CARDIOVASCULAR MEDICINE

Cardiac resynchronisation therapy in chronic atrial fibrillation: impact on left atrial size and reversal to sinus rhythm

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Objective: To evaluate the impact of long term cardiac resynchronisation therapy (CRT) on left atrial and left ventricular (LV) reverse remodelling and reversal to sinus rhythm (SR) in patients with heart failure with atrial fibrillation (AF).

Patients: 74 consecutive patients (age 68 (8) years; 67 men) with advanced heart failure and AF (20 persistent and 54 permanent) were implanted with a CRT device.

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

Results: NYHA class, quality of life score, six minute walk test, and LV ejection fraction had improved significantly after six months of CRT. In addition, left atrial and LV end diastolic and end systolic diameters had decreased from 59 (9) to 55 (9) mm, from 72 (10) to 67 (10) mm, and from 61 (11) to 56 (11) mm, respectively (all $p < 0.01$). During implantation 18 of 20 (90%) patients with persistent AF were cardioverted to SR. At follow up 13 of 18 (72%) patients had returned to AF and none had spontaneously reverted to SR; thus, only 5 of 74 (7%) were in SR.

Conclusion: Six months of CRT resulted in significant clinical benefit with significant left atrial and LV reverse remodelling. Despite these beneficial effects, 93% of patients had not reverted to SR.

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 New York Heart Association (NYHA) class IV.² The onset of AF may further worsen heart failure symptoms through the loss of regular atrioventricular (AV) 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 shown that cardiac resynchronisation therapy (CRT) can be beneficial to heart failure patients with concomitant AF in terms of improved symptoms, exercise capacity, systolic left ventricular (LV) function, and survival.^{4–7} However, minimal data exist on the impact of long term CRT on left atrial or LV reverse remodelling in patients with AF, and the results are contradictory.^{5–7} Accordingly, the objective 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 unclear whether patients with chronic AF will revert to sinus rhythm after CRT. This issue is clinically very important and in the current study the percentage of patients reverting 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 enrolled;

all underwent implantation of a CRT device. Patients with persistent (defined as recurrent AF, lasting more than seven 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 (> 120 ms or > 200 ms for a paced QRS) with left bundle branch block configuration on the ECG. Patients with ischaemic and non-ischaemic cardiomyopathy were evaluated. All patients were evaluated clinically and echocardiographically before implantation and after six months' follow up. Data from two centres, with large experience in CRT, were combined.

CRT device implantation

After a coronary sinus venogram was obtained, an LV pacing lead (Easytrack 4512–80, Guidant, Arden Hills, Minnesota, USA or Attain-SD 4189, Medtronic Inc, Minneapolis, Minnesota, USA) was inserted transvenously through the subclavian route with the help of an 8 French 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) or a CRT device (Contak TR/Contak Renewal, Guidant, or InSync III/InSync CD, Medtronic Inc).⁶ Immediately after CRT implantation,

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; CRT, cardiac resynchronisation therapy; LV, left ventricular; MUSTIC, multisite stimulation in cardiomyopathy; NYHA, New York Heart Association

electrical cardioversion to terminate AF was attempted in the 20 patients with persistent AF.

Clinical evaluation

Patients were evaluated clinically at baseline and after six 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 was used to assess the quality of life.¹⁰ To establish exercise capacity, the six minute hall walk test was used.¹¹ Cardiac rhythm was evaluated by repetitive 48 hour Holter registrations, from ECGs recorded during outpatient clinic visits and interrogation of the CRT device.

Echocardiographic evaluation

Transthoracic echocardiography was performed the day before CRT implantation and after six months of CRT. Patients were imaged in the left lateral decubitus position with a commercially available system (Vingmed Vivid 7, General Electric–Vingmed, Milwaukee, Wisconsin, USA; or Sonos 5500, Hewlett Packard, Philips Medical Systems, Eindhoven, the Netherlands). Images were obtained by a 3.5 MHz transducer at a depth of 16 cm in the parasternal and apical views (standard long axis, two chamber, and four chamber images). Standard two dimensional and colour Doppler data, triggered to the QRS complex, were saved in cine-loop format. The LV ejection fraction was derived from the conventional apical two and four chamber images with 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 semiquantitatively from colour flow Doppler in the conventional parasternal long axis and apical four chamber images. Mitral regurgitation was characterised 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 six months of CRT.

Statistical analysis

Data were expressed as mean (SD). Data were compared by Student's *t* test for paired and unpaired data when appropriate. Proportions were compared by Fisher's exact test, whereas the Wilcoxon signed rank test was applied to data with highly skewed distribution. McNemar's test for paired dichotomous data was performed to compare cardiac rhythm before versus after six months of CRT. For all tests $p < 0.05$ was considered significant.

RESULTS

Patient characteristics

Seventy four patients from two centres were studied. The study population comprised 67 men and seven women with a mean (SD) age of 68 (8) years. Fifty four (73%) patients had permanent AF and 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 right ventricular pacing 7 (4) years) and the remaining 40 patients underwent AV node ablation within three days of CRT implantation.

Heart failure was secondary to ischaemic heart disease in 32 (43%) patients. Table 1 summarises additional baseline characteristics.

Table 1 Baseline characteristics

Men/women	67/7
Age (years)	68 (8)
Atrial fibrillation classification	
Persistent	20 (27%)
Permanent	54 (73%)
Heart failure underlying aetiology	
Idiopathic dilated cardiomyopathy	37 (50%)
Ischaemic cardiomyopathy	32 (43%)
Valve disease	5 (7%)
QRS duration (ms) (non-paced, n = 63)	176 (30)
NYHA class	
III	61 (82%)
IV	13 (18%)
QOL score	39 (16)
6 min WT (m)	289 (116)
LV ejection fraction (%)	22 (7)
LV end diastolic diameter (mm)	72 (10)
LV end systolic diameter (mm)	61 (11)
Left atrial diameter (mm)	59 (9)
Mitral regurgitation	
grade 3–4+	27 (36%)
grade 2+	35 (47%)
grade 1+	10 (14%)

LV, left ventricular; NYHA, New York Heart Association; QOL, quality of life; WT, walk test.

All patients had optimised medical treatment that included angiotensin converting enzyme inhibitors (94%), β blockers (60%), diuretics (100%), digoxin (46%), and amiodarone (40%); all patients used anticoagulants. Medical treatment remained unchanged throughout the entire study.

Clinical data

At baseline, all patients were in NYHA class III (61 (82%) patients) or IV (13 (18%) patients) with an average QRS duration of 180 (31) ms (range 122–260 ms). All patients had left bundle branch block or a right ventricular paced QRS configuration on the ECG. After six 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 six minute walk distance from 289 (116) m to 383 (105) m ($p < 0.01$) after six months of CRT. Responders were defined as those patients who improved by ≥ 1 NYHA class after six months of CRT. Accordingly, 58 patients (78%) were classified as responders and 16 (22%) as non-responders. A significant difference in percentage of clinical responders favoured patients who had AV node ablation (44 of 51 (86%)) compared with patients who did not have ablation (14 of 23 (61%), $p < 0.05$). Among patients without AV node ablation, however, the percentage of ventricular pacing was 81% versus 100% of the ablated patients.

Closer examination of the clinical data showed that the non-responders in NYHA class did not improve significantly in quality of life and exercise capacity either (table 2).

Echocardiographic data

In the entire group, the LV ejection fraction at baseline was 22 (7)%, which increased significantly to 29 (10)% after six months of CRT ($p < 0.01$). In addition, significant LV reverse remodelling 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 six 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 had reverse remodelling as well, with a reduction from 59 (9) mm at baseline to 55 (9) mm ($p < 0.01$) at six months' follow up.

Table 2 Comparison of clinical parameters between implantation and six months' follow up for responders and non-responders

	Responders (n = 58)			Non-responders (n = 16)		
	Implant	6 months	p Value	Implant	6 months	p Value
NYHA	3.2 (0.4)	1.9 (0.5)	<0.01	3.1 (0.3)	3.1 (0.4)	NS
QOL	39 (17)	22 (13)	<0.01	41 (16)	34 (19)	NS
6 min WT (m)	298 (108)	411 (69)	<0.01	287 (138)	279 (150)	NS

NS, not significant.

Figure 1 Relation between change in mitral regurgitation (MR) (0: equal grade; 1: reduction by one grade; 2: reduction by two grades) and left atrial diameter (LAd) between baseline (black columns) and six months' follow up (white columns). * $p < 0.01$.

At baseline, 27 (36%) patients had severe (grade 3–4+) mitral regurgitation and 35 (47%) patients had moderate (grade 2+) regurgitation. In 45 (61%) patients the severity of mitral regurgitation had reduced by one grade or more after six months of CRT, with eight (11%) patients still having severe (grade 3–4+) regurgitation and 18 (24%) having moderate (grade 2+) regurgitation.

Figure 1 shows the relation between the changes in mitral regurgitation and left atrial dimension over time. Patients who exhibited an improvement by one or two grades in mitral regurgitation had a significant decrease in mean left atrial dimension from 58 (9) mm before to 53 (9) mm ($p < 0.01$) after six months of CRT. In contrast, patients without improvement in mitral regurgitation did not have reduced left atrial dimension (59 (9) mm *v* 60 (10) mm) after CRT. Left atrial and LV reverse remodelling were observed

only in responders to CRT; the non-responders did not have reduced left atrial and LV dimensions (fig 2).

Observations for mitral regurgitation were similar; 40 (69%) responders had improved mitral regurgitation by ≥ 1 grade as opposed to five (31%, $p < 0.01$) non-responders. In addition, three (19%) non-responders had worsened mitral regurgitation after CRT.

Persistence of AF

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 six months of CRT, however, 13 of these 18 (72%) patients had returned to AF and none reverted spontaneously to sinus rhythm (fig 3). Thus, of 74 patients with chronic AF undergoing CRT, sinus rhythm was restored in only five (7%) patients after six months of CRT.

DISCUSSION

In the present study, CRT improved symptoms, exercise capacity, systolic LV function, and LV reverse remodelling in patients with severe heart failure and chronic AF. In addition, left atrial reverse remodelling was observed in this patient population. Left atrial reverse remodelling, however, did not restore sinus rhythm in patients with heart failure with concomitant AF. These findings suggest that AV node ablation should be considered for patients with chronic AF undergoing CRT.

Clinical response to CRT

Various studies have shown that CRT is beneficial to patients with heart failure in sinus rhythm.^{5–15} Recent studies have also focused on the benefit of CRT to patients with heart failure with chronic AF, since these patients have substantially increased morbidity and mortality.³ These studies showed that patients with AF may benefit from CRT as

Figure 2 Mean left atrial diameter (LAd), left ventricular end diastolic diameter (LVedd), and left ventricular end systolic diameter (LVesd) (mm) at baseline (black columns) and after six months of cardiac resynchronisation therapy (white columns). * $p < 0.01$.

Figure 3 Percentage of patients in atrial fibrillation (AF) and sinus rhythm (SR) at implantation and at six months' follow up. * $p < 0.01$.

well.^{4–7} Leon *et al*⁷ reported improved 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 by 44%.⁷ Leclercq *et al*⁶ reported a 10% improvement in six minute walk distance in a substudy of the MUSTIC (multisite stimulation in cardiomyopathy) trial, which is the only randomised trial evaluating patients with AF. We obtained similar results in the present study. Significant improvements in NYHA class, quality of life score, and six minute hall walk test were seen after six months of CRT. However, on an individual basis, 22% of patients did not respond to CRT, in line with studies of patients with sinus rhythm.¹⁶ A significantly greater benefit was observed among 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 are difficult with medical treatment.^{7, 17} Even with optimised rate control in the non-ablated patients, an average of only 81% ventricular pacing during CRT was obtained.

Left atrial and ventricular reverse remodelling

After six months of CRT, significant reductions in LV end diastolic and LV end systolic diameters were observed. These beneficial effects of CRT have been described previously in patients with heart failure in sinus rhythm.^{18, 19} Only two studies have addressed LV reverse remodelling in AF patients undergoing CRT. Leon *et al*⁷ reported significant decreases 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*⁸ did not report changes in LV dimensions in 41 patients with AF who were enrolled in the MUSTIC study. 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 mitral regurgitation can be explained by a decreased LV sphericity secondary to LV reverse remodelling or to resynchronisation of the posterolateral wall with subsequent resynchronisation of the posterior papillary muscle, resulting in improved leaflet coaptation.^{20–22}

Similar to LV reverse remodelling, left atrial reverse remodelling was also observed. The left atrial dimension decreased significantly from 59 (9) mm before to 55 (9) mm after six months of CRT. A relation between the reduction in left atrial dimension and the decrease in mitral regurgitation was shown. Only patients with improved mitral regurgitation by ≥ 1 grade had a reduced left atrial dimension after six months of CRT, suggesting that improvement in left atrial volume overload may result in left atrial reverse remodelling.²³

Persistence of AF

After six 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 two case reports were published on spontaneous reversal to sinus rhythm after long term CRT, we found no spontaneous reversal to sinus rhythm in this relatively large group of patients with chronic AF, despite a significant decrease in left atrial dimension after six months of CRT.^{24, 25} Nattel's group developed an animal model simulating the atrial alterations occurring as a result of chronic atrial stretch secondary to heart failure.²⁶ The authors reported that atrial "structural remodelling" (that is, altered atrial tissue architecture or interstitial fibrosis) was the most important mechanism underlying AF in heart failure.²⁶ Recently Cha *et al*²⁷ showed in a canine model that left atrial structural remodelling is irreversible as opposed to "ionic remodelling" (after atrial tachyarrhythmias), the other important factor underlying AF.^{28, 29} Similar observations have been reported from studies of patients with heart failure with AF.³⁰ Thus, it appears that it is not the size of the left atrium but rather the structural remodelling that is important in predicting restoration of sinus rhythm. Since structural remodelling is an irreversible process, AV node ablation should be considered for patients with chronic AF undergoing CRT, since spontaneous reversal to sinus rhythm after CRT (secondary to a reduction in left atrial dimension) virtually does not occur.

Conclusion

The current observations showed that six months of CRT in patients with heart failure with chronic AF improved clinical parameters with significant LV and left atrial reverse remodelling 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 patients with AF who received AV node ablation responded significantly better to CRT, suggest that AV node ablation may be a useful consideration for patients with chronic AF undergoing CRT. Further studies with larger patient cohorts are warranted to confirm these results.

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IMAGES IN CARDIOLOGY .....

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Delayed hyperenhancement of the pericardium by magnetic resonance imaging as a marker of pericardial inflammation in a patient with tuberculous effusive constrictive pericarditis

A 37 year old man was evaluated for progressively worsening exertional dyspnoea and abdominal distension. On physical examination, the jugular vein was distended and the liver was enlarged. An ECG showed sinus tachycardia with low voltage QRS. Echocardiography showed a large amount of pericardial effusion without significant haemodynamic compromise. However, abnormal septal motion (septal bouncing) was noted, suspicious of constrictive physiology. Closed pericardiostomy with biopsy was performed. After pericardiostomy with drainage, echocardiographic features of constrictive physiology persisted and thus verified the presence of effusive constrictive pericarditis. Contrast enhanced image obtained by magnetic resonance imaging showed prominent delayed hyperenhancement localised at the visceral and parietal pericardium (left panel). Pathology showed severe inflammation with granuloma and caseous necrosis consistent with tuberculosis (AFB stain: positive) (right panel). This case shows that a non-invasive imaging modality—contrast enhanced magnetic resonance imaging—may be useful for the assessment of pericardial inflammation.

Left: Contrast enhanced image obtained by magnetic resonance imaging of short axis view showed prominent delayed hyperenhancement localised at the visceral and parietal pericardium. Right: Pathology showed severe inflammation with granuloma and caseous necrosis consistent with tuberculosis.

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