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ORIGINAL ARTICLE

Does permanent atrial fibrillation modify response to cardiac resynchronization therapy in heart failure patients?

Ana Abreu[a,*], Mário Oliveira[a], Pedro Silva Cunha[a], Helena Santa Clara[b], Guilherme Portugal[a], Inês Gonçalves Rodrigues[a], Vanessa Santos[b], Luís Morais[a], Mafalda Selas[a], Rui Soares[a], Luísa Branco[a], Rui Ferreira[a], Miguel Mota Carmo[c], on behalf of BETTER-HF investigators

[a] *Serviço de Cardiologia, Hospital de Santa Marta, Centro Hospitalar Lisboa Central, CHLC, Lisboa, Portugal*
[b] *Centro Interdisciplinar de Estudo da Performance Humana, CIPER, Faculdade de Motricidade Humana, Universidade de Lisboa, Portugal*
[c] *Centro de Estudos de Doenças Crónicas, CEDOC, Faculdade de Ciências Médicas, Universidade Nova, Lisboa, Portugal*

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KEYWORDS
Heart failure;
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Abstract
Introduction: The benefits of cardiac resynchronization therapy (CRT) documented in heart failure (HF) may be influenced by atrial fibrillation (AF). We aimed to compare CRT response in patients in AF and in sinus rhythm (SR).
Methods: We prospectively studied 101 HF patients treated by CRT. Rates of clinical, echocardiographic and functional response, baseline NYHA class and variation, left ventricular ejection fraction, volumes and mass, atrial volumes, cardiopulmonary exercise test (CPET) duration (CPET dur), peak oxygen consumption (VO_2max) and ventilatory efficiency (VE/VCO_2 slope) were compared between AF and SR patients, before and at three and six months after implantation of a CRT device.
Results: All patients achieved ≥95% biventricular pacing, and 5.7% underwent atrioventricular junction ablation. Patients were divided into AF (n=35) and SR (n=66) groups; AF patients were older, with larger atrial volumes and lower CPET dur and VO_2max before CRT. The percentages of clinical and echocardiographic responders were similar in the two groups, but there were more functional responders in the AF group (71% vs. 39% in SR patients; p=0.012). In SR patients, left atrial volume and left ventricular mass were significantly reduced (p=0.015 and p=0.021, respectively), whereas in AF patients, CPET dur (p=0.003) and VO_2max (p=0.001; 0.083 age-adjusted) showed larger increases.

* Corresponding author.
E-mail address: ananabreu@hotmail.com (A. Abreu).

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Conclusion: Clinical and echocardiographic response rates were similar in SR and AF patients, with a better functional response in AF. Improvement in left ventricular function and volumes occurred in both groups, but left ventricular mass reduction and left atrial reverse remodeling were seen exclusively in SR patients (ClinicalTrials.gov identifier: NCT02413151; FCT code: PTDC/DES/120249/2010).

PALAVRAS-CHAVE
Insuficiência cardíaca;
Ressincronização cardíaca;
Fibrilhação auricular;
Respondedor

A fibrilhação auricular modifica a resposta à terapêutica de ressincronização cardíaca em doentes com insuficiência cardíaca?

Resumo
Introdução: Os benefícios da terapêutica de ressincronização cardíaca (TRC), documentados na insuficiência cardíaca (IC), poderão ser influenciados pela fibrilhação auricular (FA). Pretendemos avaliar comparativamente efeitos TRC em doentes em FA e em ritmo sinusal (RS).
Métodos: Foram estudados prospetivamente 101 doentes submetidos a TRC. Percentagens de respondedores clínicos, ecocardiográficos e funcionais, valores basais e variação de classe NYHA, fração de ejeção, volumes e massa ventriculares esquerdos, volumes auriculares, duração da prova de esforço cardiorrespiratória (PECR dur), consumo pico de oxigénio (VO2p) e eficiência ventilatória de esforço (VE/VCO2) foram comparados entre grupos FA e RS, pré-implantação TRC e nos seis meses após implantação.
Resultados: Os doentes tiveram percentagens de *pacing* biventricular ≥95%, com 5,7% de ablação auriculoventricular juncional. Definimos grupo FA (n=35) e grupo RS (n=66), tendo os doentes com FA idade superior, maiores volumes auriculares, menores PECR dur e VO2p pré-CRT. Percentagens de respondedores clínicos e ecocardiográficos foram idênticas nos dois grupos, mas de respondedores funcionais foram superiores nos doentes FA (71 *versus* 39% no grupo RS; p=0,012). Nos doentes RS verificou-se a redução significativa do volume auricular esquerdo e da massa ventricular esquerda (p=0,015 e p=0,021, respetivamente) e nos doentes com FA maior aumento da PECR dur (p=0,003) e VO2p (p=0,001; p=0,083 ajustado para idade).
Conclusão: As respostas clínica e ecocardiográfica à TRC foram semelhantes nos doentes FA e RS, com resposta funcional superior em FA. A melhoria de função e dimensões ventriculares esquerdas foi idêntica nos dois grupos, contudo redução de massa ventricular esquerda e remodelagem inversa auricular esquerda foram exclusivas de doentes RS (ClinicalTrials.gov Identifier: NCT02413151; FCT code: PTDC/DES/120249/2010).

Introduction

Cardiac resynchronization therapy (CRT) is an important device-based, non-pharmacological treatment for chronic heart failure (HF). The multiple benefits of CRT in selected HF patients under optimized pharmacologic therapy include improvement in symptoms and quality of life, left ventricular (LV) remodeling and decreased mortality and hospital admissions for HF, and have been established by multiple large trials,[1–5] leading to its recommendation in current guidelines.[6] An important feature in HF is the presence of atrial fibrillation (AF), the arrhythmia most frequently associated with HF, which affects up to 45%-50% of patients, depending on the severity of HF.[7,8] For HF patients still in sinus rhythm (SR), the annual incidence of AF is approximately 5%.[9] AF is negatively related to prognosis, although some authors do not consider it an independent prognostic predictive factor after correction for age and comorbidities.[10] Atrial arrhythmias, if not appropriately managed, may have a negative impact on the clinical benefits of CRT,[11] since, in AF patients, CRT can only correct intra- and interventricular dyssynchrony. CRT is also hampered by high intrinsic ventricular rates and irregularity, leading to reduced capture, fusion and pseudo-fusion, and hence less effective biventricular pacing.[12]

Although the evidence from large randomized controlled trials is weak,[13,14] and some authors have argued that HF patients in AF may respond less well to CRT,[15–20] the European Society of Cardiology (ESC) guidelines recommend that this therapy should also be used for AF patients, as long as atrioventricular (AV) junction ablation is added in patients in whom continuous biventricular pacing is lost.[6] Recently, the CERTIFY study[21] showed that long-term survival after CRT among patients with AF and AV junction ablation is similar to

that observed among patients in SR, and that mortality in AF patients treated with rate-reducing drugs is higher. Whether CRT is effective in the context of AF is still an important question to be addressed. The purpose of the present study was to prospectively assess the response to CRT in HF patients with permanent AF compared to those in SR.

Methods

Study design

A prospective cohort study was performed in a single hospital center, including consecutive HF patients with systolic dysfunction selected for CRT according to current guidelines, over a period of 36 months.

The study protocol was approved by the hospital's Ethics Committee and complies with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Patient selection

The patients were consecutively selected for CRT between 2012 and 2014, based on current guidelines[6] and according to the following inclusion and exclusion criteria:

Inclusion criteria:

- Moderate to severe HF (New York Heart Association [NYHA] class III-IV) under optimal medical therapy
- Age >18 and <80 years
- Moderate to severe LV systolic dysfunction (LV ejection fraction [LVEF] <35%)
- QRS duration $\geq$120 ms
- Ischemic or non-ischemic etiology
- Cardiac rhythm: SR or AF
- Stable condition for >1 month (no hospitalization for HF, no change in medication, no change in NYHA functional class).

Exclusion criteria:

- Refusal to participate in the study for any reason
- Inability to perform cardiopulmonary exercise testing (CPET)
- Inability to sign informed consent
- Unstable angina

Optimal medical therapy for HF was considered to include an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker and a beta-blocker, as recommended by the guidelines, unless contraindicated.

Patients were divided in two groups according to baseline cardiac rhythm, SR or permanent AF, confirmed by electrocardiogram (ECG).

Technical procedures

Implantation was performed as previously described.[22] Patients with permanent AF underwent radiofrequency AV junction ablation whenever capture occurred less than 95% of the time. The percentage of biventricular pacing was identified by device counters, ECG and Holter in doubtful cases. All patients in the current study were provided with similar HF management following CRT implantation, including comparable and optimal pharmacologic treatment.

Assessment protocol

Clinical, echocardiographic and CPET parameters were assessed in the 48 hours before (T1) and at three and six months after CRT implantation (T2 and T3, respectively), and their variation over time (T2-T1 and T3-T1) was determined and compared between the two groups.

Clinical and electrocardiographic parameters

Age, gender, HF etiology and NYHA functional class were recorded. Cardiac rhythm, heart rate (HR) and QRS duration were determined from the ECG at inclusion and confirmed at implantation.

Cardiopulmonary exercise testing

Symptom-limited CPET was performed under HF medication, according to a modified Bruce protocol on a treadmill (Mortara Multisyn 190), with breath-by-breath gas exchange measurements (Innocor). Testing supervisors encouraged patients to exercise to exhaustion, guided by the respiratory exchange ratio (RER), with a goal of RER >1.10. Exercise test duration (CPET dur), peak oxygen consumption (VO_2max), ventilatory efficiency as measured by the slope of the linear relationship between ventilation and CO_2 output (VE/VCO_2 slope), and HR were determined.

Echocardiographic study

Transthoracic echocardiography (GE Vivid 9) was performed to assess LVEF (by Simpson's method), LV end-diastolic and end-systolic volume (LVEDV and LVESV, respectively), LV mass (LVM), and left and right atrial volume (LAV and RAV, respectively).

Clinical and echocardiographic responders to cardiac resynchronization therapy

The proportion of CRT responders in each group was calculated and compared between the two groups.

CRT response was defined according to clinical, echocardiographic and functional parameters, as follows:

- Clinical response to CRT – sustained improvement of at least one NYHA class;
- Echocardiographic response – a minimum absolute 5% increase in LVEF;
- Functional response – an absolute increase of >1 ml/kg/min in VO_2max.

Response to CRT was defined by clinical, echocardiographic or functional improvement between T1 and T2 (sustained at T3) or T1 and T3.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as absolute values and percentages. Variations in continuous variables were determined and compared by the paired t test and the non-parametric Wilcoxon test, when appropriate, for variables with and without normal distribution, respectively. Categorical variables were compared by the chi-square test. Differences in mean ± SD between the AF and SR groups were tested with the unpaired t test or the Mann-Whitney test, according to distribution. Multivariate linear regression was used for age adjustment and for baseline adjustment for VO_2max regarding change in VO_2max after CRT in the AF group. A p value <0.05 was considered significant. SPSS 22.0 (IBM SPSS, Armonk, NY) was used for the statistical analysis.

Results

Population sample

A total of 101 HF patients referred for CRT implantation, in class NYHA III or IV and with LVEF <35%, were included, 71 male (70%), mean age 68 years, 27.5% ischemic etiology. Of these, 35 patients (34%) were in permanent AF at the time of CRT implantation.

To achieve effective biventricular capture, two AF patients (5.7%) underwent radiofrequency AV junction ablation, while the other 33 (94.3%) were successfully treated with negative chronotropic drugs only (digoxin, beta-blockers, amiodarone) for rate control, maximizing biventricular pacing delivery.

The characteristics of the population sample and differences between groups are shown in Table 1. Patients in the AF group were older and more often male. Also, echocardiographic and functional data show more LV hypertrophy, atrial dilatation and worse functional capacity in this group, reflected by higher mean LVM, LAV and RAV, and lower mean CPET dur, VO_2max and percentage predicted VO_2 compared to the SR group.

Table 1 Characteristics of patients in sinus rhythm and atrial fibrillation at baseline, before cardiac resynchronization therapy.

Baseline	SR (n=66)	AF (n=35)	p
Age, years	67.4±11.8	71.4±8.9	0.024
Male	41 (62.1%)	28 (80%)	0.066
NYHA II	16 (24.2%)	7 (20%)	0.316
NYHA III	48 (72.7%)	24 (68.6%)	
NYHA IV	2 (3.0%)	3 (8.6%)	
BMI (kg/m^2)	26±5	27±4	0.730
Ischemic etiology	18 (27.3%)	10 (28.6%)	0.890
LVEF <25%	26 (39.4%)	13 (38.2%)	0.910
LVEF, %	25.8±7.1	26.6±7.3	0.638
LVEDV, ml	202.2±68.2	222.3±70.5	0.188
LVESV, ml	149.8±53.4	166.0±63.4	0.288
LVM, g	315.86±82.16	362.31±103.69	0.06
LAV, ml	68.1±34.6	106.9±50.8	0.006
RAV, ml	29.5±16.2	64.0±51.6	0.0001
CPET dur, s	432.9±250.7	242.2±183.4	0.001
HR bas, bpm	78.6±11.6	76.6±12.7	0.48
HR max, bpm	123±23	122±31	0.585
VO_2max, ml/kg/min	15.8±5.4	11.9±4.3	0.001
Predicted VO_2max, %	52.88±18.52	39.67±16	0.004
QRS, ms	143.2±20.7	145.8±24.3	0.790

AF: atrial fibrillation group; BMI: body mass index; bpm: beats per minute; CPET dur: cardiopulmonary exercise test duration; HR bas: baseline heart rate; HR max: maximum heart rate; LAV: left atrial volume; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association class; RAV: right ventricular volume; SR: sinus rhythm group; VO_2max: peak oxygen consumption.
Data are expressed as mean ± SD for continuous variables and as number and proportion (%) for categorical variables.

Clinical effects of cardiac resynchronization therapy

NYHA functional class improved significantly over time (T2-T1 and T3-T1) in both groups, with no significant difference between SR and AF, as displayed in Table 2.

Echocardiographic effects of cardiac resynchronization therapy

Changes over time after CRT (T2-T1 and T3-T1) in several echocardiographic variables showed significance in both rhythm groups (Table 2). Mean LVEF and ventricular volumes, especially LVESV, improved significantly after CRT in both SR and AF patients, without statistical difference between the groups. However, mean LV mass and LAV changed significantly, but only in SR patients at six months.

Functional effects of cardiac resynchronization therapy

Improvements in CPET dur and VO_2max were only significant in AF patients. Change in VE/VCO_2 slope was significant in AF and at three months in SR (Table 2). There were significant differences in variation in VO_2max and CPET dur between the groups. When adjusted for age, the difference in VO_2max variation loses statistical significance, but CPET dur change remains significantly different in AF, even after age adjustment. Pre- and post-CRT baseline HR was not significantly different in the two groups and post-CRT maximum HR was also similar.

Responders to cardiac resynchronization therapy

Proportions of clinical, echocardiographic and functional responders at six months in the SR and AF groups are summarized in Table 3, which shows similar percentages for clinical responders (78.6% for SR and 80.7% for AF) and for echocardiographic responders (77.4% for SR and 82.1% for AF). However, the proportion of functional responders was significantly larger in AF patients (71.4% vs. 39.3% in SR, p=0.012).

Table 2 Differences in clinical, echocardiographic and functional variables of cardiopulmonary exercise testing after cardiac synchronization therapy in patients in sinus rhythm and in atrial fibrillation.

Variable	SR (n=66)	p	AF (n=35)	p	p SR/AF
NYHA class T1-T2	-0.97 ± 0.78	0.0001	-0.96 ± 0.72	0.0001	0.884
NYHA class T1-T3	-1.14 ± 0.85	0.0001	-1.07 ± 0.94	0.0001	0.873
LVEF T1-T2, %	10.71 ± 10.44	0.0001	7.97 ± 11.15	0.001	0.269
LVEF T1-T3, %	12.9 ± 11.3	0.0001	10.9 ± 9.8	0.0001	0.305
LVEDV T1-T2, ml	-5.90 ± 63.60	0.393	-9.74 ± 50.58	0.212	0.790
LVEDV T1-T3, ml	-12.25 ± 43.60	0.040	-15.07 ± 45.51	0.036	0.694
LVESV T1-T2, ml	-13.27 ± 46.68	0.021	-27.14 ± 59.50	0.067	0.487
LVESV T1-T3, ml	-23.40 ± 39.94	0.0001	-25.97 ± 40.50	0.003	0.681
LVM T1-T2, g	-7.51 ± 89.87	0.922	5.66 ± 87.19	0.778	0.867
LVM T1-T3, g	-31.05 ± 88.39	0.021	-12.13 ± 95.80	0.527	0.486
LAV T1-T2, ml	-10.2 ± 28.81	0.093	-16.63 ± 48.82	0.483	0.919
LAV T1-T3, ml	-15.81 ± 29.83	0.015	13.77 ± 39.13	0.249	0.022
RAV T1-T2, ml	-6.10 ± 17.44	0.067	-9.63 ± 19.46	0.208	0.722
RAV T1-T3, ml	-4.46 ± 15.04	0.247	-4.58 ± 33.70	0.255	0.307
HR bas T1-T3, bpm	1.7 ± 2.3	0.77	4.8 ± 2.9	0.09	0.451
HR max T1-T3, bpm	1.09 ± 3.7	0.77	9.5 ± 5.5	0.99	0.61
VO_2max T1-T2, ml/kg/min	0.92 ± 4.74	0.246	2.18 ± 3.81	0.021	0.225
VO_2max T1-T3, ml/kg/min	-0.42 ± 4.92	0.493	3.72 ± 2.91	0.001	0.005
CPET dur T1-T2, s	44.17 ± 181.7	0.178	160.64 ± 193.3	0.001	0.018
CPET dur T1-T3, s	39.10 ± 202.7	0.343	152.62 ± 235.7	0.003	0.009
VE/CO_2 slope T1-T2	-5.31 ± 9.21	0.006	-8.54 ± 8.82	0.005	0.220
VE/CO_2 slope T1-T3	-3.1 ± 11.6	0.36	-6.4 ± 10.9	0.08	0.322

AF: atrial fibrillation group; bpm: beats per minute; CPET dur: cardiopulmonary exercise test duration; HR bas: baseline heart rate; HR max: maximum heart rate; LAV: left atrial volume; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association class; RAV: right ventricular volume; SR: sinus rhythm group; T1: before cardiac resynchronization therapy (CRT); T2: 3 months after CRT; T3: 6 months after CRT; VO_2max: peak oxygen consumption. Data expressed as mean ± SD.

Table 3 Proportions of clinical, echocardiographic and functional responders in sinus rhythm and atrial fibrillation patients.

Total population (n=101)	SR (n=66)	AF (n=35)	p
Clinical responders, n (%)	44 (78.6%)	46 (80.7%)	NS
Echocardiographic responders, n (%)	24 (77.4%)	23 (82.1%)	NS
Functional responders, n (%)	26 (39.3%)	25 (71.4%)	0.012

AF: atrial fibrillation group; SR: sinus rhythm group.
Data expressed as numbers and proportions (%).

Discussion

In the present study, patients with permanent AF, one third of the study population, showed good response to CRT in the majority of cases without the need for AV junction ablation, in contrast to several previous studies.[19]

To date, randomized studies on CRT have been mainly restricted to patients in SR, excluding patients in permanent AF. This contrasts with the high prevalence of CRT use in AF patients in routine clinical practice, as observed in our data (35%) and as previously indicated by ESC surveys,[23,24] which indicate a prevalence of 23%.[23]

It is well known that the likelihood of coexistent AF and HF is strongly related to the severity of the disease represented by NYHA functional class: prevalence of 5% for NYHA class I, 10%-25% for class II/III, and 50% for class IV.[10] The probable reason for the higher prevalence of AF observed in our study population is their greater clinical severity (95% NYHA class III/IV, 5% class II) compared to patients in the European cardiac resynchronization registry (78% class III/IV, 22% class I/II).[23] In our sample, AF patients were older, with worse functional capacity, as in previous studies, which may have influenced the effects of CRT in AF compared to SR patients.[25,26] Our data are also in accordance with the greater proportion of men among AF patients, as previously demonstrated,[27] and additionally showed a higher percentage of nonischemic cardiomyopathy.

Regarding the management of our patients, which followed the consensus for mandatory continuous biventricular

capture, it assured rate control and rhythm regularization, in order to maximize the clinical benefit and improve prognosis of patients with permanent AF.[28] This requires AV junction ablation in some cases, since pharmacological treatment may be inadequate to control ventricular rate at rest and during exercise. In the second ESC CRT survey,[24] 74% of European centers implanting CRT devices scheduled AV junction ablation only in the presence of uncontrolled HR, and only a minority of centers (11%) proceeded directly to AV junction ablation, regardless of HR. Frequent biventricular pacing, as previously defined, was taken as ≥95% of biventricular capture.[29] In our study, only 5.7% of AF patients underwent AV junction ablation during the first six months after implantation, the other 94.3% being treated with pharmacological therapy for HR control. The low proportion of patients needing AV junction ablation could be explained by good pharmacologic HR control with adequate dosages of beta-blockers, digoxin and other drugs with bradycardia effects, carefully titrated and increased whenever needed. Furthermore, some of these patients underwent CRT implantation due to left ventricular dysfunction, heart failure and indication for pacing due to bradyarrhythmia. However, there was no control group to compare these effects, since the other group was made up of SR patients, who might not need the same drugs or the same dosages. At this point, it is important to note that pre- and post-CRT baseline HR and maximum HR during CPET were not significantly different between SR and AF patients.

Concerning the effects of CRT in this real-life study, several clinical, echocardiographic and functional variables of exercise testing changed significantly after CRT in both SR and AF patients: NYHA class, LVEF, LVESV and VE/VCO_2 slope (at three months), and LVEDV and VE/VCO_2 (at six months). Similarly, some authors have shown that CRT in AF patients improves symptoms,[14,30] while others suggest that CRT is only effective after AV junction ablation, which was certainly not the case in our patients. In contrast to our results, some previous studies in AF patients demonstrated that, despite similar changes in LVEF, there was less improvement in NYHA functional class.[25,26,31]

An important issue is the CRT response rate, bearing in mind that definitions of CRT response in the literature differ widely.[32] It is interesting to observe that neither SR nor permanent AF significantly influenced the percentage of responders in this sample, either clinical (SR 78.6% vs. AF 80.7%) or echocardiographic (SR 77.4% vs. AF 82.1%). Some studies, however, have shown different results. In a meta-analysis by Wilton et al., which included 33 studies (7495 patients), a lower rate of CRT response was observed in AF patients than in SR, with no response in 34.5% vs. 26.7%, respectively (p=0.01).[26] Also, a more recent study[33] confirmed the benefit of CRT in HF patients with AF, although inferior to that of SR patients, with more frequent non-response. In contrast to the results of these two publications and to our own data, single-center randomized studies have demonstrated little evidence regarding CRT effectiveness in AF.[34] The RAFT study[35] included more patients with permanent AF than all other published studies combined. RAFT failed, however, to demonstrate a clear improvement in any clinical or surrogate outcome with CRT in patients with permanent AF, despite a trend for fewer HF hospitalizations. This poor outcome might be attributed to suboptimal delivery of CRT, because only one third of patients received ≥95% ventricular pacing.[35] It should be noted that in this study many patients were in NYHA class II. To increase the percentage of pacing in AF, AV junction ablation was applied in our study, increasing CRT response.[26]

In the present study, there was a significant mean increase in LVEF at three and six months in both groups, which was not statistically greater in SR patients. Despite the significant decrease in both groups in mean LVESV and LVEDV (only at six months), other authors found less improvement in LVESV in AF patients.[26] Mean LVM and LAV decreased significantly at six months, but only in the SR group. It is known that HF facilitates atrial remodeling, which promotes the development and maintenance of AF,[36] explaining the larger LAV in AF patients. LAV was smaller in SR patients, and consequently the changes were less marked, which facilitated reverse remodeling after CRT. We may hypothesize that LA reverse remodeling and more profound LV reverse remodeling take longer (more than three months) until a significant change is achieved after CRT, and are probably positively influenced by the presence of SR.

On the other hand, regarding the functional effects as assessed by CPET, although VE/VCO_2 slope decreased significantly in both groups, only patients with AF had a significant increase in CPET dur (an absolute increase three times that of SR) and also in VO_2max three months after CRT. Interestingly, after adjusting for age and baseline VO_2max (which was higher in SR and lower in AF patients), there was no longer a statistically significant improvement in VO_2max in AF patients (multivariate linear regression, p=0.083). This shows the importance of baseline VO_2max and age in the VO_2max response observed after CRT in AF.

A previous study[37] demonstrated that treatment of HF patients with CRT improves exercise capacity and that this increase is most substantial among patients with a lower baseline VO_2max (percentage predicted for age), the authors concluding that baseline CPET can therefore be used to identify patients who are more likely to exhibit functional improvement after CRT. Those with predicted VO_2max <40% had much greater improvement in VO_2max. In agreement with this, our AF patients had lower mean pre-CRT VO_2max (probably related to older age, and also predicted VO_2max) and more improved VO_2max after CRT than SR. Also, HF patients with mean baseline VO_2max <14 ml/kg/min, which was the case in our AF group, benefited most from the implantation of a CRT device.[39] The percentage of functional CPET responders was significantly higher in AF patients than in SR patients, for the reasons mentioned above. Despite these better values, post-CRT mean VO_2max in AF did not exceed that in SR, and values at six months were similar in the two study groups.

In patients with advanced HF, variation in VO_2max is an important predictor of outcomes, including clinical deterioration or death, especially in patients with ischemic cardiomyopathy or not receiving beta-blockers.[39] Exercise capacity is objectively quantified by measurement of VO_2max, carbon dioxide production (VCO_2), and minute ventilation.[40] Not surprisingly, VO_2max has a strong linear correlation with both cardiac output and skeletal muscle blood flow.[41] Peak exercise capacity is defined as the maximum ability of the cardiovascular system to deliver oxygen to exercising skeletal muscle and of the exercising muscle to

extract oxygen from the blood.[42] As a result, exercise capacity is determined by three factors: pulmonary gas exchange; cardiovascular performance, including the peripheral vascular tree; and skeletal muscle metabolism. It has been demonstrated that CRT significantly improves all ventilation and metabolic parameters of patients with HF and ventricular conduction delay. Patients with more depressed metabolic and ventilation parameters and higher HR at baseline seem to benefit most from this therapeutic approach.[38] These results are in agreement with those observed in our study. AF patients were more deconditioned, with worse physical condition and lower exercise capacity, related to severe HF and aging, as demonstrated, and after CRT they had greater improvement in cardiovascular performance. Mean CPET dur increased in both groups, early at three months, with a more than three-fold change in AF patients, in whom the change was statistically significant (unlike in SR patients), attaining similar values for CPET dur after CRT. CRT did not significantly alter exercise capacity in SR patients, but this finding is not surprising in patients whose exercise capacity was not so severely impaired at baseline. This observation is consistent with the study referred to above, which demonstrated that HF patients with relatively preserved exercise capacity at baseline achieve only minor improvement in exercise capacity during CRT.[38]

As mentioned above, the mean decrease in VE/VCO_2 slope was significant at three months in both groups, which is also an important beneficial effect of CRT, since a lower VE/VCO_2 slope in HF is associated with better prognosis.[43]

In conclusion, beneficial effects of CRT were demonstrated in HF patients, both in permanent AF and in SR, with similar proportions of clinical and echocardiographic responders.

Both groups showed LV reverse remodeling independently of cardiac rhythm, to a larger extent in SR patients, who also showed LV mass reduction and LA reverse remodeling, which were not present in AF patients. Additionally, AF patients, initially with less exercise functional capacity, had a greater improvement, with more functional responders. According to our results, permanent AF should not by itself be considered a factor against deciding to treat selected HF patients with CRT.

Study limitations

This work, analyzing the use of CRT in HF patients in permanent AF, has the inherent limitations of an observational study. It involves a medium-sized population sample, so the present results need to be treated with caution and should be reproduced in a larger permanent AF population, preferably in a prospective controlled clinical trial on CRT in AF, to confirm its results. Longer follow-up studies are needed.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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References

1. Cazeau S, Leclercq C, Lavergne, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001;344:873–80.
2. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346:1845–53.
3. Auricchio A, Stellbrink C, Sack S, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol. 2002;39:2026–33.
4. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140–50.
5. Cleland JGF, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352:1539–49.
6. Brignole M, Auricchio, Baron-Esquivias, 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). Eur Heart J. 2013;34:2281–329.
7. Khan NK, Goode KM, Cleland JG, et al. ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. Eur J Heart Fail. 2007;9:491–501.
8. Khand AU, Rankin AC, Kaye GC, et al. Systematic review of the management of atrial fibrillation in patients with heart failure. Eur Heart J. 2000;21:614–32.
9. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol. 2003;91:2D–8D.
10. Crijns HJ, Tjeerdsma G, de Kam PJ, et al. Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. Eur Heart J. 2000;21:1238–45.
11. Gasparini M, Regoli F, Galimberti P, et al. Cardiac resynchronization therapy in patients with heart failure in atrial fibrillation. Europace. 2009;11 Suppl 5:v82–6.
12. Leyva F, Nisam S, Auricchio A. 20 years of cardiac resynchronization therapy. J Am Coll Cardiol. 2014;64:1047–58.
13. Brignole M, Botto G, Mont L, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction

ablation for permanent atrial fibrillation: a randomized trial. Eur Heart J. 2011;32:2420–9.
14. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J. 2002;23:1780–7.
15. Khadjooi K, Foley PW, Chalil S, et al. Long-term effects of cardiac resynchronization therapy in patients with atrial fibrillation. Heart. 2008;94:879–88.
16. Gasparini M, Auricchio A, Regoli F, et al. Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. J Am Coll Cardiol. 2006;48:734–43.
17. Gasparini M, Auricchio A, Metra M, et al. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrioventricular junction ablation in patients with permanent atrial fibrillation. Eur Heart J. 2008;29:1644–52.
18. Gasparini M, Steinberg JS, Arshad A, et al. Resumption of sinus rhythm in patients with heart failure and permanent atrial fibrillation undergoing cardiac resynchronization therapy: a longitudinal observational study. Eur Heart J. 2010;31:976–83.
19. Gasparini M, Leclercq C, Lunati M, et al. Cardiac resynchronization therapy in patients with atrial fibrillation: the CERTIFY study (Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry). JCHF. 2013;1:500–7.
20. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American College of Chest Physicians, Heart Rhythm Society and International Society for Heart and Lung Transplantation. Circulation. 2013;128:e240–327.
21. Dickstein K, Vardas PE, Auricchio A, et al. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy, Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Eur J Heart Fail. 2010;12:1143–53.
22. Daubert JC, Saxon L, Adamson PB, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Heart Rhythm. 2012;9:1524–76.
23. Dickstein K, Bogale N, Priori S, et al. The European cardiac resynchronization therapy survey. Eur Heart J. 2009;30:2450–60.
24. Sciaraffia E, Dagres N, Hernandez-Madrid A, et al. Do cardiologists follow the European guidelines for cardiac pacing and resynchronization therapy? Results of the European Heart Rhythm Association survey. Europace. 2015;17:148–51.
25. Upadhyay GA, Choudry NK, Auricchio A, et al. Cardiac resynchronization in patients with atrial fibrillation: a meta-analysis of prospective cohort studies. J Am Coll Cardiol. 2008;52:1239–46.
26. Wilton SB, Leung AA, Ghali WA, et al. Outcomes of cardiac resynchronization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. Heart Rhythm. 2011;8:1088–94.
27. Kannel WB, Abbott RD, Savage DD, et al. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med. 1982;306:1018–22.
28. Ferreira AM, Adragao P, Cavaco DM, et al. Benefit of cardiac resynchronization therapy in atrial fibrillation patients vs. patients in sinus rhythm: the role of atrioventricular junction ablation. Europace. 2008;10:809–15.
29. Koplan BA, Kaplan AJ, Weiner S, et al. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal of 100% biventricular pacing necessary? J Am Coll Cardiol. 2009;53:355–60.
30. Linde C, Leclercq C, Rex S, et al., on behalf of the MUltisite STimulation In Cardiomyopathies (MUSTIC) Study Group. Long-term benefits of biventricular pacing in congestive heart failure: results from the Multisite Stimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol. 2002;40:111–8.
31. Wein S, Voskoboinik A, Wein L, et al. Extending the boundaries of cardiac resynchronization therapy: efficacy in atrial fibrillation, New York Heart Association class II, and narrow QRS heart failure patients. J Card Fail. 2010;16:432–8.
32. Fornwalt BK, Sprague WW, BeDell P, et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation. 2010;121:1985–91.
33. Lopes C, Pereira T, Barra S. Cardiac resynchronization therapy in patients with atrial fibrillation: a meta-analysis. Rev Port Cardiol. 2014;33:717–25.
34. Prinzen FW, Vernooy K, Auricchio A. Cardiac resynchronization therapy: state-of-the-art of current applications, guidelines, ongoing trials, and areas of controversy. Circulation. 2013;128:2407–18.
35. Healey JS, Hohnloser SH, Exner DV, et al., on behalf of the RAFT Investigators. 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.
36. Darby AE, DiMarco JP. Management of atrial fibrillation in patients with structural heart disease. Circulation. 2012;125:945–57.
37. Arora S, Aarones M, Aakhus S, et al. Peak oxygen uptake during cardiopulmonary exercise testing determines response to cardiac resynchronization therapy. J Cardiol. 2012;60:228–35.
38. Auricchio A, Kloss M, Trautmann SI, et al. Exercise performance following cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. Am J Cardiol. 2002;89:198–203.
39. MacGowan GA, Pohwani A, Murali S. Dynamic analysis of exercise oxygen consumption predicts outcomes in advanced heart failure. Congest Heart Fail. 2007;13:313–8.
40. McElroy PA, Janicki JS, Weber KT. Cardiopulmonary exercise testing in congestive heart failure. Am J Cardiol. 1988;62:35A.
41. Reddy HK, Weber KT, Janicki JS, et al. Hemodynamic, ventilatory and metabolic effects of light isometric exercise in patients with chronic heart failure. J Am Coll Cardiol. 1988;12:353.
42. Dennis C. Rehabilitation of patients with coronary artery disease. In: Braunwald E, editor. Heart disease, a textbook of cardiovascular medicine. 4th ed. Philadelphia: Saunders; 1992. p. 1382.
43. Francis DP, Shamin W, Ceri Davies L, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO2 slope and peak VO2. Eur Heart J. 2000;21:154–61.