ORIGINAL ARTICLE

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

Ana Abreu (A.*), Mário Oliveira, Pedro Silva Cunha, Helena Santa Clara, Guilherme Portugal, Inês Gonçalves Rodrigues, Vanessa Santos, Luís Morais, Mafalda Selas, Rui Soares, Luisa Branco, Rui Ferreira, Miguel Mota Carmo,
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 Matrículidade Humana, Universidade de Lisboa, Portugal
c Centro de Estudos de Doenças Crônicas, CEDOC, Faculdade de Ciências Médicas, Universidade Nova, Lisboa, Portugal

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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 (VO2max) and ventilatory efficiency (VE/VCO2 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 VO2max 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 VO2max (p=0.001; 0.083 age-adjusted) showed larger increases.

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

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**PALAVRAS-CHAVE**

Insuficiência cardíaca; Ressincronização cardíaca; Fibrilação auricular; Respondedor

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**A fibrilação 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 fibrilação auricular (FA). Pretendemos avaliar comparativamente efeitos TRC em doentes em FA e em ritmo sinusal (RS).

**Métodos:** Foram estudados prospectivamente 101 doentes submetidos a TRC. Percentagens de respondentes 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 oxigênio (VO2p) e eficiência ventilatória de esforço (VE/VO2) 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 auriculovertricular junccional. 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).

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**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, leading to its recommendation in current guidelines. 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. For HF patients still in sinus rhythm (SR), the annual incidence of AF is approximately 5%. AF is negatively related to prognosis, although some authors do not consider it an independent prognostic predictive factor after correction for age and comorbidities. Atrial arrhythmias, if not appropriately managed, may have a negative impact on the clinical benefits of CRT, since, in AF patients, CRT can only correct intra- and interventricular dysynchrony. 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.

Although the evidence from large randomized controlled trials is weak, and some authors have argued that HF patients in AF may respond less well to CRT, 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. Recently, the CERTIFY study 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 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 >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. 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 (Innocrin). 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 (VO2max), ventilatory efficiency as measured by the slope of the linear relationship between ventilation and CO2 output (VE/VCO2 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 VO2max.

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\textsubscript{2max} regarding change in VO\textsubscript{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\textsubscript{2max} and percentage predicted VO\textsubscript{2} compared to the SR group.

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\textsubscript{2max} were only significant in AF patients. Change in VE/VCO\textsubscript{2} slope was significant in AF and at three months in SR (Table 2). There were significant differences in variation in VO\textsubscript{2max} and CPET dur between the groups. When adjusted for age, the difference in VO\textsubscript{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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SR (n=66)</th>
<th>AF (n=35)</th>
<th>p</th>
<th>p SR/AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class T1-T2</td>
<td>-0.97±0.78</td>
<td>-0.96±0.72</td>
<td>0.0001</td>
<td>0.884</td>
</tr>
<tr>
<td>NYHA class T1-T3</td>
<td>-1.14±0.85</td>
<td>-1.07±0.94</td>
<td>0.0001</td>
<td>0.873</td>
</tr>
<tr>
<td>LVEF T1-T2, %</td>
<td>7.32±10.44</td>
<td>7.97±11.15</td>
<td>0.0001</td>
<td>0.269</td>
</tr>
<tr>
<td>LVEF T1-T3, %</td>
<td>12.9±11.3</td>
<td>10.9±9.8</td>
<td>0.0001</td>
<td>0.305</td>
</tr>
<tr>
<td>LVEDV T1-T2, ml</td>
<td>-5.90±63.60</td>
<td>-7.94±50.58</td>
<td>0.212</td>
<td>0.790</td>
</tr>
<tr>
<td>LVEDV T1-T3, ml</td>
<td>-12.25±43.60</td>
<td>-15.07±45.51</td>
<td>0.036</td>
<td>0.694</td>
</tr>
<tr>
<td>LVESV T1-T2, ml</td>
<td>-13.27±46.68</td>
<td>-27.14±59.50</td>
<td>0.067</td>
<td>0.487</td>
</tr>
<tr>
<td>LVESV T1-T3, ml</td>
<td>-23.40±39.94</td>
<td>-25.97±40.50</td>
<td>0.003</td>
<td>0.681</td>
</tr>
<tr>
<td>LVM T1-T2, g</td>
<td>-7.51±89.87</td>
<td>5.66±87.19</td>
<td>0.778</td>
<td>0.867</td>
</tr>
<tr>
<td>LVM T1-T3, g</td>
<td>-31.05±88.39</td>
<td>-12.13±95.80</td>
<td>0.527</td>
<td>0.486</td>
</tr>
<tr>
<td>LAV T1-T2, ml</td>
<td>-10.2±28.81</td>
<td>-16.63±48.82</td>
<td>0.483</td>
<td>0.919</td>
</tr>
<tr>
<td>LAV T1-T3, ml</td>
<td>-15.81±29.83</td>
<td>13.77±39.13</td>
<td>0.249</td>
<td>0.022</td>
</tr>
<tr>
<td>RAV T1-T2, ml</td>
<td>-6.10±17.44</td>
<td>-9.63±19.46</td>
<td>0.208</td>
<td>0.722</td>
</tr>
<tr>
<td>RAV T1-T3, ml</td>
<td>-4.46±15.04</td>
<td>-4.58±33.70</td>
<td>0.255</td>
<td>0.307</td>
</tr>
<tr>
<td>HR bas T1-T3, bpm</td>
<td>1.7±2.3</td>
<td>4.8±2.9</td>
<td>0.09</td>
<td>0.451</td>
</tr>
<tr>
<td>HR max T1-T3, bpm</td>
<td>1.09±3.7</td>
<td>9.5±5.5</td>
<td>0.99</td>
<td>0.61</td>
</tr>
<tr>
<td>VO₂max T1-T2, ml/kg/min</td>
<td>0.92±4.74</td>
<td>2.18±3.81</td>
<td>0.021</td>
<td>0.225</td>
</tr>
<tr>
<td>VO₂max T1-T3, ml/kg/min</td>
<td>-0.42±4.92</td>
<td>3.72±2.91</td>
<td>0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>CPET dur T1-T2, s</td>
<td>44.17±181.7</td>
<td>160.64±193.3</td>
<td>0.001</td>
<td>0.018</td>
</tr>
<tr>
<td>CPET dur T1-T3, s</td>
<td>39.10±202.7</td>
<td>152.62±235.7</td>
<td>0.003</td>
<td>0.009</td>
</tr>
<tr>
<td>VE/CO₂ slope T1-T2</td>
<td>-5.31±9.21</td>
<td>-8.54±8.82</td>
<td>0.005</td>
<td>0.220</td>
</tr>
<tr>
<td>VE/CO₂ slope T1-T3</td>
<td>-3.1±11.6</td>
<td>-6.4±10.9</td>
<td>0.08</td>
<td>0.322</td>
</tr>
</tbody>
</table>

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; RA: right ventricular volume; SR: sinus rhythm group; T1: before cardiac resynchronization therapy (CRT); T2: 3 months after CRT; T3: 6 months after CRT; VO₂max: peak oxygen consumption. Data expressed as mean ± SD.

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

<table>
<thead>
<tr>
<th></th>
<th>SR (n=66)</th>
<th>AF (n=35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical responders, n (%)</td>
<td>44 (78.6%)</td>
<td>46 (80.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Echocardiographic responders, n (%)</td>
<td>24 (77.4%)</td>
<td>23 (82.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Functional responders, n (%)</td>
<td>26 (39.3%)</td>
<td>25 (71.4%)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

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. 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, which indicate a prevalence of 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. 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). 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. Our data are also in accordance with the greater proportion of men among AF patients, as previously demonstrated, and additionally showed a higher percentage of nonischemic cardiomyopathy.

Regarding the management of our patients, which followed the consensus for mandatory continuous biventricular
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. 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, 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 LV 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/VCO₂ 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 VO₂max three months after CRT. Interestingly, after adjusting for age and baseline VO₂max (which was higher in SR and lower in AF patients), there was no longer a statistically significant improvement in VO₂max in AF patients (multivariate linear regression, p=0.083). This shows the importance of baseline VO₂max and age in the VO₂max response observed after CRT in AF.

A previous study demonstrated that treatment of HF patients with CRT improves exercise capacity and that this increase is most substantial among patients with a lower baseline VO₂max (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 VO₂max <40% had much greater improvement in VO₂max. In agreement with this, our AF patients had lower mean pre-CRT VO₂max (probably related to older age, and also predicted VO₂max) and more improved VO₂max after CRT than SR. Also, HF patients with mean baseline VO₂max <14 ml/kg/min, which was the case in our AF group, benefited most from the implantation of a CRT device. 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 VO₂max 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 VO₂max is an important predictor of outcomes, including clinical deterioration or death, especially in patients with ischemic cardiomyopathy or not receiving beta-blockers. Exercise capacity is objectively quantified by measurement of VO₂max, carbon dioxide production (VCO₂), and minute ventilation. Not surprisingly, VO₂max has a strong linear correlation with both cardiac output and skeletal muscle blood flow. 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. 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. 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.

As mentioned above, the mean decrease in VE/VCO₂ slope was significant at three months in both groups, which is also an important beneficial effect of CRT, since a lower VE/VCO₂ slope in HF is associated with better prognosis.

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


