Cardiac resynchronization therapy in chronic atrial fibrillation: Impact on left atrial size and reversal to sinus rhythm
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Running Head: Cardiac resynchronization therapy in chronic atrial fibrillation

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Abstract

Objective: Evaluation of the impact of long-term cardiac resynchronization therapy (CRT) on left atrial and left ventricular (LV) reverse remodeling and reversal to sinus rhythm (SR) in heart failure (HF) patients with atrial fibrillation (AF).

Background: The onset of AF in patients with advanced HF is associated with an increased morbidity and mortality.

Patients: 74 consecutive patients (age 67±7 yrs; 67 men) with advanced HF and AF (20 persistent; 54 permanent) were implanted with a CRT-device.

Main outcome measures: Patients were evaluated clinically (NYHA class, quality of life, 6 minute walk test) and echocardiographically (LV ejection fraction, LV diameters and left atrial diameters) before and after 6 months of CRT. Additionally, restoration of SR was evaluated after 6 months of CRT.

Results: NYHA class, quality of life score, 6 minute walking test and LV ejection fraction had improved significantly after 6 months of CRT. In addition, left atrial and LV enddiastolic and endystolic diameters had decreased from 59±9 to 55±9mm, from 72±10 to 67±10mm and from 61±11 to 56±11mm respectively (all: p<0.01). During implantation 18/20 (90%) patients with persistent AF were cardioverted into SR. At follow-up 13/18 (72%) patients had returned to AF and no spontaneous reversal into SR had occurred, thus only 5/74 (7%) were in SR.

Conclusion: Six months of CRT resulted in significant clinical benefit with significant left atrial and LV reverse remodeling. Despite these beneficial effects, reversal to SR was not established in 93% of patients.
Introduction
An estimated 30-40% of patients with severe heart failure develop atrial fibrillation (AF) over time.[1] The incidence of AF increases in parallel to the increase in severity of heart failure, approaching 50% of patients affected in NYHA class IV.[2] The onset of AF may further worsen heart failure symptoms through the loss of regular atrioventricular conduction, the irregularity of the ventricular rhythm and the frequently rapid ventricular response rate. Once AF develops in patients with heart failure, morbidity and mortality increase steeply.[3]
Several studies have demonstrated that cardiac resynchronization therapy (CRT) can be beneficial in heart failure patients with concomitant AF in terms of improved symptoms, exercise capacity, systolic left ventricular (LV) function and survival.[4][5][6][7] However, currently minimal data exist on the impact of long-term CRT on left atrial and/or LV reverse remodeling in patients with AF and the results are contradictory.[5] [7] Accordingly, the aim of this study was to evaluate the impact of long-term CRT on left atrial and LV dimensions. In addition, the exact treatment of patients with AF undergoing CRT is unclear; concomitant AV-node ablation has been proposed to avoid non-capture of pacing during AF. On the other hand, it has been suggested that patients may return to sinus rhythm after CRT, making AV-node ablation unnecessary. However, it is currently unclear whether patients with chronic AF will reverse to sinus rhythm after CRT. This issue is clinically very important and in the current study the percentage of patients reversing to sinus rhythm after CRT was also evaluated.
Patients and Methods

Study Population, Study Protocol

In the current study, 74 consecutive patients with advanced heart failure and concomitant AF were included; all underwent implantation of a CRT device. Patients with persistent (defined as recurrent AF, lasting more than 7 days and requiring electrical cardioversion to terminate, without recurrence in 24 hours) and permanent AF (defined as AF failing to terminate after cardioversion or recurrence within 24 hours after termination) were included.[8]

Eligibility for CRT was based on the following criteria: 1) advanced heart failure with NYHA functional class III or IV, 2) LV ejection fraction <35%, and 3) wide QRS complex (>120ms or >200 ms for a paced QRS) with left bundle-branch block configuration on the ECG. Patients with ischemic and non-ischemic cardiomyopathy were evaluated. All patients were evaluated clinically and echocardiographically before implantation and after 6 months follow-up. Data from 2 centers, with large experience in CRT, were combined.

Cardiac Resynchronization Therapy - Device Implantation

After obtaining a coronary sinus venogram, a LV pacing lead (Easytrack 4512-80, Guidant, MN, USA or Attain-SD 4189, Medtronic Inc., MN, USA) was inserted transvenously via the subclavian route with the help of an 8F guiding catheter, and positioned in a (postero-)lateral vein.[9] The leads were connected to either a standard DDDR device (with AV delay set at the shortest possible value[6]) or a CRT device (Contak TR/ Contak Renewal, Guidant, MN, USA or InSync III/ InSync CD, Medtronic Inc., MN, USA). Immediately after CRT implantation, electrical cardioversion to terminate AF was attempted in the 20 patients with persistent AF.

Clinical Evaluation

Patients were evaluated clinically at baseline and after 6 months of CRT. A surface ECG was obtained (12 leads at a paper speed of 50 mm/s) to establish QRS morphology and duration. Heart failure symptoms were classified according to the NYHA score and the Minnesota Living with Heart Failure questionnaire[10] was used to assess the quality of life. In order to establish exercise capacity, the 6-minute hall walk test[11] was used. Cardiac rhythm was evaluated using repetitive 48-hours Holter registrations, using ECGs during out-patient clinic visits and interrogation of the CRT device.

Echocardiographic Evaluation

Transthoracic echocardiography was performed the day before CRT implantation and after 6 months of CRT. Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid 7, General Electric – Vingmed, Milwaukee, WI, USA or Sonos 5500; Hewlett Packard, Philips Medical Systems, Eindhoven, the Netherlands). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis, 2-chamber and 4-chamber images). Standard 2-dimensional and color Doppler data, triggered to the QRS complex, were saved in cine loop format. The LV ejection fraction was derived from the conventional apical 2- and 4-chamber images using the biplane Simpson’s rule.[12] Left atrial and LV dimensions were determined from M-mode echocardiography under two-dimensional guidance in the parasternal long-axis view, according to the guidelines of the American Society of Echocardiography.[13] The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler in the conventional parasternal long-axis and apical 4-chamber images.
Mitral regurgitation was characterized as: minimal=1+ (jet area/left atrial area<10%), moderate=2+ (jet area/left atrial area 10-20%), moderately severe =3+ (jet area/left atrial area 20-45%), and severe=4+ (jet area/left atrial area >45%).[14] All data were obtained at baseline and after 6 months of CRT.

**Statistical Analysis**

Data were expressed as mean ± SD. Comparison of data was performed using the Student t-test for paired and unpaired data when appropriate. Proportions were compared using the Fisher's exact test, whereas the Wilcoxon signed rank test was performed in case of markedly skewed distribution of the data. McNemar's test for paired dichotomous data was performed to compare cardiac rhythm before and after 6 months of CRT. For all tests a p-value <0.05 was considered significant.
Results

Patient Characteristics

Seventy-four patients from 2 centers were included. The study population comprised 67 men, 7 women with a mean age of 68±8 years. Fifty-four (73%) patients had permanent AF whereas 20 (27%) patients had persistent AF. A total of 51 (69%) patients underwent AV-node ablation. In 11 patients, AV-node ablation was performed >1 year before CRT implantation (mean duration of RV pacing 7±4 years), and the remaining 40 patients underwent AV-node ablation within 3 days of CRT implantation.

Heart failure was secondary to ischemic heart disease in 32 (43%) patients. Additional baseline characteristics are summarized in Table 1.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Men/Women</th>
<th>67/7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>68±8</td>
</tr>
<tr>
<td>Atrial fibrillation classification:</td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td>20 (27%)</td>
</tr>
<tr>
<td>Permanent</td>
<td>54 (73%)</td>
</tr>
<tr>
<td>Heart failure underlying etiology:</td>
<td></td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>37 (50%)</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>32 (43%)</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>QRS duration (ms) (non-paced, n=63)</td>
<td>176±30</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>61 (82%)</td>
</tr>
<tr>
<td>IV</td>
<td>13 (18%)</td>
</tr>
<tr>
<td>Quality-of-life score</td>
<td>39±16</td>
</tr>
<tr>
<td>6-Minute walking test (m)</td>
<td>289±116</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>22±7</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>72±10</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>61±10</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>59±9</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td></td>
</tr>
<tr>
<td>grade 3-4+</td>
<td>27 (36%)</td>
</tr>
<tr>
<td>grade 2+</td>
<td>35 (47%)</td>
</tr>
<tr>
<td>grade 1+</td>
<td>10 (14%)</td>
</tr>
</tbody>
</table>

NYHA: New York Heart Association; LV: left ventricular

All patients had optimized medical therapy that included ACE-inhibitors (94%), beta-blockers (60%), diuretics (100%), digoxin (46%) and amiodarone (40%); all patients used anticoagulants. Medical therapy remained unchanged throughout the entire study.
Clinical Data

At baseline, all patients were in NYHA class III (61 patients, 82%) or IV (13 patients, 18%) with an average QRS duration of 180±31ms (range 122-260ms). All patients had left bundle branch block or a RV paced QRS configuration on the ECG. After 6 months of CRT, the NYHA class decreased significantly from 3.2±0.4 at baseline to 2.2±0.6 (p<0.01) at six months follow-up. The quality-of-life score decreased from 39±16 to 25±15 (p<0.01). In addition, the exercise capacity improved, reflected by a significant improvement in the 6-minute walking distance from 289±116 m to 383±105 m (p<0.01) after 6 months of CRT. Responders were defined as those patients who improved ≥1 class in NYHA score after 6 months of CRT. Accordingly, 58 patients (74%) were classified as responders and 16 (21%) as non-responders. There was a significant difference in percentage of clinical responders that favoured patients who had AV-node ablation (44/51, 86%) compared with patients who did not have ablation (14/23, 61%, p<0.05). In patients without AV-node ablation however, the percentage of ventricular pacing was 81% vs 100% in the ablated patients. Closer examination of the clinical data demonstrated that the non-responders in NYHA class did not improve significantly in quality-of-life and exercise capacity either (Table 2).

Table 2. Comparison of clinical parameters between implant and 6-months follow-up for responders (n=58) and non-responders (n=16)

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=58)</th>
<th>Non-Responders (n=16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA</td>
<td>3.2±0.4</td>
<td>3.1±0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>QOL</td>
<td>39±17</td>
<td>41±16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>6minWT</td>
<td>298±108</td>
<td>287±138</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

NYHA: New York Heart Association; QOL: Quality of life; 6 min WT: 6-minute walking test

Echocardiographic Data

In the entire group, the LV ejection fraction at baseline was 22±7%, which increased significantly to 29±10% after 6 months of CRT (p<0.01). In addition, significant LV reverse remodeling was observed during follow-up, as evidenced by the decrease in LV end-diastolic diameter from 72±10 mm at baseline to 67±10 mm (p<0.01) after 6 months of CRT and the decrease in LV end-systolic diameter from 61±11 mm to 56±11 mm (p<0.01). The left atrium showed reverse remodeling as well, with a reduction from 59±9 mm at baseline to 55±9 mm (p<0.01) at 6-months follow-up. At baseline, 27 (36%) patients had severe (grade 3-4+) mitral regurgitation, whereas 35 (47%) patients had moderate (grade 2+) regurgitation. In 45 (61%) patients the severity of mitral regurgitation had reduced by 1 grade or more after 6 months of CRT, with 8 (11%) patients still having severe (grade 3-4+) regurgitation and 18 (24%) having moderate (grade 2+) regurgitation. The relation between the changes in mitral regurgitation and left atrial dimension over time is displayed in Figure 1. Patients who exhibited an improvement by 1 or 2 grades in mitral regurgitation showed a significant decrease in mean left atrial dimension from 58±9mm before to 53±9mm (p<0.01) after 6 months of CRT. In contrast,
patients without improvement in mitral regurgitation did not show reduction in left atrial dimension (59±9 mm vs 60±10mm) after CRT. Left atrial and LV reverse remodeling was only observed in responders to CRT; the non-responders did not show a reduction in left atrial and LV dimensions (Figure 2). Similar observations were noted for mitral regurgitation: 40 (69%) responders showed an improvement in mitral regurgitation by 1 grade or more as opposed to 5 (31%, p<0.01) non-responders. In addition, 3 (19%) non-responders showed worsening in mitral regurgitation after CRT.

Persistence of Atrial Fibrillation

Before implantation of the CRT device all patients were in AF. Immediately after implantation, sinus rhythm was successfully restored by electrical cardioversion in 18 of the 20 patients with persistent AF. After 6 months of CRT however, 13 of these 18 (72%) patients had returned to AF and no spontaneous reversal into SR had occurred (Figure 3). Thus, of 74 patients with chronic AF undergoing CRT, sinus rhythm was restored in only 5 (7%) patients after 6 months of CRT.
Discussion
In the present study, CRT resulted in improved symptoms, exercise capacity, systolic LV function and LV reverse remodeling in patients with severe heart failure and chronic AF. In addition, left atrial reverse remodeling was demonstrated in this patient population. The left atrial reverse remodeling however did not result in restoration to sinus rhythm in heart failure patients with concomitant AF. These findings suggest that AV-node ablation should be considered in patients with chronic AF undergoing CRT.

Clinical response to CRT
Various studies have demonstrated that CRT is beneficial in heart failure patients with sinus rhythm.[5][15] Recent studies have also focused on the benefit of CRT in heart failure patients with chronic AF, since these patients have a substantially increased morbidity and mortality.[3] These studies demonstrated that patients with AF may benefit from CRT as well.[4][5][6][7] Leon et al showed an improvement in clinical parameters in 20 patients with chronic AF. In particular, NYHA class improved by 29%, quality of life by 33% and the LV ejection fraction improved by 44%.[7] Leclercq et al reported a 10% improvement in 6-minute walking distance in a substudy from the Multisite Stimulation in Cardiomyopathies (MUSTIC) trial, which is the only randomized trial evaluating AF patients.[6] Similar results were obtained in the present study. A significant improvement in NYHA class, quality-of-life score and 6-minute hall walk test were demonstrated after 6 months of CRT. However, on an individual basis, 22% of patients did not respond to CRT, in line with studies in patients with sinus rhythm.[16] A significantly greater benefit was observed in patients who had an AV-node ablation. This may be explained by the fact that AV-node ablation ensures 100% ventricular capture, whereas 100% capture and rate control is difficult with medical therapy.[7][17] Even with optimized rate control in the non-ablated patients, only an average of 81% ventricular pacing during CRT was obtained.

Left Atrial and Ventricular Reverse Remodeling
After 6 months of CRT, a significant reduction in LV end-diastolic and LV end-systolic diameter was observed. These beneficial effects of CRT have been described previously in heart failure patients in sinus rhythm.[18][19] Only 2 studies have addressed LV reverse remodeling in AF patients undergoing CRT. Leon et al reported a significant decrease in LV end-diastolic diameter (6.5%) and end-systolic diameter (8.5%) in 22 patients with permanent AF and prior AV-node ablation after 3-6 months of CRT.[7] In contrast, Linde et al did not report changes in LV dimensions in 41 patients with AF who were enrolled in the Multisite Stimulation in Cardiomyopathy (MUSTIC) study.[5] The authors did however report a 50% reduction in severity of mitral regurgitation. This observation was confirmed in the current study, with 45 (61%) patients improving ≥1 grade in mitral regurgitation. Reduction of the mitral regurgitation can by explained by a decreased LV sphericity secondary to LV reverse remodeling[20] or to resynchronization of postero-lateral wall with subsequent resynchronization of the posterior papillary muscle, resulting in improved leaflet coaptation.[20][21][22] Similar to LV reverse remodeling, left atrial reverse remodeling was also observed. The left atrial dimension decreased significantly from 58±9 mm before to 53±9 mm after 6 months of CRT. A relation between the reduction in left atrial dimension and
the decrease in mitral regurgitation was shown. Only patients with an improvement in mitral regurgitation by 1 grade or more showed a reduced left atrial dimension after 6 months of CRT, suggesting that improvement in left atrial volume overload may result in left atrial reverse remodeling.[23]

Persistence of atrial fibrillation
After 6 months of CRT, 69 (93%) patients were in AF including 13 of 18 patients who had been successfully cardioverted to sinus rhythm at the time of CRT implantation. Although 2 case-reports were published[24][25] on a spontaneous reversal to sinus rhythm after long-term CRT, we could not demonstrate a spontaneous reversal to sinus rhythm in this relatively large group of patients with chronic AF, even despite a significant decrease in left atrial dimension after 6 months of CRT. Nattel et al developed an animal model, simulating the atrial alterations occurring as a result of chronic atrial stretch secondary to heart failure.[26] The authors demonstrated that atrial "structural remodeling" (i.e. altered atrial tissue architecture or interstitial fibrosis) was the most important mechanism underlying AF in heart failure.[26] Recently Cha et al[27] demonstrated in a canine model that left atrial structural remodeling is irreversible as opposed to "ionic remodeling" (following atrial tachyarrhythmias), the other important factor underlying AF.[28][29] Similar observations have been reported in studies in heart failure patients with AF.[30] Thus, it appears that not the size of the left atrium, but rather the structural remodeling is important in predicting restoration of sinus rhythm. Since structural remodeling is an irreversible process, AV-node ablation should be considered in patients with chronic AF undergoing CRT, since spontaneous reversal to sinus rhythm after CRT (secondary to a reduction in left atrial dimension) does virtually not occur.

Conclusion
The current observations demonstrate that 6 months of CRT in heart failure patients with chronic AF resulted in improvement in clinical parameters with significant LV and left atrial reverse remodeling together with a significant decrease in mitral regurgitation. Despite these beneficial effects, reversal to sinus rhythm was not established. These results, together with the observation that AF patients with AV-node ablation responded significantly better to CRT, suggest that AV-node ablation may be a useful consideration in patients with chronic AF undergoing CRT. Further studies with larger patient cohorts are warranted to confirm these results.
Figure 1

Change in MR (grade) vs. LAd (mm) for different time points:
- 0 (n=15): LAd = 59, 60
- 1 (n=26): LAd = 57, 53
- 2 (n=19): LAd = 61, 54

* indicates statistical significance.
Figure 2.

Responders vs Non-Responders

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders</th>
<th>Non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAd</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>LVedd</td>
<td>66</td>
<td>70</td>
</tr>
<tr>
<td>LVesd</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>LVesd</td>
<td>61</td>
<td>61</td>
</tr>
</tbody>
</table>

* indicates a significant difference.
Figure 3

Bar chart showing the percentage of Implant and 6-months follow-up.

- Implant:
  - AF: 80%
  - SR: Some percentage

- 6-months follow-up:
  - AF: 100%
  - SR: Some percentage with an asterisk (*) indicating a significant difference.
Legends

**Figure 1** Relation between the change in mitral regurgitation (MR) (0: equal grade; 1= reduction by 1 grade; 2= reduction by 2 grades) and the left atrial diameter (LAd) between baseline (black columns) and 6 months follow-up (white columns) * p<0.01

**Figure 2** Mean left atrial- (LAd), left ventricular end-diastolic- (LVedd) and left ventricular end-systolic diameter (mm) at baseline (black columns) and after 6 months of CRT (white columns) * p<0.01

**Figure 3** Percentage of patients in atrial fibrillation (AF) and sinus rhythm (SR) at implant and at 6 months follow-up * p<0.01

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We have no competing interests to declare
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