ORIGINAL PAPER

IJCP THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Cardiac resynchronisation therapy response predicts occurrence of atrial fibrillation in non-ischaemic dilated cardiomyopathy

S. L. D'Ascia,[1] C. D'Ascia,[1] V. Marino,[1] A. Lombardi,[2] R. Santulli,[3] M. Chiariello,[1,*] G. Santulli[1,4]

SUMMARY

Aim: The aim of this study was to determine whether or not cardiac resynchronization therapy (CRT) has a favourable effect on the incidence of new-onset atrial fibrillation (AF) in a homogeneous population of patients with non-ischaemic idiopathic-dilated cardiomyopathy and severe heart failure. **Methods:** We designed a single-centre prospective study and enrolled 58 patients AF naïve when received CRT. After 1 year of follow-up our population was subdivided into responders (72.4%) and non-responders (27.6%), so as to compare the incidence of AF after 1, 2 and 3 years of follow-up in these two groups. **Results:** Already after 1 year, there was a significant ($p < 0.05$) difference in new-onset AF in non-responder patients with respect to responders (18.2% vs. 3.3%). These data were confirmed at 2 years (33.3% vs. 12.2%) and 3 years (50.0% vs. 15.0%) follow-up. In particular, 3 years after device implantation non-responders had an increased risk to develop new-onset AF (OR = 5.67). **Conclusions:** This is the first study analysing long-term effects of CRT in a homogeneous population of patients with non-ischaemic dilated cardiomyopathy, indicating the favourable role of this non-pharmacological therapy on the prevention of AF.

What's known

Albeit several studies examined the association between cardiac resynchronization therapy and atrial fibrillation in heart failure, results are still unclear and quite conflicting.

What's new

In this study we show that in patients with non-ischemic dilated cardiomyopathy a positive response to cardiac resynchronization therapy has a favorable role on the prevention of new-onset atrial fibrillation.

[1]Division of Cardiology, Department of Clinical Medicine, Cardiovascular and Immunologic Sciences, ''Federico II'' University, Naples, Italy
[2]Faculty of Mathematical, Physical and Natural Sciences, University of Salento, Lecce, Italy
[3]Department of Mathematics, University of Salerno, Fisciano (SA), Italy
[4]College of Physicians and Surgeons, Columbia University Medical Center, New York, NY, USA

Correspondence to:
Dr Gaetano Santulli,
Division of Cardiology,
Department of Clinical Medicine, Cardiovascular and Immunologic Sciences,
''Federico II'' University, Naples, Italy
Tel/Fax: +39 081 746 3075
Email: gaetano.santulli@unina.it

Disclosures
None.

*Since this paper was submitted this author has died.

Introduction

Cardiac resynchronisation therapy (CRT) has emerged as a highly effective treatment for patients with advanced heart failure (HF) and ventricular conduction delay (1). Several studies have showed the haemodynamic and functional improvement obtained with biventricular pacing, with a subsequent reduction of hospitalisations and a decrease in mortality (2). Nevertheless, despite the positive effects of CRT on haemodynamic, functional status and mortality in HF, approximately 30% of patients do not respond to this therapy, emphasising the need for better selection criteria (1,2). Furthermore, the primary cardiac cause of exacerbation of HF is atrial fibrillation (AF) that is also an independent risk factor for sudden death. HF and AF often coexist; both are responsible for increased mortality, more frequent hospitalisations, reduced exercise capacity and decreased quality-of-life (QoL). Besides, AF and HF are believed to directly predispose to each other (3). In particular, in the setting of advanced HF, 30–40% of patients will develop AF during the course of the disease. So, if CRT influences the occurrence of AF, this might influence patient selection and possibly programming of the device.

On these grounds, the aims of the present study were: to identify preimplantation characteristics that best can predict which patients will benefit the most from biventricular pacing, in order to make out suitable candidates for CRT (4); to compare the incidence of new-onset AF after 1, 2 and 3 years of follow-up in responder and non-responder patients, so as to assess a possible favourable role of CRT, through means of an atrial reverse remodelling, on the prevention of this arrhythmia.

Methods

Study population

This is a single-centre prospective study that included all the consecutive CRT implants from July 2004 until June 2007 performed at our institution on patients with non-ischaemic idiopathic-dilated cardiomyopathy (coronary angiography failed to reveal stenosis > 30%), following the previously described eligibility criteria for CRT (5). All patients had New York Heart Association (NYHA) functional class III

doi: 10.1111/j.1742-1241.2011.02732.x

or IV symptoms for at least 6 months before enrolment, despite optimal pharmacological treatment (including β blockers, loop diuretics, vasodilators, nitrate, digitalis, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and spironolactone when tolerated; no antiarrhythmic drugs for VT were administered to the patients), left ventricular ejection fraction (LVEF) ≤ 35% and QRS duration > 120 ms measured on at least three leads on the surface ECG. Exclusion criteria were: recent (previous 3 months) acute coronary syndrome or planned coronary revascularization, previous pacemaker or implantable cardioverter defibrillator (ICD) implantation, requirement of continuous intravenous therapy, a life expectancy of < 1 year due to non-cardiac diseases, history of AF, patients whose major echocardiographic parameters could not be obtained because of poor image quality, systolic blood pressure > 170 or < 80, heart rate > 140 and kidney failure with serum creatinine levels > 250 μmol/l (5). Detailed clinical and instrumental data (ECG, echocardiogram, QoL evaluation, 6-min walk test, cardiopulmonary exercise test) were collected, with scheduled visits, before implantation and at the 1-, 2- and 3-year follow-up. Patients were also given a diary in which the information of any medical contacts between their follow-up visits was to be recorded. The detection of AF relied on electrocardiography, 24 h Holter examination and strips from continuous telemetric control of implanted devices (every 3 to 6 months, when ICDs were systematically checked) (6). AF was defined as an episode, with or without symptoms, lasting at least 10 min (7,8), similar to a large sub-study of the CARE-HF trial reported by UC. Hoppe et al. (9). Patients were also assessed for HF symptoms (NYHA functional class). QoL was evaluated by the Minnesota Living with HF questionnaire (scores range from 0 to 105, with higher scores reflecting a poorer QoL) (10), while the 6-min walk test was carried out according to Bittner's recommendations (11). The 6-min walk distance and QoL tests were administered by study nurses who had no knowledge of the patients' treatment. Coronary angiography was performed prior to implantation in all patients, also to exclude causes of HF amenable to surgery or intervention. This study protocol was designed in compliance with the Helsinki declaration and approved by the local Ethics Committee. Written informed consent was obtained from each participant.

Non-responders were defined after 12 months of follow-up as patients with at least one of the following characteristics: deteriorating function (HF-related death, need for heart transplantation), increase in LVEF ≤ 4 absolute percentage points (12), worsening in peak oxygen consumption, in QoL score or in the distance walked in 6 min, as previously described (13,14).

ICD implantation and optimisation

Patients were implanted with a biventricular ICD (Contak Renewal 1 or 2; Guidant Inc., part of Boston Scientific, Natick, MA, USA). All procedures were performed under local anaesthesia. Three transvenous leads were inserted, through the left subclavian vein. The atrial lead was placed in the high right atrium; the right ventricular lead was positioned, in the apex or in the high interventricular septum, as far as possible from the LV lead; LV pacing was obtained after coronary sinus (CS) angiography, advancing a bipolar lead into the lateral or posterolateral cardiac vein. The final lead position was chosen on the basis of visual inspection, assessed by anteroposterior and lateral chest radiography. The atrioventricular interval (electrical delay between atrial and ventricular excitation) was optimised by Doppler echocardiography 1 day after implantation to reach maximal transmitral diastolic filling and maximal biventricular capture and checked every year. Patients in whom transvenous LV lead implantation was acutely unsuccessful ($n = 5$), attributable to several causes [failure to cannulate the CS ($n = 2$), high threshold to chronic pacing ($n = 1$), CS dissection ($n = 1$) and impossibility to obtain a stable lead placement ($n = 1$)] were obviously excluded from the study.

Echocardiographic evaluation

A trans-thoracic, two-dimensional echocardiogram was serially performed in all patients using a Sonos 5500 ultrasound system (Philips, Amsterdam, Netherlands), equipped with a 2.5-MHz transducer. The examination included two-dimensional, M-mode and Doppler data. All recordings were made, as previously described, with the patient in the lateral recumbent position, according to the American Society of Echocardiography recommendations (4). The following parameters were measured using the different axis: LV end-diastolic and end-systolic diameters, LVEF (biplane LV end-systolic and end-diastolic volumes were calculated from apical views according to the modified Simpson's rule), LV end-systolic volume index, left atrial diastolic and systolic areas, amount of mitral regurgitation (calculated as the area of the colour-flow Doppler regurgitant jet divided by the area of the left atrium in systole, both in square centimetres). All echocardiographic studies were performed and analysed by the same study-independent physicians, blinded to the study protocol and to the patients' status. Echocardiographic

measurements were systematically averaged in five consecutive samples (15).

Cardiopulmonary exercise test

Symptom-limited cardiopulmonary exercise testing (Treadmills 'Rammill Series'; Morgan Italia, Bologna, Italy) was performed, conducted on an upright bicycle ergometer with a 10-W/min step protocol, starting with 2 min of unloaded cycling. Measurements of oxygen consumption (VO_2), were taken at rest and during exercise using a moving average of eight breaths. During each stage of exercise, data on heart rate and rhythm and BP were collected. All patients were encouraged to exercise until they felt unable to continue because of dyspnoea and/or fatigue. The ventilatory threshold was measured by the V-slope method (16). The maximum VO_2 was defined as the highest VO_2 value measured (peak VO_2).

Statistical analysis

Unless otherwise specified, data are presented as the mean value ± SD or absolute numbers with percentages for categorical variables, unless otherwise specified. Data normality was evaluated through the Kolmogorov–Smirnov test. Comparison of quantitative variables was performed using the Student's *t*-test for paired and unpaired data when appropriate, with a Bonferroni correction when multiple comparisons were made (15). Dichotomous or categorical data were assessed with the χ^2 test or Fisher's exact test. The non-normally distributed data within patient groups were compared using the nonparametric Wilcoxon test. Odds ratios were given with the 95% confidence interval (CI). Differences in event rates (AF, death) over time were calculated according to the Kaplan–Meier method and analysed with the use of Cox proportional hazard models.

Table 1 Baseline characteristics of the patients included in the analysis, then (1-year follow-up) sub-divided in responders and non-responders

	All patients	Responders	Non-responders
No.	58	42	16
Age (years)	62.5 ± 11.1	62.4 ± 14.2	62.5 ± 11.9
Male sex: No. (%)	37 (63.8)	27 (64.3)	10 (62.5)
Height (cm)	168.41 ± 6.9	167.7 ± 7.38	170.86 ± 4.9
Weight (kg)	72.37 ± 13.6	70.3 ± 13.6	75.65 ± 14.5
Body mass index	25.41 ± 3.92	25.07 ± 3.7	25.8 ± 4.33
Body surface (m^2)	1.81 ± 0.18	1.77 ± 0.192	1.86 ± 0.18
Heart rate (bpm)	70.89 ± 5.9	71.5 ± 5.51	72.23 ± 7.8
QRS duration from surface ECG (ms)	170.8 ± 6.1	167.3 ± 20.6	171.2 ± 8.5
Systolic blood pressure (mmHg)	122.7 ± 15.5	122.8 ± 15.9	125.0 ± 17.4
Diastolic blood pressure (mmHg)	74.4 ± 13.4	74.7 ± 14.6	70.1 ± 12.8
Diabetes (%)	31.0	28.6	37.5
Hypertension (%)	24.1	23.8	25.0
Smoking (current or former) (%)	19.0	19.0	18.8
Dyslipidemia (%)	41.5	40.0	45.5
NYHA class	3.19 ± 0.395	3.19 ± 0.397	3.19 ± 0.403
NYHA III: No. (%)	47 (81.0)	34 (81.3)	13 (81.0)
NYHA IV: No. (%)	11 (19.0)	8 (19.0)	3 (18.8)
LVEF (%)	27.6 ± 5.6	27.9 ± 5.5	26.7 ± 5.7
LV end-diastolic diameter (mm)	69.8 ± 6.9	68.1 ± 7.1	73.2 ± 9.1*
LV end-systolic diameter (mm)	57 ± 8.7	56 ± 9.2	59 ± 10.7
LV end-systolic volume index (ml/m^2)	121.2 ± 13.2	118.4 ± 13.1	121.3 ± 13.0
LV filling time (s)	0.46 ± 0.04	0.51 ± 0.05	0.45 ± 0.04
Left atrial diastolic area (cm^2)	17.8 ± 3.7	17.2 ± 3.8	21.5 ± 4.2
Left atrial systolic area (cm^2)	26.9 ± 5.9	26.3 ± 5.4	29.8 ± 5.9
Mitral regurgitation area (% of left atrial systolic area)	0.24 ± 0.02	0.20 ± 0.02	0.28 ± 0.02*
QoL score	39.7 ± 10.8	40.8 ± 10.01	36.6 ± 12.5
Distance walked in 6 min (m)	309.7 ± 5.74	310.2 ± 5.79	308.4 ± 5.52
Oxygen uptake at peak exercise (ml/kg/min)	12.5 ± 0.73	12.5 ± 0.7	12.3 ± 0.6
Oxygen uptake at anaerobic threshold (ml/kg/min)	9.43 ± 0.9	9.60 ± 0.9	8.96 ± 0.7

*= $p < 0.05$ vs. Responders.

Finally, we performed a linear regression analysis to characterise the predictors of AF and a subsequent backward stepwise multivariable analysis, tested for goodness-of-fit, built using only the variables that were associated with new-onset FA in the first regression analysis.

All tests that we performed were two-tailed and a p-value < 0.05 was considered statistically significant. All statistical tests were performed with the SPSS 18.0 statistical package (SPSS Inc., Chicago, IL) and GraphPad Prism 5.01 (GraphPad software, San Diego, CA) (17).

Results

Population characteristics

We enrolled 58 Caucasian patients who met the inclusion/exclusion criteria. Baseline characteristics of these subjects are depicted in Table 1. The mean age was 62.5 ± 11.1 years; there was a male predominance (63.8%), with a mean LVEF of 27.6 ± 5.6%. Drug therapy for HF did not change significantly over the follow-up period, and all patients had stable biventricular stimulation.

After 1 year, 42 patients (72.4%) were considered responders to CRT according to the previously defined criteria. There were 16 non-responders (27.6%), with 4 HF-related hospitalizations. Two patients died before the 2-year follow-up visit (one responder and one non-responder); four patients died before the 3-year follow-up visit (one responder and three non-responder). No difference in survival was evidenced by Kaplan–Meier analysis (Figure 1A).

Clinical outcomes

Our most interesting finding is that, already after 1 year, there is a significant difference in new-onset AF in non-responder patients (18.2%) vs. responders (3.3%). These data are confirmed at 2 years (33.3% vs. 12.2%) and 3 years (50.0% vs. 15.0%) follow-up. In particular, at 3-year follow-up, non-responders have a markedly increased risk to develop new-onset AF (OR = 5.67, 95% CI = 1.36–23.59, p = 0.019). Hence, this disparity in risk persisted throughout the 3-year follow-up period. Furthermore, Kaplan–Meier curves showed a significant difference in developing new-onset AF between the two groups ($p < 0.05$; Figure 1B). Finally, the multivariable analysis confirmed the non-response to CRT as an additive risk factor for new onset AF (OR = 4.32, CI = 2.46–9.63, $p < 0.05$).

As expected, we observed a favourable improvement of clinical status in the group of CRT responders, already evidenced at 1-year follow-up, and supported after 2 and 3 years (Table 2).

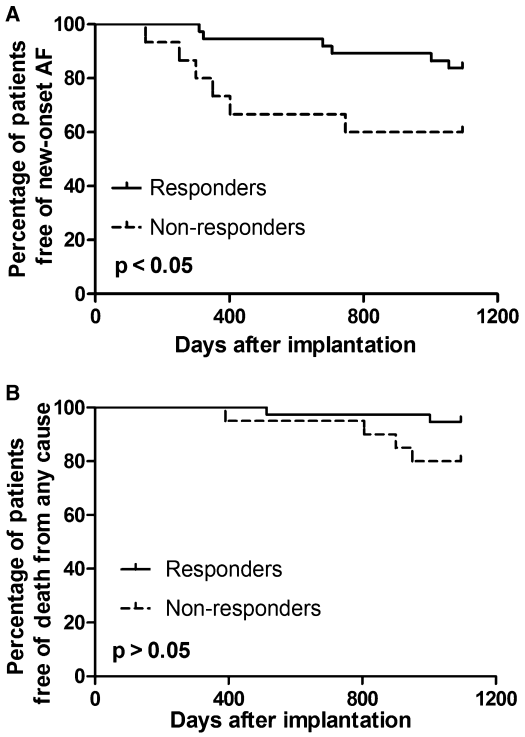

Figure 1 Kaplan–Meier estimate of time to first onset of atrial fibrillation (AF). There is no significant difference in mortality (Panel A), while first onset of AF was significantly earlier in non-responder patients (dotted line) than in responders (continuous line) (Panel B)

Discussion

This is the first study that analyses long-term effects of CRT in a population of patients with idiopathic-dilated cardiomyopathy, with a follow-up of 3 years. The present work confirms the clinical benefit of treating HF patients with CRT and suggests a role of this non-pharmacological therapy in prevention of AF.

The loss of coordination of ventricular contraction contributes to the pathophysiology of HF, reducing the already diminished contractile reserve of the heart. Specifically, dyssynchronous contraction exacerbates inefficient use of energy by the heart (mechano-energetic uncoupling). Indeed, the left lateral wall is activated well after the septum contracts (18). This leads to contraction of the lateral wall during relaxation of the septum resulting in marked mechanical dysfunction. The dyssynchronous failing heart also exhibits deep alterations in protein expression (19,20), such as changes in local calcium handling, as exemplified by a strong decrease of phospholamban in the delayed activated myocardium (21). The purpose of CRT is to restore ventricular relaxation and contraction sequences by simulta-

Table 2 Characteristics of the patients at follow-up visits

	All patients 1 year	Responders 1 year	Non-responders 1 year	Responders 2 years	Non-responders 2 years	Responders 3 years	Non-responders 3 years
No.	58	42	16	41	15	40	12
Age (years)	63.5 ± 11.9	63.5 ± 11.1	63.4 ± 14.2	63.5 ± 10.4	62.9 ± 14.2	64.5 ± 10.4	63.0 ± 14.01
Male sex: No. (%)	37 (63.8)	27 (64.3)	10 (62.5)	26 (63.4)	9 (60.0)	26 (65.0)	8 (66.7)
Height (cm)	168.11 ± 6.9	167.1 ± 7.38	170.86 ± 4.9	167.1 ± 7.41	170.85 ± 4.9	167.1 ± 7.38	170.86 ± 5.0
Weight (kg)	72.39 ± 13.5	70.85 ± 13.01	76.44 ± 14.4	70.4 ± 13.9	76.8 ± 14.62	70.2 ± 14.1	77.95 ± 14.7
Body mass index	25.42 ± 3.9	25.09 ± 3.7	26.2 ± 4.4	25.07 ± 3.8	24.78 ± 7.11	25.0 ± 3.9	25.07 ± 7.32
Body surface (m^2)	1.80 ± 0.183	1.78 ± 0.182	1.87 ± 0.18	1.77 ± 0.196	1.88 ± 0.17	1.77 ± 0.197	1.89 ± 0.18
Heart rate (bpm)	68.41 ± 6.5	67.55 ± 6.19	70.69 ± 7.05	68 ± 6.05	68.3 ± 7.01	67.95 ± 7.05	69 ± 7.5
QRS duration from surface ECG (ms)	168.3 ± 18.1	169.9 ± 17.1	172.9 ± 17.7	169.8 ± 16.8	173.4 ± 17.1	169.7 ± 17.2	173.4 ± 17.0
Systolic blood pressure (mmHg)	123 ± 15.1	122 ± 15.2	124 ± 14.7	125 ± 13.6	122 ± 14.3	126 ± 16.2	118 ± 19.5
Diastolic blood pressure (mmHg)	74.0 ± 13.5	74.7 ± 13.7	71.9 ± 12.9	75 ± 14.1	71.1 ± 10.8	75 ± 11.2	71.4 ± 10.9
NYHA class	2.53 ± 0.82	2.38 ± 0.79	2.94 ± 0.77*	2.32 ± 0.79	3.00 ± 0.84*,†	2.28 ± 0.81	3.0 ± 0.8*,†,‡
NYHA I: No. (%)	2 (4.8)	2 (4.8)	–	3 (7.3)	–	4 (10)	–
NYHA II: No. (%)	33 (59.6)	28 (66.7)	5 (31.3)*	27 (65.9)	5 (33.3)*,†	26 (65)	4 (33.3)*,†,‡
NYHA III: No. (%)	13 (22.4)	6 (14.3)	7 (43.8)*	6 (14.3)	5 (33.3)	5 (12.5)	4 (33.3)†,‡
NYHA IV: No. (%)	10 (17.2)	6 (14.3)	4 (25)*	5 (12.2)	5 (33.3)†	5 (12.5)	4 (33.3)†,‡
LVEF (%)	32.8 ± 6.1	34.3 ± 5.5	28.9 ± 6.0*	33.2 ± 5.2	29.5 ± 5.6*,†	34.1 ± 5.2	29.7 ± 5.8*,†,‡
LV end-systolic volume index (ml/m^2)	121.2 ± 13.8	117.4 ± 12.9	121.1 ± 13.4	117.1 ± 12.2	121.1 ± 13.1	115.4 ± 13.0	121.8 ± 13.1
LV filling time (s)	0.47 ± 0.05	0.52 ± 0.05	0.45 ± 0.03	0.51 ± 0.04	0.45 ± 0.04	0.52 ± 0.03	0.46 ± 0.03
Left atrial diastolic area (cm^2)	17.8 ± 2.5	18.2 ± 2.4	20.5 ± 2.4	18.2 ± 2.4	20.5 ± 2.3	17.6 ± 2.5	23.1 ± 2.4‡
Left atrial systolic area (cm^2)	26.9 ± 2.8	27.3 ± 2.7	28.8 ± 2.7	27.3 ± 2.7	28.8 ± 2.8	27.8 ± 2.8	31.2 ± 3.0
Mitral regurgitation area (% of left atrial systolic area)	0.24 ± 0.02	0.21 ± 0.02	0.27 ± 0.03*	0.21 ± 0.02	0.27 ± 0.02*,†	0.20 ± 0.02	0.28 ± 0.02*,†,‡
QoL score	40 ± 14	34 ± 19	40 ± 16*	33 ± 14	41 ± 15*,†	29.5 ± 15	41.3 ± 21*,†,‡
Distance walked in 6 min (m)	305 ± 10	338 ± 11	304 ± 11*	341 ± 13	302 ± 10*,†	342 ± 11	302 ± 9*,†,‡
Oxygen uptake at peak exercise (ml/kg/min)	12.5 ± 0.73	14.9 ± 0.7	12.5 ± 0.7*	15.2 ± 0.7	12.6 ± 0.7*,†	15.7 ± 0.6	12.6 ± 0.8*,†,‡
Oxygen uptake at anaerobic threshold (ml/kg/min)	9.43 ± 0.9	11.5 ± 0.6	10.0 ± 0.6*	11.7 ± 0.6	10.0 ± 0.4*,†	11.9 ± 0.7	9.9 ± 0.4*,†,‡
New-onset Atrial Fibrillation: No. (%)	–	2 (3.3)	4 (18.2)*	4 (9.7)	5 (33.3)*,†	6 (15.0)	6 (50.0)*,†,‡

*= $p < 0.05$ vs. Responders 1 year; †= $p < 0.05$ vs. Responders 2 years; ‡= $p < 0.05$ vs. Responders 3 years.

neously pacing both ventricles. Numerous studies have reported positive long-term effects in terms of symptoms, exercise tolerance, QoL and HF prognosis after CRT (22,23) and our work corroborates these findings. A prospective study examining the relation between CRT and AF using as control a HF population that does not receive CRT would be neither ethical nor practical, given the proven efficacy of this therapy in treating HF. So, we decide to compare a homogeneous population of CRT recipients, then subdivided into responders and non-responders. One of the most pressing unresolved questions, however, remained how to identify patients that will not respond to CRT, and how to define whether or not response is really central to the entire issue (4,24), since there is relatively poor correlation between the various measures of CRT response. Thus, as mentioned in methods, we used clear and reproducible criteria for the definition of non-responder patients, also to avoid any case of misinterpretation.

We recruited only patients with non-ischaemic-dilated cardiomyopathy. Indeed, albeit CRT is an effective alternative therapy in patients with dilated heart disease whether of ischaemic or non-ischaemic origin, the response tends to be slightly lower when the heart disease is ischaemic, maybe because of the presence of necrotic tissue. This is the first study that focalizes on this topic, assuring a homogeneous study population. Indeed, heterogeneity may explain controversial results concerning this issue emerged in literature.

Another chief issue to discuss in analysing the occurrence of AF is how the same AF is detected. We defined AF as an episode, with or without symptoms, lasting 10 min or more, identified by electrocardiography, Holter examination and using the

continuous monitoring capability offered by implanted devices, which were programmed uniformly to capture AF episodes (25–27). During follow-up, device interrogation was scheduled every 3–6 months and all printouts were carefully checked for new-onset AF episodes. Other studies have used a variety of different definitions for AF, also relied on symptoms, which appear clearly inadequate in assessing overall AF burden.

Despite the extensive evidence of the benefits of CRT on ventricular function, data about the effects of CRT on atrial function and on incidence of new-onset AF are conflicting (2,7,28). *Post hoc* analysis of the CARE-HF trial suggested that CRT had no favourable impact on the incidence of AF compared with medical therapy alone, but many of these patients (19%) already had a history of AF (9). A study by the group of JJ. Bax confirmed the clinical importance of new-onset AF after CRT, showing that recipients of CRT who develop new-onset AF have less echocardiographic response to CRT and more cardiac adverse events during follow-up (28). Another recent article described, consistently with our findings, that more than 20% of the overall HF patient population treated with CRT suffered episodes of paroxysmal atrial tachycardia (25).

Anyway, the potential mechanisms to take into account for the effect attributed to CRT in the prevention of AF could be related to an improvement in left ventricular systolic function and a decrease of the degree of mitral regurgitation, with a reduction of structural atrial remodelling of the electrophysiological substrate responsible for the initiation/triggers of atrial arrhythmias (29). Anyway, non-responders have larger atriae, larger ventricles and more mitral regurgitation already at baseline. So we cannot exclude these parameters predicting AF independent of supposed non-response to CRT. Indeed, the fact that after 3-year follow-up non-responder patients show an increased left atrial diastolic area than responders is a strong evidence for supporting the hypothesis that CRT may prevent AF through atrial reverse remodelling (29), probably as a result of a reduction of the overload in the atria (18). What is more, as shown in a previous study by JW. Fung and coll. (30), we also noted a trend of a greater left atrial diastolic area in patients who developed AF. Nevertheless, atrial function is relatively complex, and more quantitative methods are needed to better explore atrial functional improvement. Moreover, because patients with HF who develop AF have a worse outcome (3), it could be interesting to know whether or not the outcome might be improved by CRT.

Our study is limited by the relatively small number of subjects, although they constitute a remarkable patient population, because of selective inclusion and exclusion criteria. The percentage of patients who developed new-onset AF although reach statistical significance when analysed, the absolute number is small. Another limitation is the non-randomised nature of the study. Thus, the results must be interpreted cautiously and further randomised studies, pooling data from multiple centres, are needed to confirm our findings and to assess their clinical impact.

Acknowledgements

We thank the patients and families who have sought clinical evaluation at ''Federico II'' University Hospital and all of the physicians, technicians and nurses for their tremendous contribution to the data.

Author contributions

GS and CDA and conceived the study; GS, AL and RS performed data analysis, GS and SLDA drafted the manuscript, VM and AL helped to draft the manuscript and collect the data, AL and MC participated in the design and coordination of the study; all authors read and approved the manuscript.

References

1 Anand IS, Carson P, Galle E et al. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. *Circulation* 2009; **119**: 969–77.

2 Cleland JG, Calvert MJ, Verboven Y, Freemantle N. Effects of cardiac resynchronization therapy on long-term quality of life: an analysis from the CArdiac Resynchronisation-Heart Failure (CARE-HF) study. *Am Heart J* 2009; **157**: 457–66.

3 Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003; **91**: 2D–8D.

4 Bax JJ, Gorcsan J 3rd. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study in perspective. *J Am Coll Cardiol* 2009; **53**: 1933–43.

5 Vardas PE, Auricchio A, Blanc JJ et al. Guidelines for cardiac pacing and cardiac resynchronization therapy: the task force for cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Eur Heart J* 2007; **28**: 2256–95.

6 D'Ascia SL, Santulli G, Liguori V et al. Advanced algorithms can lead to electrocardiographic misinterpretations. *Int J Cardiol* 2010; **141**: e34–6.

7 Fung JW, Yu CM, Chan JY et al. Effects of cardiac resynchronization therapy on incidence of atrial fibrillation in patients with poor left ventricular systolic function. *Am J Cardiol* 2005; **96**: 728–31.

8 Santulli G. Coffee and cardiovascular system. *Cardiol Sci* 2006; **4**: 186–8.

9 Hoppe UC, Casares JM, Eiskjaer H et al. Effect of cardiac resynchronization on the incidence of atrial

fibrillation in patients with severe heart failure. *Circulation* 2006; **114**: 18–25.
10 Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. *Am Heart J* 1992; **124**: 1017–25.
11 Bittner V. Six-minute walk test in patients with cardiac dysfunction. *Cardiologia* 1997; **42**: 897–902.
12 Mangiavacchi M, Gasparini M, Faletra F et al. Clinical predictors of marked improvement in left ventricular performance after cardiac resynchronization therapy in patients with chronic heart failure. *Am Heart J* 2006; **151**: 477 e1–e6.
13 St John Sutton MG, Plappert T, Abraham WT et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003; **107**: 1985–90.
14 Lawo T, Borggrefe M, Butter C et al. Electrical signals applied during the absolute refractory period: an investigational treatment for advanced heart failure in patients with normal QRS duration. *J Am Coll Cardiol* 2005; **46**: 2229–36.
15 Santulli G, Campanile A, Spinelli L et al. G Protein-coupled receptor kinase 2 in patients with acute myocardial infarction. *Am J Cardiol* 2011; **107**: 1125–30.
16 Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; **60**: 2020–7.
17 Santulli G, Basilicata MF, De Simone M et al. Evaluation of the anti-angiogenic properties of the new selective alphaVbeta3 integrin antagonist RGDechiHCit. *J Transl Med* 2011; **9**: 7.
18 Sade LE, Demir O, Atar I et al. Effect of mechanical dyssynchrony and cardiac resynchronization therapy on left ventricular rotational mechanics. *Am J Cardiol* 2008; **101**: 1163–9.
19 Santulli G, Illario M, Cipolletta E et al. Deletion of the CaMK4 gene in mice determines a hypertensive phenotype. *Cardiovasc Res* 2010; **87**: 89.
20 Vanderheyden M, Bartunek J. Cardiac resynchronization therapy in dyssynchronous heart failure: zooming in on cellular and molecular mechanisms. *Circulation* 2009; **119**: 1192–4.
21 Spragg DD, Leclercq C, Loghmani M et al. Regional alterations in protein expression in the dyssynchronous failing heart. *Circulation* 2003; **108**: 929–32.
22 Gasparini M, Regoli F, Ceriotti C et al. Remission of left ventricular systolic dysfunction and of heart failure symptoms after cardiac resynchronization therapy: temporal pattern and clinical predictors. *Am Heart J* 2008; **155**: 507–14.
23 Jansen AH, van Dantzig J, Bracke F et al. Improvement in diastolic function and left ventricular filling pressure induced by cardiac resynchronization therapy. *Am Heart J* 2007; **153**: 843–9.
24 Yu CM, Wing-Hong Fung J, Zhang Q, Sanderson JE. Understanding nonresponders of cardiac resynchronization therapy–current and future perspectives. *J Cardiovasc Electrophysiol* 2005; **16**: 1117–24.
25 Leclercq C, Padeletti L, Cihak R et al. Incidence of paroxysmal atrial tachycardias in patients treated with cardiac resynchronization therapy and continuously monitored by device diagnostics. *Europace* 2010; **12**: 71–7.
26 Bottoni N, Donateo P, Quartieri F et al. Outcome after cavo-tricuspid isthmus ablation in patients with recurrent atrial fibrillation and drug-related typical atrial flutter. *Am J Cardiol* 2004; **94**: 504–8.
27 Fuster V, Ryden LE, Asinger RW et al. ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation) Developed in Collaboration with the North American Society of Pacing and Electrophysiology. *Circulation* 2001; **104**: 2118–50.
28 Borleffs CJ, Ypenburg C, van Bommel RJ et al. Clinical importance of new-onset atrial fibrillation after cardiac resynchronization therapy. *Heart Rhythm* 2009; **6**: 305–10.
29 Wijffels MC, Kirchhof CJ, Dorland R et al. Electrical remodeling due to atrial fibrillation in chronically instrumented conscious goats: roles of neurohumoral changes, ischemia, atrial stretch, and high rate of electrical activation. *Circulation* 1997; **96**: 3710–20.
30 Fung JW, Yip GW, Zhang Q 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.

Paper received March 2011, accepted May 2011