Europace (2016) **18**, 1211–1219
doi:10.1093/europace/euv382

Atrial reverse remodelling is associated with outcome of cardiac resynchronization therapy†

Mariëlle Kloosterman, Michiel Rienstra, Bart A. Mulder, Isabelle C. Van Gelder, and Alexander H. Maass*

Department of Cardiology, Thoraxcenter, University of Groningen, University Medical Center Groningen, P.O. Box 30.001, Groningen RB 9700, The Netherlands

Received 1 April 2015; accepted after revision 25 October 2015; online publish-ahead-of-print 30 December 2015

Aims To study the prognostic effect of atrial reverse remodelling on outcome of cardiac resynchronization therapy (CRT).

Methods and results Patients receiving a CRT device in the University Medical Centre Groningen were included. Atrial reverse remodelling was defined as a $\geq$10% reduction in left atrial volume index at 6-month follow-up. Success of CRT was defined as ventricular reverse remodelling with a reduction in left ventricular end-systolic volume of $\geq$15% at 6-month follow-up. Primary endpoint was all-cause mortality or heart failure hospitalizations. A total of 365 patients (mean age 65.1 $\pm$ 11.0 years, 73% men) were included; among them, 221 (61%) were in sinus rhythm and had no prior atrial fibrillation (AF), and 144 patients (39%) had a history of AF. During a mean follow up of 2.0 $\pm$ 1.0 years, 49 patients died. Cox regression analysis revealed that patients with *no* atrial and *no* ventricular reverse remodelling had the worst outcome (hazard ratio 3.1, 95% confidence interval 1.4–7.1, $P = 0.006$). Outcome in patients with *only* atrial reverse remodelling was comparable with outcome in patients with *both* atrial and ventricular reverse remodelling (hazard ratio 2.0, 95% confidence interval 0.7–5.6, $P = 0.21$).

Conclusion Patients without atrial and ventricular reverse remodelling have the worst outcome. Patients with only atrial reverse remodelling have improved left ventricular diastolic filling during follow-up and demonstrate a comparable outcome with patients with both atrial and ventricular reverse remodelling. Assessment of atrial reverse remodelling may provide additional prognostic information in determining CRT outcome.

Keywords Cardiac resynchronization therapy • Reverse remodelling • Left atrial volume • Outcome • Diastolic dysfunction

Introduction

Improvement of left ventricular (LV) systolic function has been well established in patients receiving cardiac resynchronization therapy (CRT). It is associated with reduced morbidity and mortality, making it an effective treatment for patients with heart failure and cardiac dyssynchrony.[1–3]

Not only left ventricular function but also left atrial (LA) function is an integral part of cardiac function, since the atrial contraction augments the ventricular volume.[4] The loss of atrial contraction has been known to increase mitral and tricuspid regurgitation and reduce diastolic filling, thereby decreasing cardiac index.[5] Further, LA size is a powerful outcome predictor in patients with heart failure, independent of left ventricular geometry, systolic and diastolic function.[5–8]

The relationship between the left atrium and left ventricle can be characterized as dynamic and interactive, and the left atrium can, to a certain extent, respond to changing haemodynamics. However, there is a limit to the atria's adaptive mechanisms.[5] The impaired ventricular relaxation that occurs during diastolic dysfunction leads to elevated intra-ventricular pressure, which in turn causes pressure and volume overload of the left atrium. Because of its thin-walled structure, it tends to dilate and remodel with increasing pressure.[9] Unloading this pressure may improve the atrial function and size. Indeed, improvement of atrial function, as well as reversed atrial remodelling, can be seen after successful CRT.[10–13]

The role of simultaneous atrial and ventricular reverse remodelling on outcome of CRT and the presence of discordance between atrial and ventricular changes during CRT have not been adequately evaluated. Therefore, the purpose of this study was to explore the

* Corresponding author. Tel: +31 50 3611327; fax: +31 50 3614391. *E-mail address*: a.h.maass@umcg.nl

†Part of this manuscript was presented in abstract form during the Scientific Sessions of the American Heart Association in Chicago on 15 November 2014.

What's new?

- There is discordance in atrial and ventricular reverse remodelling in a significant number of patients who receive cardiac resynchronization therapy (CRT): a decrease in left ventricle size can be accompanied by an increase in LA size, just as that an increase in left ventricle size can be accompanied by a decrease in LA size.
- Patients with only atrial reverse remodelling showed an improvement in left ventricular diastolic filling time, filling fraction, and velocity time integral of the diastolic transmitral flow during follow-up.
- The event-free survival of patients with *only* atrial reverse remodelling did not significantly differ compared with patients with *both* atrial and ventricular reverse remodelling.
- Adverse atrial and ventricular remodelling seems to be an important contributor to a worse outcome.
- Ventricular reverse remodelling should not merely be the focus in assessing outcome after CRT. Atrial reverse remodelling may provide additional prognostic information.

prognostic implications of concordant and discordant atrial and ventricular reverse remodelling on outcome of CRT in patients with either sinus rhythm (SR) or atrial fibrillation (AF).

Methods

Patient population and study protocol

This was a single-centre, retrospective, observational study performed at the University Medical Centre Groningen in the Netherlands. Consecutive patients who received a CRT device from January 2001 until December 2012 were identified. Eligibility criteria for CRT implantation were based on the standard European Society of Cardiology guidelines.[3] The presence of AF was not an exclusion criterion for CRT implantation. Our standard CRT protocol has been described before.[14,15] At enrolment and 6-montly thereafter all patients were seen according to a standard follow-up protocol at the outpatient clinic for regular follow-up and CRT interrogation. This included a detailed medical history, physical examination, transthoracic echocardiography, and treadmill cardiopulmonary exercise testing as well as a standard 12-lead electrocardiogram. As stated in our CRT protocol, all patients received echocardiography-based atrioventricular (AV) delay optimization 2–4 weeks after implantation (AHM) as well as regular device interrogations by pacemaker technicians. Device counters were used to assess the percentage of biventricular pacing. All patients performed a treadmill cardiopulmonary exercise test to ensure biventricular pacing during exercise, i.e. during higher heart rates. Atrial fibrillation was monitored during follow-up, and patients were treated according to our standardized rhythm control strategy. The protocol emphasized aggressive rhythm or rate control strategy. Initial rhythm control included electrical cardioversion or chemical cardioversion with amiodarone if needed. When rhythm control was no longer an option, AF was accepted and rate control therapy was instituted aiming for pharmacological strict rate control, as assessed by exercise testing, to confirm continuous biventricular pacing. Atrioventricular node (AVN) ablation was only performed if the pharmaceutical treatment was not sufficient and AF prevented continuous biventricular pacing.

Device implantation

All patients were implanted with a CRT defibrillator or pacemaker. All market-released devices were used in the registry. Lead location depended on venous vasculature. In all patients, the most desirable position for the LV pacing lead, being mid/basal postero-lateral, was pursued. In post-myocardial infarction patients, the LV lead was placed outside segments that contained scar tissue if possible. The right ventricle lead was placed in apical position in most patients, with a few leads placed septally. The right atrial pacing lead was fixated into the right atrial appendage if present and accessible. If this was not the case, the lead was fixated to the anterior or lateral free wall.

Echocardiographic evaluation

Transthoracic echocardiography was performed at baseline and 6 months after CRT implantation. Images were obtained from the parasternal (long- and short-axis) and apical (two- and four-chamber) views. Atrial and ventricular dimensions were assessed by standard measurements. Left ventricular end-diastolic (LVEDV) and end-systolic volumes (LVESV) were measured with the modified biplane Simpson method using the apical two- and four-chamber views. Left atrial size was also measured from standard apical two- and four-chamber views, according to the biplane Simpson method, by manually tracing the blood–tissue boundary of the maximal frame occurring close to LV end systole. The borders consisted of the walls of the left atrium and a line drawn across the mitral annulus. Attention was paid to bridge the ostia of pulmonary veins (when visualized), as well as the LA appendage to not include these in the measurement. After correcting for body surface area, these measurements resulted in the left atrial volume index (LAVI). The measurements of the ventricles and atria were performed at the central echo core-lab located in the UMCG by two independent investigators (B.A.M. and M.K.) unaware of the clinical response of the patient. Left ventricular ejection fraction (LVEF) was calculated from LVEDV and LVESV. Diastolic filling parameters were measured (AHM) in patients with only atrial reverse remodelling by measuring EA time, RR time, and the velocity time integral (VTI) of the diastolic transmitral flow at baseline and during follow-up.

Definitions

Atrial fibrillation or atrial tachyarrhythmias were defined as any episode lasting at least 30 s with an atrial rate of >180 beats per minute as verified by electrocardiogram, Holter recording, or device interrogation. Patients were considered to have a history of AF if there were documented AF episodes before implantation. Atrial fibrillation burden was defined as the time being in AF during follow-up as assessed by device counters. In the current literature, there is no definition or agreement on what constitutes clinically relevant atrial reverse remodelling. We pre-specified atrial reverse remodelling as a reduction in LAVI of 10% or more after 6 months of therapy. Ventricular reverse remodelling was defined as a reduction in left ventricular end-systolic volume of 15% or more, 6 months after CRT implantation. Patients were categorized into four groups based on the presence or the absence of atrial and ventricular reverse remodelling. Patients had either *both* atrial and ventricular reverse remodelling, *only* ventricular reverse remodelling without atrial reverse remodelling, *only* atrial reverse remodelling without ventricular reverse remodelling or *no* atrial and ventricular reverse remodelling. The amount of mitral regurgitation was graded on a four-point scale, and mitral regurgitation was defined as Grade III (moderately severe) or IV (severe). Creatinine clearance was calculated using the Cockcroft-Gault formula.

Table 1 Baseline characteristics

	Total study population (*n* = 365)	Atrial and ventricular reverse remodelling (*n* = 76)	Only ventricular reverse remodelling (*n* = 125)	Only atrial reverse remodelling (*n* = 40)	No atrial and ventricular reverse remodelling (*n* = 124)	*P*-value for trend
Age (year)	65.1 ± 11.0	65.4 ± 11.0	65.0 ± 11.2	61.9 ± 11.4	66.0 ± 10.7	0.2
Male sex, *n* (%)	268 (73)	52 (68)	92 (74)	30 (75)	94 (76)	0.7
History of AF, *n* (%)	144 (40)	23 (30)	54 (43)	11 (28)	56 (45)	0.06
Type of AF, *n* (%)						0.3
Paroxysmal	35 (10)	6 (8)	13 (10)	4 (10)	12 (10)	
Persistent	65 (18)	12 (16)	25 (20)	5 (13)	23 (18)	
Permanent	44 (12)	5 (7)	16 (13)	2 (5)	21 (17)	
None	221 (61)	53 (70)	71 (57)	29 (73)	68 (55)	
Total AF duration, median (IQR)—years	5.1 (1.1–10.2)	5.4 (1.3–10.1)	5.2 (0.9–11.2)	2.5 (1.2–6.0)	5.5 (1.1–9.9)	0.4
AV node ablation, *n* (%)	14 (4)	3 (4)	7 (6)	0 (0)	4 (3)	0.4
Ischaemic cardiomyopathy (CAD/MI), *n* (%)	174 (48)	33 (43)	55 (44)	18 (45)	68 (55)	0.3
Previous cardiac surgery (CABG/valve surgery), *n* (%)	102 (28)	19 (25)	36 (29)	10 (25)	37 (30)	0.9
Hypertension, *n* (%)	179 (49)	40 (53)	59 (47)	22 (55)	58 (47)	0.7
Diabetes mellitus, *n* (%)	75 (21)	18 (24)	23 (18)	11 (28)	23 (19)	0.5
NYHA class for heart failure (%)						0.6
II/III/IV	36/60/4	34/65/1	40/55/5	40/57/3	31/64/5	
Blood pressure (mmHg)						
Systolic blood pressure	118 ± 20	118 ± 20	120 ± 19	119 ± 20	117 ± 20	0.5
Diastolic blood pressure	72 ± 11	71 ± 12	73 ± 11	74 ± 10	71 ± 11	0.2
Body mass index[b] (kg/m^2)	27.0 ± 4.5	27.2 ± 5.4	26.8 ± 3.8	27.6 ± 5.8	27.0 ± 4.1	0.8
Peak VO_2 (mL/min/kg)	15.2 ± 4.8	14.5 ± 5.1	16.2 ± 5.5	14.7 ± 3.7	14.7 ± 3.8	0.08
Electrocardiogram						
Heart rate, mean ± SD—bpm	75 ± 15	74 ± 17	75 ± 15	77 ± 12	75 ± 13	0.7
QRS duration, mean ± SD—ms	159 ± 25	166 ± 24	160 ± 26	162 ± 22	153 ± 24	0.006
Left bundle branch block, *n* (%)	270 (74)	57 (75)	97 (78)	32 (80)	84 (68)	0.2
PR duration, mean ± SD—ms	191 ± 43	182 ± 38	189 ± 38	189 ± 63	197 ± 43	0.2
Medication, *n* (%)						
Beta-blocker (including sotalol)	324 (89)	71 (93)	110 (88)	33 (83)	110 (89)	0.3
ACE inhibitor	277 (76)	54 (71)	98 (78)	29 (73)	96 (77)	0.6
ARB	68 (19)	14 (18)	25 (20)	9 (23)	20 (16)	0.8
Diuretic	302 (83)	64 (84)	103 (82)	33 (83)	102 (82)	0.9
Digoxin	46 (13)	7 (9)	15 (12)	6 (15)	18 (15)	0.7
Amiodaron	51 (14)	14 (18)	15 (12)	6 (15)	16 (13)	0.6
Statin	196 (54)	38 (50)	64 (51)	22 (55)	72 (58)	0.6

Continued

Table 1 *Continued*

	Total study population (*n* = 365)	Atrial and ventricular reverse remodelling (*n* = 76)	Only ventricular reverse remodelling (*n* = 125)	Only atrial reverse remodelling (*n* = 40)	No atrial and ventricular reverse remodelling (*n* = 124)	*P*-value for trend
Nitrate	52 (14)	8 (11)	21 (17)	5 (13)	18 (15)	0.7
Oral anticoagulation	257 (70)	53 (70)	88 (70)	27 (68)	89 (72)	0.9
Aspirin	100 (27)	21 (28)	31 (25)	15 (38)	33 (27)	0.5
Echocardiographic parameters						
Left atrial size, parasternal—mm	48 ± 8	47 ± 10	48 ± 9	47 ± 6	48 ± 8	0.7
Left atrial volume index (mL/m^2)	43 ± 19	44 ± 17	40 ± 21	45 ± 14	43 ± 19	0.4
Right atrial size, length—mm	58 ± 10	58 ± 11	57 ± 11	57 ± 10	60 ± 9	0.1
Septal thickness (mm)	10 ± 2	10 ± 2	10 ± 2	9 ± 2	9 ± 2	0.3
Posterior wall thickness (mm)	9 ± 2	9 ± 2	9 ± 1	9 ± 2	9 ± 2	0.9
LV end-diastolic volume (mL)	231 ± 100	258 ± 121	232 ± 93	227 ± 108	213 ± 86	0.03
LV end-systolic volume (mL)	174 ± 83	190 ± 91	184 ± 83	171 ± 95	155 ± 69	0.01
Left ventricular volume index (mL/m^2)	87 ± 40	97 ± 45	92 ± 41	85 ± 44	77 ± 33	0.002
LVEF (%)	24 ± 9	24 ± 10	24 ± 9	22 ± 8	25 ± 10	0.2
Mitral valve regurgitation,[c] *n* (%)	96 (26)	26 (34)	24 (19)	13 (33)	33 (27)	0.09
Tricuspid valve regurgitation,[c] *n* (%)	38 (10)	12 (16)	7 (6)	3 (8)	16 (13)	0.08
PA-TDI interval (ms)	126 ± 36	126 ± 39	128 ± 39	123 ± 27	122 ± 27	0.8
TAPSE	19 ± 5	19 ± 5	19 ± 5	19 ± 5	18 ± 5	0.2
Laboratory values						
Creatinine, median (IQR)—μmol/L	100 (83–128)	103 (83–141)	94 (82–122)	99 (81–117)	104 (86–127)	0.2
NT-proBNP, median (IQR)—pg/mL	1371 (596–2991)	1845 (650–3695)	1251 (523–2877)	1399 (575–3326)	1426 (648–2801)	0.3

ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blockers; CABG, coronary artery bypass surgery; CAD, coronary artery disease; LV, left ventricular; MI, myocardial infarction; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PA-TDI, total atrial conduction time assessed by tissue Doppler imaging; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.
[a]Plus–minus values are mean ± SD.
[b]The body mass index is the weight in kilograms divided by the square of the height in meters.
[c]Mitral and tricuspid valve regurgitation denotes moderately severe (Grade III) or severe (Grade IV) regurgitation.

All-cause mortality was defined as any death or heart transplantation. Heart failure hospitalization was defined as admission to a health-care facility lasting more than 24 h with symptoms of congestive heart failure requiring intravenous diuretics. Since group definitions were determined after 6 months follow-up, any deaths or hospitalizations during the first 6 months after inclusion were not counted in the study's results and were not used in determining outcome.

Statistical analysis

Patients' demographic and disease characteristics at baseline are presented for the total study population, as well as the four different groups. They are presented as mean ± standard deviation or median (interquartile range) for continuous variables and numbers with percentages for categorical variables, as required. Differences between the four groups were evaluated by one-way ANOVA, Kruskal–Wallis, or χ^2 test depending on normality and type of the data. Differences between two groups were evaluated by independent samples Student's *t*-test, Mann–Whitney *U* test, χ^2 test, or Fisher's exact test depending on normality and type of data. To compare paired echocardiographic data at baseline and during follow-up, the paired Student's *t*-test, Wilcoxon's signed rank test, or McNemar's test was used depending on normality and type of data. Uni- and multivariate logistic regression analyses were performed to analyse which parameters were associated with atrial or ventricular reverse remodelling at 6 months. Backward stepwise multivariable regression analysis was conducted using all variables with $P \leq 0.1$ from the univariate analysis. The final multivariate model included all variables with $P < 0.05$. The Kaplan–Meier analyses were used to assess the incidence of all-cause mortality or heart failure hospitalizations. The Cox regression analyses were performed with the model being adjusted for gender, age at implantation, mitral regurgitation (Grade III/IV), ischaemic cardiomyopathy, creatinine clearance, and AF. Analyses were performed with SPSS 22.0.0.1 for Windows. A *P*-value of < 0.05 was considered statistically significant.

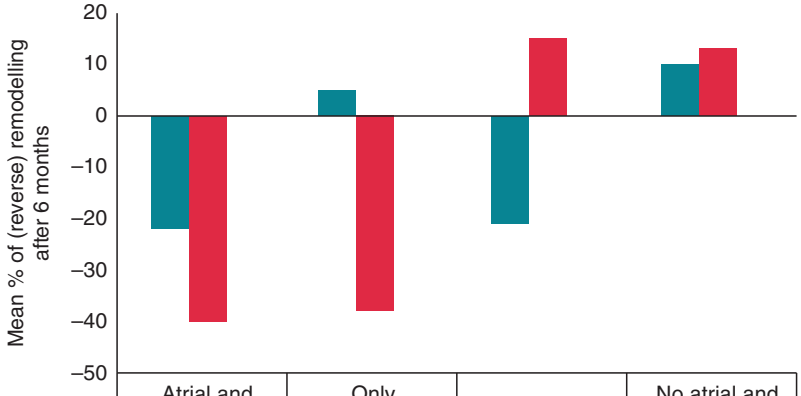
Results

Baseline characteristics

A total of 365 patients were included. Of them, 221 patients (61%) had SR and no prior history of AF; 144 patients (39%) had a history of AF, of which 80 patients (56%) had AF at baseline. A total of 14 patients (4%) had an AVN ablation prior to receiving the CRT. These patients were equally divided among the four groups based on the presence or absence of reverse remodelling of the left atrium and ventricle. Patients' characteristics are outlined in *Table 1*. Underlying diseases were equally distributed among the groups. Patients with both atrial and ventricular reverse remodelling had larger LVESV (190 ± 91 vs. 155 ± 69 mL, $P = 0.005$) and LVEDV (258 ± 121 vs. 213 ± 86 mL, $P = 0.006$) when compared with patients with no atrial and ventricular reverse remodelling. A smaller left atrium at baseline was an important determinant of maintaining SR. Also, patients without atrial reverse remodelling presented more often with a history of AF [110 (44%) vs. 34 (29%), $P = 0.007$].

Follow-up

After 6 months, the overall degree of atrial reverse remodelling was comparable between patients with both atrial and ventricular reverse remodelling, and atrial reverse remodelling only (22 and 21%, respectively, *Figure 1*). The overall degree of ventricular reverse remodelling was comparable between patients with both atrial and ventricular reverse remodelling and ventricular reverse remodelling only (40 and 38%, respectively, *Figure 1*). Patients with no atrial and ventricular reverse remodelling had, when compared with patients with ventricular reverse remodelling only, a relatively bigger increase in LA volume from baseline to 6 months (10 vs. 5% increase, $P = 0.01$, *Figure 1*). Only patients without atrial and



	Atrial and ventricular reverse remodelling	Only ventricular reverse remodelling	Only atrial reverse remodelling	No atrial and ventricular reverse remodelling
ΔLAVI (%)	–22	5	–21	10
ΔLVESV (%)	–40	–38	15	13
Number of patients	76	125	40	124

Figure 1 The extent of atrial and ventricular reverse remodelling after 6 months. LAVI, left atrial volume index; LVESV, left ventricular end-systolic volume.

Table 2 Echocardiographic and laboratory measurements at baseline and 6 months follow-up

	Atrial and ventricular reverse remodelling ($n = 76$)		Only ventricular reverse remodelling ($n = 125$)		Only atrial reverse remodelling ($n = 40$)		No atrial and ventricular reverse remodelling ($n = 124$)		*P*-value (between groups at 6 months)
	Baseline	6 months	Baseline	6 months	Baseline	6 months	Baseline	6 months	
LV end-diastolic volume, mean ± SD—ml	258 ± 121	176 ± 77**	232 ± 93	176 ± 77**	227 ± 108	247 ± 115*	213 ± 86	231 ± 88**	<0.001
LV end-systolic volume, mean ± SD—ml	190 ± 91	112 ± 57**	184 ± 83	113 ± 59**	171 ± 95	186 ± 98*	155 ± 69	172 ± 78**	<0.001
LV volume index, mean ± SD—ml/m^2	97 ± 45	57 ± 28**	92 ± 41	56 ± 29**	85 ± 44	92 ± 45*	77 ± 33	85 ± 37**	<0.001
Left atrial volume index, mean ± SD—ml/m^2	44 ± 17	34 ± 14**	40 ± 21	42 ± 22**	45 ± 14	36 ± 12**	43 ± 19	47 ± 20**	<0.001
LV ejection fraction, mean ± SD—%	24 ± 10	35 ± 13*	24 ± 9	35 ± 12**	22 ± 8	26 ± 9*	25 ± 10	27 ± 11	<0.001
Mitral Regurgitation,[a] *n* (%)	26 (34%)	6 (8%)**	24 (19%)	14 (11%)**	13 (33%)	11 (28%)	33 (27%)	34 (27%)	<0.001
NT-proBNP, median (IQR)—pg/ml	1845 (650–3695)	767 (342–1624)**	1251 (523–2877)	1001 (312–2246)*	1399 (575–3326)	1619 (910–2773)	1426 (648–2801)	1649 (663–2621)	<0.001

LV, left ventricular; IQR, interquartile range; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SD, standard deviation.
[a]Mitral valve regurgitation denotes moderately severe (Grade III) or severe (Grade IV) regurgitation.
*$P < 0.05$ for change at 6 months when compared with baseline.
**$P < 0.001$ for change at 6 months when compared with baseline.

Table 3 Diastolic filling parameters of the LV at baseline and after 6 months follow-up in patients with only atrial reverse remodelling

	Only atrial reverse remodelling ($n = 40$)		*P*-value
	Baseline	6 months	
Diastolic filling time (EA duration), ms	334 ± 120	435 ± 124	<0.001
RR interval duration, ms	860 ± 191	885 ± 134	0.54
Diastolic filling ratio (EA/RR), %	38.5 ± 9.3	48.4 ± 7.3	<0.001
VTI of the diastolic transmitral flow (EA VTI), cm	16.1 ± 5.6	19.3 ± 6.5	<0.001

VTI, velocity time integral.
[a]Plus–minus values are mean ± SD.

ventricular reverse remodelling experienced no improvement in LVEF after 6 months (*Table 2*).

In the group with only atrial reverse remodelling LV diastolic filling time (334 ± 120 vs. 435 ± 124, $P < 0.001$), diastolic filling ratio (38.5 ± 9.3 vs. 48.4 ± 7.3, $P < 0.001$) and VTI of the diastolic transmitral flow (16.1 ± 5.6 vs. 19.3 ± 6.5, $P < 0.001$) improved during follow-up (*Table 3*). Atrioventricular delay optimization allowed E and A wave separation, resulting in maximum diastolic filling time without truncation of the A wave (*Figure 2*).

In a multivariate logistic regression analysis, a longer QRS duration, the presence of mitral regurgitation, and the absence of AF in the patient's history were associated with atrial reverse remodelling (*Table 4*). Factors that were associated with ventricular reverse remodelling included a larger LVESV, a smaller LA size, and the absence of ischaemic cardiomyopathy (*Table 4*). The absence of both atrial and ventricular reverse remodelling was associated with a smaller LVESV, a large LA size, and the presence of ischaemic cardiomyopathy (*Table 4*).

During the first 6 months, 10 patients developed new-onset AF (5%). There was no difference between the patients with atrial reverse remodelling and patients without atrial reverse remodelling regarding new-onset AF [5 (6%) vs. 5 (4%), $P = 0.4$].

Outcome

During a mean follow-up of 2.0 ± 1.0 years, a total of 49 patients died (19 with a history of AF). A total of 24 patients had a heart failure hospitalization. This was not significantly different between the four groups ($P = 0.2$). Even though the mean AF burden during the first 6 months after implantation did not differ among the four groups, dividing the burden in tertiles showed that those with *no* atrial reverse remodelling experienced more often an AF burden of 100% ($P = 0.005$, *Table 5*).

Figure 3 shows the cumulative survival curves for all-cause mortality or heart failure hospitalizations. The Cox regression analysis revealed that patients with *no* atrial and ventricular reverse remodelling had the worst outcome (hazard ratio 3.1, 95% confidence interval 1.4–7.1, $P = 0.006$). After adjusting for other potential confounders, including gender, age at implantation,

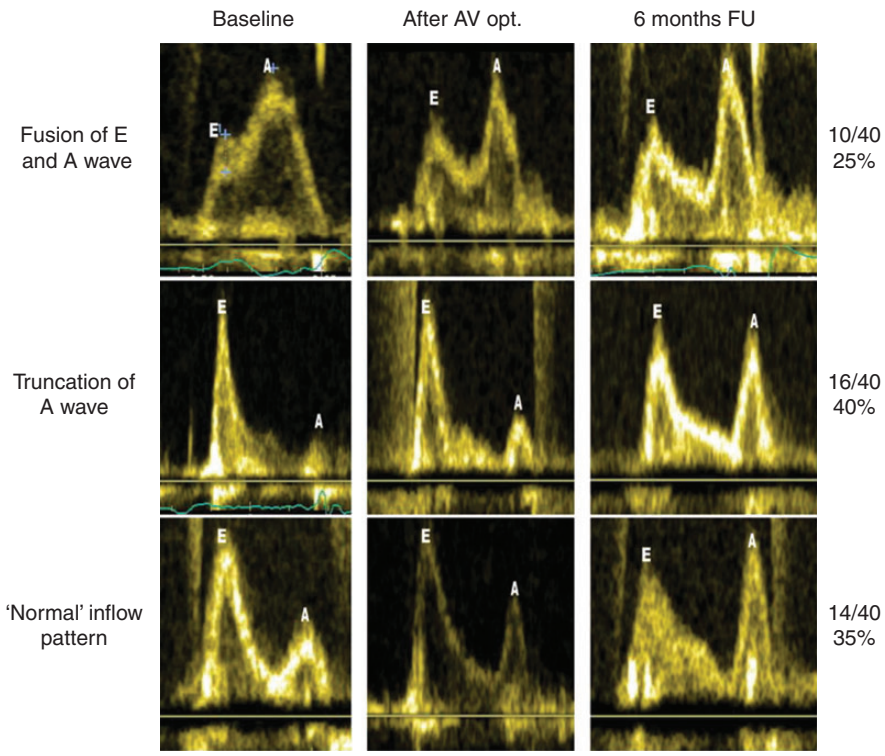


Figure 2 The transmitral flow profiles observed in the group with only atrial reverse remodelling ($n = 40$). (*A*) Fusion of E and A wave at baseline resulting in diastolic dysfunction, which had disappeared at 6-month follow-up. (*B*) Truncation of the A wave of mitral inflow at baseline resulting in delayed LA contraction after closure of the mitral valve that had disappeared at 6-month follow-up. (*C*) 'Normal' mitral inflow that is qualitatively unchanged but augmented by AV optimization or reverse remodelling. AV opt., atrioventricular optimization; FU, follow-up.

Table 4 Multivariate logistic regression analyses for determinants of reverse remodelling

	Atrial reverse remodelling		Ventricular reverse remodelling		No atrial and ventricular reverse remodelling	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95%CI)	*P*-value
QRS duration (per 10 ms increase)	1.14 (1.03–1.27)	0.01				
Left ventricular end-systolic volume (per 25 ml increase)			1.17 (1.08–1.26)	<0.001	0.86 (0.79–0.93)	<0.001
Left atrial length (per 5 ml increase)			0.84 (0.75–0.94)	0.002	1.17 (1.04–1.32)	0.010
Mitral regurgitation[a]	2.1 (1.23–3.68)	0.007				
History of AF	0.56 (0.32–0.97)	0.04				
Ischaemic cardiomyopathy			0.64 (0.41–1.0)	0.05	1.82 (1.13–2.93)	0.014

AF, atrial fibrillation; CI, confidence interval; OR, odds ratio.
[a]Mitral valve regurgitation denotes moderately severe (Grade III) or severe (Grade IV) regurgitation.

mitral regurgitation (Grade III/IV), ischaemic cardiomyopathy, creatinine clearance, and AF, these patients continue to have the worst outcome (hazard ratio 3.0, 95% confidence interval 1.3–6.9, $P = 0.01$).

Patients with atrial reverse remodelling *only* had a comparable outcome with patients with *both* atrial and ventricular reverse remodelling (hazard ratio 2.0, 95% confidence interval 0.7–5.6, $P = 0.21$), also after adjusting for gender, age at implantation, mitral regurgitation (Grade III/IV), ischaemic cardiomyopathy, creatinine clearance, and AF (hazard ratio 2.1, 95% confidence interval 0.7–6.1, $P = 0.16$).

Discussion

Our study shows that discordance in atrial and ventricular reverse remodelling occurs in a significant number of patients. We demonstrate that patients with no atrial and ventricular reverse remodelling have the worst outcome. Patients with atrial reverse

Table 5 Outcome: mortality, hospitalizations, ICD shocks, percentage of biventricular pacing, and AF burden

	Atrial and ventricular reverse remodelling ($n = 76$)	Only ventricular reverse remodelling ($n = 125$)	Only atrial reverse remodelling ($n = 40$)	No atrial and ventricular reverse remodelling ($n = 124$)	*P*-value for trend
All-cause mortality, *n* (%)	6 (8)	13 (10)	5 (13)	25 (20)	0.05
Heart failure hospitalization, *n* (%)	1 (1)	8 (6)	4 (10)	11 (9)	0.2
Shocks, *n* (%)					
Appropriate	1 (1)	6 (5)	9 (23)	11 (9)	<0.001
Inappropriate	2 (3)	9 (7)	1 (3)	5 (4)	0.4
Percentage pacing, mean ± SD	95.1 ± 11.7	95.9 ± 8.7	95.0 ± 7.9	93.4 ± 11.4	0.2
AF burden 6 months, tertiles—%	($n = 24$)	($n = 53$)	($n = 16$)	($n = 58$)	0.005
<2%	5 (21)	20 (38)	6 (38)	14 (24)	
2–99.9%	13 (54)	9 (17)	9 (56)	22 (38)	
100%	6 (25)	24 (45)	1 (6)	22 (38)	

AF, atrial fibrillation; SD, standard deviation.

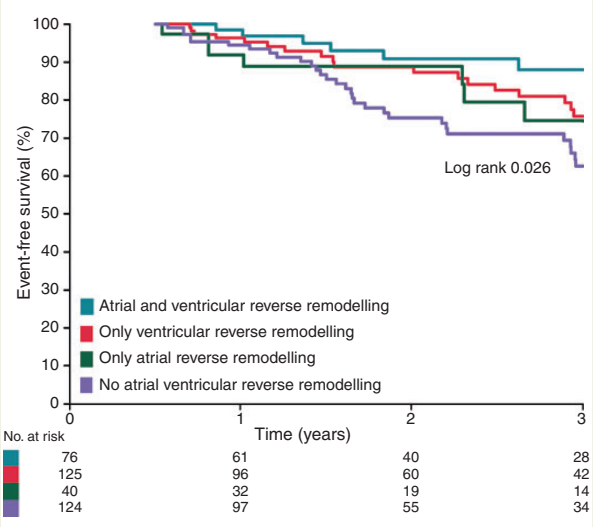


Figure 3 The Kaplan–Meier curve showing the incidence of all-cause mortality or heart failure hospitalizations for the different groups.

remodelling in the absence of ventricular remodelling demonstrate an intermediate outcome, both in terms of echocardiographic changes as well as in long-term mortality and heart failure hospitalizations. Prediction of whether and how a patient may benefit from CRT is a challenge and involves many parameters, including ventricular reverse remodelling, QRS duration, and ischaemic cardiomyopathy. We believe that the presence or the absence of atrial reverse remodelling may provide additional prognostic information in determining CRT outcome.

The role of atrial remodelling

We observed that atrial remodelling might improve outcome in CRT patients, even in the absence of ventricular remodelling. Left atrial volume and function are well-known predictors of outcome in HF patients, providing additional prognostic information beyond systolic and diastolic functions of the left ventricle.[5,8,16] Successful CRT can reduce LA size and improve LA pump function.[10–12,17] Kuperstein *et al.*[13] have shown that LA volume is a strong correlate of subsequent clinical outcomes in mild HF patients treated with CRT. Yu *et al.*[12] showed that patients with LV reverse remodelling experienced significant improvement in LAA-EF (LA emptying fraction based on the change in areas) and LAV-EF (LA emptying fraction based on the change in volumes) functions. Responders also had significant decrease in LA size area and volumetric measurements. These parameters were unchanged in the non-responders. Our findings confirm that response to CRT can lead to atrial reverse remodelling. However, we show that a decrease in atrial volume can occur without a concomitant decrease in ventricular volume leading to a new group of patients with discordant atrial and ventricular responses after CRT.

The group of patients *without* atrial reverse remodelling, i.e. the group with ventricular reverse remodelling only and the group with no atrial and no ventricular reverse remodelling might reflect patients with severely remodelled and fibrotic atria due to long-standing AF and/or underlying structural heart disease. The relevance and interaction between atrial reverse remodelling and AF became evident once more in our study. Patients with atrial reverse remodelling less often had a history of AF than those without atrial reverse remodelling. Also, a smaller LA size at baseline was an independent predictor of maintaining SR. In addition, atrial reverse remodelling may reduce AF burden. In the Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy (MADIT-CRT) study, atrial reverse remodelling after CRT was associated with a 50% risk reduction for developing AF.[18] This was neither observed in the Cardiac Resynchronization in Heart Failure study (CARE-HF)[2] nor in the present study.

Beneficial effect of atrial reverse remodelling in the absence of ventricular reverse remodelling

Atrial reverse remodelling in the absence of ventricular reverse remodelling might be explained by improvement in diastolic filling.

Atrial volume is an expression of left ventricular filling pressures and diastolic dysfunction, which are both associated with increased wall tension, dilation, and remodelling of the left atrium.[19] Although the importance of AV synchrony is unquestioned, the need for routine, systematic AV delay optimization in all patients undergoing CRT remains controversial, even though haemodynamic studies have demonstrated the importance of AV delay on cardiac function in the context of CRT.[20] However, these data do not exclude possible utility in selected patients who do not respond to CRT. These patients with prolonged AV conduction due to inter-atrial or AV nodal conduction delay appear to derive benefit from echo-guided AV delay optimization due to improvement of diastolic dysfunction. Possible mechanisms include (1) improved in diastolic filling time by ventricular preexcitation and (2) prevention of delayed LA contraction after closure of the mitral valve. Both phenomena were observed in the group of patients with only atrial reverse remodelling as shown in *Figure 2*. After 6 months, all patients in this group had normal mitral inflow patterns and improved diastolic function. In *Table 3*, we show a significant improvement in LV diastolic filling time and filling fraction after 6 months of CRT therapy. In addition, the VTI of transmitral flow improved during follow-up, indicating not only longer but also augmented diastolic filling of the LV. These results suggest the importance of AV interval optimization for all patients, even in the absence of ventricular structural remodelling.

Strengths and limitations

Strength of the present analysis is the prospective data collection and uniform treatment of patients according to our CRT protocol. Furthermore, the study population was taken from clinical practice. The current study is a single-centre, retrospective study that is limited by its small sample size, and it was not powered on the primary endpoint. Larger, multicentre, prospective trials are needed to confirm and extend our results. Regarding the mechanism of atrial reverse remodelling in CRT, it may be more comprehensive if factors, such as atrial strain, will also be taken into consideration. This will be prospectively studied in the Markers and Response to Cardiac Resynchronisation Therapy (MARC) clinical study (ClinicalTrials.gov Identifier: NCT01519908).

Conclusion

Discordance in atrial and ventricular reverse remodelling occurs in a significant number of patients who receive CRT. Patients without atrial and ventricular reverse remodelling have the worst outcome. Patients with only atrial reverse remodelling have improved diastolic filling during follow-up and demonstrate a comparable outcome with patients with both atrial and ventricular reverse remodelling. The latter may, in part, explain why 'CRT non-responders' report clinical improvement in the absence of ventricular reverse remodelling on echocardiography. Therefore, atrial reverse remodelling may provide additional prognostic information in determining outcome of CRT and warrants further investigation.

Conflict of interest: I.C.V.G. reports receiving grant support for the institution from Medtronic, Biotronik, and St. Jude Medical. A.H.M. reports receiving lecture fees from Biotronik, Boston Scientific, Medtronic, Sorin, and St. Jude Medical.

References

1. Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. *Circulation* 2003;**108**:2596–603.
2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L *et al.* The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–49.
3. European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA *et al.* 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;**15**:1070–118.
4. Stefanadis C, Dernellis J, Toutouzas P. A clinical appraisal of left atrial function. *Eur Heart J* 2001;**22**:22–36.
5. Blume GG, Mcleod CJ, Barnes ME, Seward JB, Pellikka PA, Bastiansen PM *et al.* Left atrial function: physiology, assessment, and clinical implications. *Eur J Echocardiogr* 2011;**12**:421–30.
6. Patel DA, Lavie CJ, Milani RV, Shah S, Gilliland Y. Clinical implications of left atrial enlargement: a review. *Ochsner J* 2009;**9**:191–6.
7. Patel DA, Lavie CJ, Milani RV, Ventura HO. Left atrial volume index predictive of mortality independent of left ventricular geometry in a large clinical cohort with preserved ejection fraction. *Mayo Clin Proc* 2011;**86**:730–7.
8. Ristow B, Ali S, Whooley MA, Schiller NB. Usefulness of left atrial volume index to predict heart failure hospitalization and mortality in ambulatory patients with coronary heart disease and comparison to left ventricular ejection fraction (from the Heart and Soul Study). *Am J Cardiol* 2008;**102**:70–6.
9. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;**54**:230–46.
10. Fung JW, Yip GW, Zhang Q, Fang F, Chan JY, Li CM *et al.* Improvement of left atrial function is associated with lower incidence of atrial fibrillation and mortality after cardiac resynchronization therapy. *Heart Rhythm* 2008;**5**:780–6.
11. Kies P, Leclercq C, Bleeker GB, Crocq C, Molhoek SG, Poulain C *et al.* Cardiac resynchronisation therapy in chronic atrial fibrillation: impact on left atrial size and reversal to sinus rhythm. *Heart* 2006;**92**:490–4.
12. Yu CM, Fang F, Zhang Q, Yip GW, Li CM, Chan JY *et al.* Improvement of atrial function and atrial reverse remodeling after cardiac resynchronization therapy for heart failure. *J Am Coll Cardiol* 2007;**50**:778–85.
13. Kuperstein R, Goldenberg I, Moss AJ, Solomon S, Bourgoun M, Shah A *et al.* Left atrial volume and the benefit of cardiac resynchronization therapy in the MADIT-CRT trial. *Circ Heart Fail* 2014;**7**:154–60.
14. Maass AH, Buck S, Nieuwland W, Brugemann J, van Veldhuisen DJ, Van Gelder IC. Importance of heart rate during exercise for response to cardiac resynchronization therapy. *J Cardiovasc Electrophysiol* 2009;**20**:773–80.
15. Buck S, Rienstra M, Maass AH, Nieuwland W, Van Veldhuisen DJ, Van Gelder IC. Cardiac resynchronization therapy in patients with heart failure and atrial fibrillation: importance of new-onset atrial fibrillation and total atrial conduction time. *Europace* 2008;**10**:558–65.
16. Rossi A, Temporelli PL, Quintana M, Dini FL, Ghio S, Hillis GS *et al.* Independent relationship of left atrial size and mortality in patients with heart failure: an individual patient meta-analysis of longitudinal data (MeRGE Heart Failure). *Eur J Heart Fail* 2009;**11**:929–36.
17. Healey JS, Hohnloser SH, Exner DV, Birnie DH, Parkash R, Connolly SJ *et al.* Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail* 2012;**5**:566–70.
18. Brenyo A, Link MS, Barsheshet A, Moss AJ, Zareba W, Wang PJ *et al.* Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). *J Am Coll Cardiol* 2011;**58**:1682–9.
19. Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM. Diastolic dysfunction and left atrial volume: a population-based study. *J Am Coll Cardiol* 2005;**45**:87–92.
20. Eicher JC, Laurent G, Mathe A, Barthez O, Bertaux G, Philip JL *et al.* Atrial dyssynchrony syndrome: an overlooked phenomenon and a potential cause of 'diastolic' heart failure. *Eur J Heart Fail* 2012;**14**:248–58.