patients treated with CRT at our institution between 2002 and 2008 who fulfilled the following criteria: left ventricular ejection fraction \(< 35\%\), complete left bundle branch block with intrinsic or paced QRS duration \(< 130\text{ ms}\), and NYHA functional class III or ambulatory class IV heart failure symptoms on optimal medical therapy. All patients were divided into two groups, SR and AF (persistent or permanent), at the time of CRT device implantation. Baseline characteristics were collected at the time of implantation. All patients had high dependency on ventricular pacing (paced percentage > 90\%) because of complete atrioventricular block or AF with slow ventricular rate.

All implantations were performed via intravenous approach. Pacing leads were inserted into cephalic or subclavian veins using standard implantation techniques. Left ventricular pacing leads were placed in a lateral, posterolateral, or posterior cardiac vein. Programming of atrioventricular delay in SR patients was optimized using mitral inflow pulse wave Doppler image. Programming of biventricular pacing was based on aortic outflow velocity-time integral.

Echocardiographic examinations (Vivid 7; GE Medical Systems, Milwaukee, WI, USA) were performed 2 days before and 6 months after device implantation. Left ventricular end-systolic and end-diastolic volumes and ejection fraction were measured according to the guidelines of the American Society of Echocardiography. Mitral regurgitation was quantitatively estimated by calculating the area of the regurgitant orifice using the proximal isovelocity surface area method. Septal-posterior wall motion delay was measured by the time difference between maximal systolic motions from the septum to the posterior wall in M-mode. To calculate left ventricular synchronicity, 12 segments of left ventricle (basal and mid-septal, basal and mid-lateral, basal and mid-inferior, basal and mid-anterior, basal and mid-posterior, and basal and mid-anteroseptal) were analyzed using apical four-chamber, two-chamber, and apical long-axis views, respectively. A 10-mm sample volume was used to calculate the duration between initiation of QRS and peak longitudinal myocardial velocity (TpV) and strain (TpS). To assess the severity of dyssynchrony, standard deviations of TpV and TpS were calculated. Echo responders (reverse remodeling) were defined as those with a decrease in left ventricular end-systolic volume \(\geq 15\%\).

The effects of CRT on left ventricular size and function, mitral regurgitation, NYHA functional class, echo responder rate, and standard deviation of time to peak systolic strain rate were compared between patients with AF and those in SR.

Statistical analysis

Continuous variables with normal distribution were expressed as mean \(\pm\) standard deviation, and variables without normal distribution as median [first quartile; third quartile]. Categorical variables were presented as patient number (percentage). The chi-squared or Fisher’s exact tests were used to compare categorical variables. Unpaired Student’s \(t\)-test was used to compare continuous variables with normal distribution between two groups. For continuous variables without normal distribution, the Mann-Whitney \(U\) test was used to compare differences between the two groups. To compare two paired data, we used paired \(t\)-test for variables with normal distribution, Wilcoxon signed test for variables without normal distribution, and McNemar’s test for two paired proportions. Significance was set at a 2-tailed \(p\) value of < .05. All statistical analyses were performed using the SPSS software (version 15.0, SPSS Inc, Chicago, Illinois, USA).

RESULTS

Among these 56 patients, 40 (71\%) were in SR and 16 (29\%) had AF. Baseline characteristics and pre-implantation medications of both group patients were shown in Table 1. Pre-CRT QRS duration was 169 \(\pm\) 17
ms in the SR group and 166 ± 23 ms in the AF group (p = NS). There was no statistically significant difference in medical comorbidities: diabetes mellitus (40% in SR vs. 38% in AF), hypertension (53% vs. 50%), hyperlipidemia (38% vs. 13%), and coronary artery disease (25% vs. 50%). Medication usages between both groups also showed no statistical difference except for a higher rate of spironolactone use in AF patients (35% vs. 69%, p = 0.04). Table 2 shows the analysis of CRT responses. Both groups showed significant improvement 6 months after cardiac resynchronization therapy, but no statistical difference in clinical (72% vs. 94%, p = NS) and echocardiographic responder rate (59% vs. 50%, p = NS). Left ventricular ejection fraction significantly improved in both groups (SR group: 26 ± 7% to 38 ± 15%, p < 0.001; AF group: 27 ± 7% to 34 ± 11%, p < 0.004). All indices of synchronicity significantly had improved in both groups at six months: QRS duration 169 ± 17 ms to 149 ± 19 ms in SR, and 166 ± 23 ms to 147 ± 19 ms in AF; septal-posterior wall motion delay 217 ± 99 ms to 62 ± 27 ms in SR and 225 ± 96 ms to 165 ± 113 ms in AF; standard deviation of time to peak tissue velocity (SDTpV) 120 ± 70 ms to 046 ± 18 ms in SR and 098 ± 55 ms to 42 ± 24 ms in AF, all p < 0.001). There was also a significant reduction in the severity of dyssynchrony as shown by the standard variation of TpS (SDTpS) in both groups. However, the effect of CRT on mitral regurgitation was less significant in AF patients.

Of the 16 AF patients during CRT, 5 required interventions to terminate persistent AF due to relatively small left atrial size (< 50 mm); 3 electric cardioversion, 2 pharmacological intervention, and 2 surgical procedures.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>SR group (n = 40)</th>
<th>AF group (n = 16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>66 ± 14</td>
<td>68 ± 13</td>
<td>0.62</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>168 ± 18</td>
<td>166 ± 23</td>
<td>0.64</td>
</tr>
<tr>
<td>Female, sex (%)</td>
<td>13 (33%)</td>
<td>5 (31%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>16 (40%)</td>
<td>6 (38%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>21 (53%)</td>
<td>8 (50%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>15 (38%)</td>
<td>2 (13%)</td>
<td>0.11</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>10 (25%)</td>
<td>8 (50%)</td>
<td>0.11</td>
</tr>
<tr>
<td>ACEI/ARB (%)</td>
<td>33 (83%)</td>
<td>14 (88%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Beta blockers (%)</td>
<td>32 (80%)</td>
<td>12 (75%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Spironolactone (%)</td>
<td>14 (35%)</td>
<td>11 (69%)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>32 (80%)</td>
<td>16 (100%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Nitrate (%)</td>
<td>16 (40%)</td>
<td>10 (63%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>17 (43%)</td>
<td>5 (31%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Defibrillator (%)</td>
<td>14 (40%)</td>
<td>10 (63%)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker; AF, atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; SR, sinus rhythm.

Data was presented as mean ± standard deviation or number of patients (percentage).

*p < 0.05

Table 2. Echocardiographic variables, QRS durations and NYHA functional classes before and after CRT in both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>SR group (n = 40)</th>
<th>AF group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-CRT</td>
<td>Post-CRT</td>
</tr>
<tr>
<td></td>
<td>3 [3; 3]</td>
<td>72%</td>
</tr>
<tr>
<td>Subjective responder</td>
<td>149 ± 19***</td>
<td></td>
</tr>
<tr>
<td>Echo responder rate</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>169 ± 17</td>
<td>149 ± 19***</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>26 ± 7</td>
<td>38 ± 15***</td>
</tr>
<tr>
<td>MR scale</td>
<td>1 [1; 1]</td>
<td>10 [1; 2]***</td>
</tr>
<tr>
<td>SDtpS (ms)</td>
<td>120 ± 70</td>
<td>46 ± 18***</td>
</tr>
<tr>
<td>SDtpV (ms)</td>
<td>118 ± 53</td>
<td>77 ± 37***</td>
</tr>
<tr>
<td>SPWMD (ms)</td>
<td>217 ± 99</td>
<td>62 ± 27***</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA Fc, New York Heart Association functional class; SDtpS, standard deviation of time to peak systolic strain rate; SDtpV, standard deviation of time to peak systolic tissue velocity; SPWMD, septal-posterior wall motion delay; SR, sinus rhythm.

Variables with normal distribution are presented as mean ± standard deviation. Variables without normal distribution are presented as median [first quartile; third quartile]. Categorical variables are shown as percentages.

*p < 0.05; **p < 0.005; ***p < 0.001.

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one pharmacological cardioversion, and one hybrid therapy for atrial flutter and AF. Three of these 5 patients (60%) remained in SR 6 months after CRT.

**DISCUSSION**

Heart failure and AF are two increasingly prevalent conditions that predispose to each other and frequently co-exist. The prevalence of AF is closely related to NYHA functional class. Although the prevalence of AF is 0.4% of the general population, the prevalence is 5% for NYHA functional class I, 10% to 25% for class II to III, and 50% for class IV. The permanent form of AF is present in 10% to 30% of patients with heart failure and is associated with increased morbidity and mortality. AF adversely affects cardiac hemodynamics by several mechanisms. Loss of atrial contraction can limit net filling and delay mitral valve closure, augmenting pre-systolic regurgitation. Diastolic filling is further impaired by short cycle lengths with rapid AF. Persistently rapid rates can eventually lead to systolic depression. Rate irregularity itself may negatively impact cardiac performance.

CRT is an important device-based, non-pharmacological approach to improve the outcome in selected patients with heart failure. Because all major trials of CRT have enrolled patients in SR, the current standard indications of CRT include LVEF < 35%, QRS duration ≤ 120 ms, SR, and NYHA functional class III or ambulatory class IV heart failure symptoms on optimal medical therapy. On the other hand, data on CRT in patients with AF and heart failure are limited. The efficacy of CRT in patients with permanent AF was first investigated in a short-term study which showed a significant improvement in hemodynamics during biventricular stimulation. Subsequent observational studies and small randomized crossover trials suggested a benefit from CRT in patients with AF. In the most recent ESC recommendations, AF patients were considered eligible to receive CRT. The ACC/AHA/HRS guidelines also favorably considered CRT in heart failure patients with AF.

Our study also shows that patients with AF may benefit from CRT. In our study, both patients in SR and in AF showed similar responses to CRT at six-months, as assessed by clinical and echocardiographic responses. Patients with AF also had a significant improvement in NYHA functional class and left ventricular ejection fraction. To assess synchronicity, we measured not only the QRS duration and septal-posterior wall motion delay, but also TpS and TpV. All indices of synchronicity significantly improved in both groups.

The only statistically significant difference of baseline characteristics between the two groups was the use of spironolactone. Since previous studies had shown that spironolactone improved long-term outcomes in heart failure patients, we performed multivariate analysis to assess the influence of this confounding factor. By logistic regression analysis (not shown), difference between two groups in the use of spironolactone did not influence the subjective responder rate or the echo responder rate.

For patients with AF, an important issue is the consistent and complete delivery of CRT. The delivery of CRT is dependent on effective and complete biventricular capture. In patients with AF, there is no atrioventricular synchrony and therefore inability to establish coordinated atrioventricular sequential pacing. Biventricular capture is more difficult to achieve. Furthermore, patients with AF often have intermittently or persistently accelerated ventricular rates even when pacing rates are well programmed. In addition to pharmacological rate control, atrioventricular junction ablation in AF is increasingly being used as an important adjunct to ensure adequate CRT delivery. Several trials have suggested that atrioventricular junction ablation plus CRT significantly improve left ventricular function and functional capacity compared to CRT alone. However, our study showed that patients who did not undergo atrioventricular junction ablation also had an improved functional capacity and responder rate.

Rhythm control of AF may be achieved by either pharmacological or non-pharmacological means, e.g. electrical cardioversion or pulmonary vein isolation. In our study, 5 of 16 patients with AF during CRT implantation required interventions (electrical cardioversion, pharmacological cardioversion, or hybrid therapy) to terminate persistent AF. Three of these 5 patients (60%) remained in SR 6 months after CRT.

At present, limited data are available comparing CRT with or without atrioventricular junction ablation or AF ablation in patients with heart failure. Khan et al.

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showed that pulmonary vein isolation had a high success rate and that, compared to the best possible rate control and rate regulation strategies (atrioventricular junction ablation with CRT), pulmonary vein isolation provided superior morphologic and functional improvements.

**CONCLUSION**

This retrospective analysis shows that patients in both normal SR and AF may benefit from CRT. CRT should be considered in AF patients with persistent heart failure symptoms and electro-mechanical dyssynchrony after optimal medical therapy.

**REFERENCES**


