

# Cardiac resynchronization therapy in heart failure patients with atrial fibrillation

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Cardiac resynchronization therapy (CRT) is an important device-based, non-pharmacological approach that has shown, in large randomized trials, to improve left ventricular (LV) function and reduce both morbidity and mortality rates in selected patients affected by advanced heart failure (HF): New York Heart Association (NYHA) functional class III–IV, reduced LV systolic function with an ejection fraction (EF)  $\leq 35\%$ , QRS duration  $\geq 120$  ms, on optimal medical therapy, and who were in sinus rhythm. For the first time, the latest ESC and AHA/ACC/HRS Guidelines have considered atrial fibrillation (AF) patients, who constitute an important subgroup of HF patients, as eligible to receive CRT. Nevertheless, these Guidelines did not include a strategy for defining differentiated approaches according to AF duration or burden. In this review, the authors explain in which way AF may interfere with adequate CRT delivery, how to manage different AF burden, and finally present a brief overview on the effects of CRT in AF patients.

**Keywords** Atrial fibrillation • Heart failure • Resynchronization • Defibrillators • Ablation

## Introduction

Cardiac resynchronization therapy (CRT) is an important device-based, non-pharmacological approach that has shown to improve the outcome in selected patients with chronic heart failure (HF). Large randomized trials have demonstrated that CRT improves left ventricular (LV) function and reduces both morbidity and mortality rates.<sup>1–5</sup> Until recently, CRT was indicated in patients with advanced HF [New York Heart Association (NYHA) functional class III–IV], reduced LV systolic function [ejection fraction (EF)  $\leq 35\%$ ], evidence of electrical dyssynchrony (QRS duration  $\geq 120$  ms), receiving optimal medical therapy, and who were in sinus rhythm (SR).<sup>6</sup> In the last ESC recommendations,<sup>7</sup> for the first time, atrial fibrillation (AF) patients, who constitute an important subgroup of HF patients treated with CRT,<sup>8</sup> have been considered as eligible to receive CRT on the condition that the effects of underlying rhythm be neutralized by atrio-ventricular junction (AVJ) ablation. The AHA/ACC/HRS Guidelines<sup>9</sup> also favourably considered CRT in HF patients with AF, without however emphasizing the possible need for aggressive rate control. Also, these Guidelines remain imprecise in defining differentiated approaches according to the forms of AF other than permanent. The present review explains, in the first instance, in which way AF interferes with adequate CRT. Secondly, a brief overview

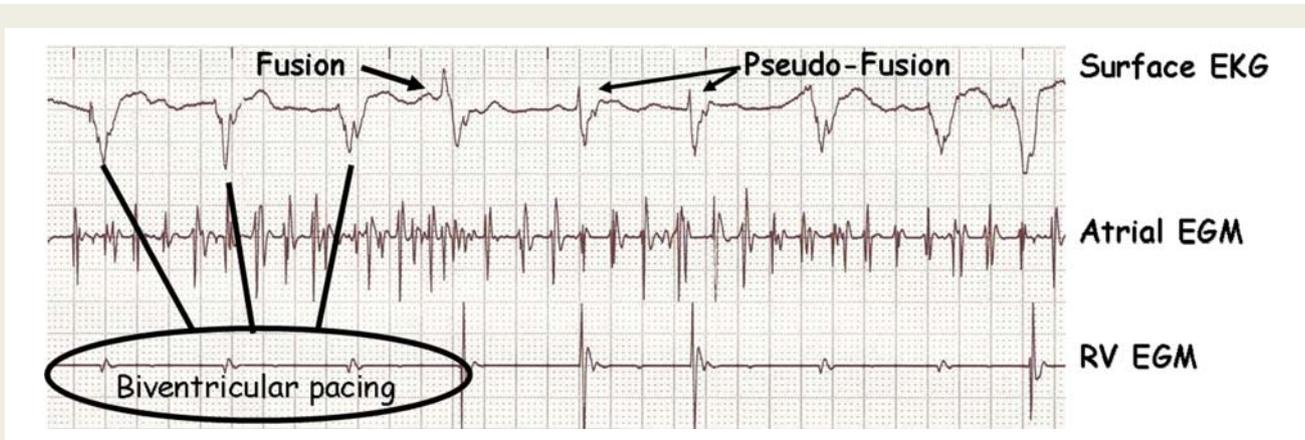
on the effects of CRT in AF patients is presented, followed by some recommendations, based on current evidence, on the most adequate approach according to patient characteristics, emphasizing the extent of atrial arrhythmic [atrial tachycardia (AT)/AF] burden. It is important to point out that these recommendations remain unsupported by evidence derived from randomized controlled trials (RCTs), which are much needed.<sup>10</sup>

## Atrial fibrillation rhythm interferes with adequate cardiac resynchronization therapy delivery

Atrial fibrillation (whether permanent, persistent, or paroxysmal) poses a number of challenges for adequate CRT delivery. An intrinsic, intermediate-to-high, irregular spontaneous AF rhythm reduces the percentage of effectively biventricular paced captured beats (BVP%). Even in a patient who has normal rate AF, phases of effective biventricular capture alternate with phases of competing AF rhythm which causes spontaneous, fusion, or pseudo-fusion beats (*Figure 1*). This suggests that the global effective 'CRT-dose' may be markedly reduced compared with atrial-synchronous rhythm with a short AV interval (as is achieved during SR) since the number of effective biventricular captured beats are reduced. Moreover, in AF patients, during

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**Figure 1** A patient with AF and HF treated with CRT, spontaneous irregular intrinsic beats alternate with fusion and pseudo-fusion beats, thus markedly reducing effective CRT. As shown in the figure, this may occur even during normal rate AF.

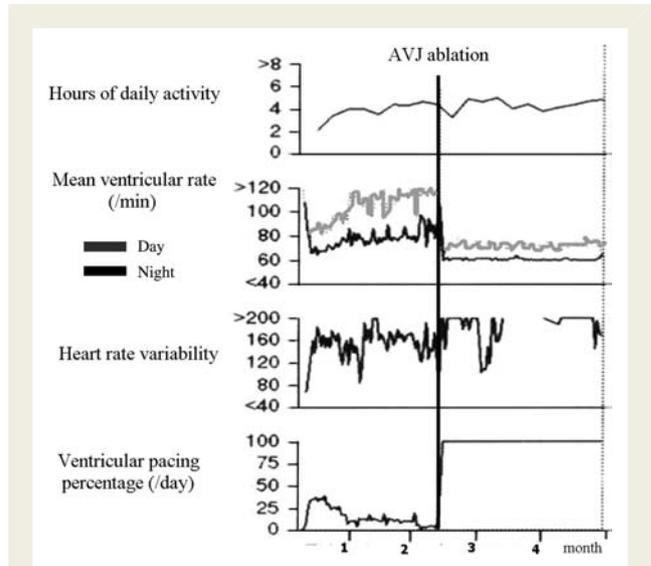
exertion, spontaneous ventricular rate tends to override BVP rates, determining a further reduction of paced beats precisely when patients are most in need of having biventricular capture, thus greatly limiting functional capacity. Another problem is the possible negative impact on prognosis of using combinations of negative chronotropic therapy to achieve adequate rate control. In fact, some studies have ‘indirectly’ suggested that the use of either digoxin or amiodarone in HF may increase morbidity and mortality.<sup>4</sup>

Adequate management of AF and other atrial arrhythmias is primarily based on defining the AT/AF burden and how it impacts negatively on CRT delivery.

### Defining atrial fibrillation/atrial tachycardia burden in heart failure patients treated with cardiac resynchronization therapy

Defining atrial arrhythmic burden is derived from integrating clinical, device-derived data, as well as instrumental findings (such as echocardiographic measures). Any HF patient with a history of atrial arrhythmias requires particular attention, especially in the first months of CRT, in order to ensure that resynchronization be adequately delivered.

From a clinical standpoint, it is important to identify symptoms such as palpitations, and more importantly, worsening effort dyspnoea which may suggest that the resynchronization effect is reduced because of the interference of the underlying atrial rhythm. These clinical aspects should be substantiated by instrumental echocardiographic data, which may show unchanged or further progression of LV dysfunction expressed through increased ventricular volumes and further EF reduction. Retrieving relevant information (BVP%, duration, and numbers of ‘mode switch’ episodes, etc.) through device monitoring (Figure 2) may complement clinical and echocardiographic data and, thus, provide a more complete picture on the extent of AF/AT burden in each patient. These different aspects, all obtainable during a routine outpatient visit, allow provision of an approximation of the effective AF/AT burden influencing CRT delivery. Atrial tachycardia/AF burden may be



**Figure 2** Different aspects of CRT patients with AF before and after AVJ ablation, which may be appreciated through device features. In a 59-year-old female with permanent AF treated with a CRT-D device, AVJ ablation yielded the following improvements: better functional status as shown by the number of hours of activity per day; maximization of BVP%; and improvement of heart rate variability profile.

considered high, intermediate, or low. Recently, Kamath<sup>11</sup> pointed out the importance of an accurate evaluation of CRT-dose using sophisticated 12-lead Holter monitoring, which seemed to be more accurate than conventional device-based information.

### Medical therapeutical and device-based options for ‘rate control’ in low atrial tachycardia/atrial fibrillation burden

Rate control strategy encompasses treatment options which effectively reduce and regularize heart rate in patients who usually have

permanent AF or a persistent AF which cannot be readily cardioverted to SR. The rate control strategy embodies two aspects which act favourably on cardiac mechanics. First, lowering heart rate to intermediate-to-low rate allows better diastolic filling and increases stroke volume in hearts with conserved Frank–Starling mechanism. Secondly, the regularization of heart rate further reinforces favourable effects on diastolic function.<sup>12</sup> The recourse to rate control drugs and/or activation of device-based algorithms is reasonable as first-line approach when AF/AT burden is low/intermediate.

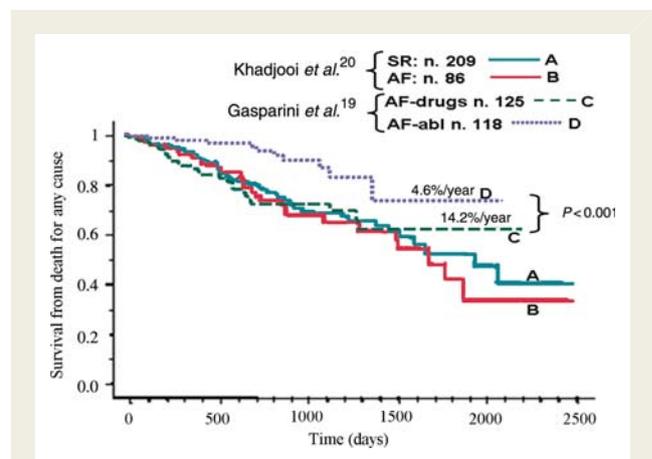
Rate control drugs considered effective in HF patients with depressed LV function include digoxin, amiodarone, and beta-blockers. However, more recent findings derived from randomized trials have suggested caution in the use of digoxin and amiodarone in patients with HF.<sup>13</sup>

Some device-derived features may be helpful to improve rate control and thus improve CRT delivery. These features include ventricular rate regularization (VRR) which consists in performing BVP, which ‘overrides’ intrinsic rhythm, through faster ventricular-paced depolarization allowing to reduce short cycles through retrograde concealed penetration of the AV node.<sup>14,15</sup> The benefits of rate control achieved by activating VRR function is well established in patients with chronic AF and no or only mild HF treated with a single chamber right ventricular (RV) pacing. In these patients, VRR has been demonstrated to confer acute haemodynamic benefits,<sup>16</sup> to restore autonomic balance,<sup>17</sup> and to provide a more regular rhythm during exercise,<sup>14</sup> thus potentially improving functional status.

Another useful feature is ‘ventricular sense response’ (also called ‘trigger’ function) which triggers LV pacing after a premature RV sense event is detected:<sup>17</sup> this option may be activated in all CRT devices of the latest generation.

In the context of CRT, the effectiveness of such rate control and rate regularization algorithms combined with the use of rate control drugs has not been investigated in an RCT. Findings derived from different large observational cohort studies on the effects of CRT in patients with permanent AF have yielded contrasting results. One of these studies<sup>18</sup> observed that treatment combining negative chronotropic drugs and activation of device features (VRR and trigger mode), even if permitting 85% of biventricular stimulation, did not yield significant long-term improvements in functional status, LVEF, or LV end-systolic volume (LVESV) reduction. The ineffectiveness of this approach further found confirmation through another more extensive multicentre European study, which reported relatively high death rate, particularly occurring for worsening progressive HF in AF patients treated with negative chronotropic drugs.<sup>19</sup> Quite differently, other smaller studies have advocated<sup>20</sup> that to achieve good results after CRT in terms of survival, aggressive rate control strategy is not necessary. It is worth emphasizing, however, that when the survival curves of the HF patients with AF treated with a combined device-based/drug regimen are compared,<sup>21</sup> yearly death rate for any cause is considered to be remarkably high, amounting to over 14%/year in both separate cohorts of non-ablated patients (Figure 3).

It therefore follows that in HF patients treated with CRT who present a high or intermediate AT/AF burden, the pursuit of an aggressive treatment strategy, such as AVJ ablation, is warranted.



**Figure 3** Comparison of Kaplan–Meier analysis for freedom from death for any cause between the Gasparini et al.<sup>19</sup> and the Khadjooi et al.<sup>20</sup> studies. The figure is adapted from Gasparini et al.<sup>19</sup> and Khadjooi et al.<sup>20</sup> SR, sinus rhythm; AF, atrial fibrillation; AF-drugs: atrial fibrillation with preserved AV node conduction; AF-abl, atrial fibrillation group with ablated AV node.

## Atrio-ventricular junction ablation for the management of atrial fibrillation and atrial rhythm issues in heart failure patients treated with cardiac resynchronization therapy

Atrio-ventricular junction ablation is commonly performed in patients with symptomatic, drug-refractory, fast, permanent AF as part of the conventional ‘ablate and pace’ strategy, and has been shown to confer symptomatic relief.<sup>22–24</sup> Atrio-ventricular junction ablation in individuals with AF treated with CRT has mainly been confined to selected patients in whom high-rate AF or AT jeopardizes satisfactory biventricular stimulation, and in CRT-implantable cardioverter defibrillator (ICD) recipients determines inappropriate ICD interventions.<sup>25</sup> The problem of inappropriate ICD therapies during AF, constituting ~30% of all ICD interventions,<sup>25</sup> has an important negative impact on the quality of life of patients and may be completely resolved after AVJ ablation. However, in the context of CRT in HF patients with concomitant AF, a growing amount of evidence has demonstrated that AVJ ablation may be useful to optimize CRT delivery by eliminating the deleterious haemodynamic effects of a competing, irregular, spontaneous intrinsic rhythm. The MUSTIC AF randomized trial,<sup>26</sup> besides being the first randomized trial demonstrating possible benefits of CRT in HF patients with permanent AF and conventional indication for CRT, also showed that in these patients, the preferred mode of ventricular stimulation was biventricular as opposed to RV. The study enrolled AF patients with either slow-rate AF or those who underwent ablation of the AV node; the effects between pacing modes were compared using a crossover design with two 3-month periods. Although no result was found in the

intention-to-treat analysis between the two modes (because of high numbers of dropouts), HF patients who completed the study improved in terms of functional status<sup>26</sup> with BVP. These effects were maintained after 1 year for most patients.<sup>27</sup>

Two other prospective studies investigated the effects of pacing mode in the management of AF with rapid ventricular rates following AVJ ablation. The OPSITE trial<sup>28</sup> showed that 'rate control' achieved following AVJ ablation significantly improved symptoms and functional status with no difference between the pacing modalities, whether LV or RV, but in a population with much better LV function. The PAVE<sup>29</sup> trial further confirmed the benefits of the 'ablate and pace' approach using different pacing modes. The latter study observed a greater benefit of the BVP mode in patients with depressed LVEF ( $\leq 45\%$ ) and/or in NYHA functional class III.

Further observational studies have investigated the acute and short-term effects of AVJ ablation in HF patients with AF treated with CRT and have demonstrated an increase in global LV function, a reduction of mitral regurgitation, and an increase in exercise capacity,<sup>30–32</sup> others have confirmed the chronic effects of CRT in this patient subgroup, reporting improvements in NYHA class, exercise capacity, and global LV function.<sup>18,26,27,33,34</sup> It is important to stress that these benefits appear to be confined to AF patients with previous AVJ ablation or spontaneous low-rate AF.

One large observational prospective investigation<sup>18</sup> specifically evaluated the effects of AVJ ablation on CRT delivery using a pre-defined protocol. This study showed that only those AF patients who underwent AVJ ablation (and thus approaching 100% effective BVP) showed significant improvements in LVEF, LVESV, and exercise capacity. Furthermore, a significantly higher proportion of responders (response defined as a  $\geq 10\%$  reduction in LVESV) were observed in the AVJ ablation group (68%) compared with the non-ablated group (18%) at 12 months. As later observed by the same groups in a more extensive observational multicentre study, CRT combined with AVJ ablation conferred a significant reduction of deaths for any cause compared with CRT alone, particularly by reducing deaths for progressive HF.

Taken together, based on current observational data on AF populations treated with CRT, the benefits of AVJ ablation in allowing appropriate CRT delivery seem to outweigh the risks associated with creating pacemaker dependency. The peculiarity of CRT devices (using an RV and an LV pacing leads) should, theoretically, at least reduce the risks of pacemaker dependency related to lead fractures or malfunction. Nonetheless, the fear of pacemaker dependency remains a limiting aspect for the wider diffusion of AVJ ablation.

## The need for randomized controlled clinical trials

Further studies are of course needed<sup>10</sup> to investigate the extensive benefits of adding AVJ ablation to CRT in HF patients with AF following a prospective, randomized, multicentre design. The AVERT-AF<sup>35</sup> (Atrio-Ventricular Junction Ablation Followed by Resynchronization Therapy in patients with CHF and AF) and the An-Art study<sup>36</sup> (AV node ablation in CRT) are both concerned with establishing whether AVJ ablation coupled with BVP may

significantly improve functional capacity compared with pharmacological therapy in HF patients with permanent AF and depressed EF. It should be stated that such studies aiming to assess the effects of CRT according to soft/subjective endpoints may add little to the current recommendations. There is a great need to design RCTs with strong endpoints, even though such designs may be difficult to implement for ethical and financial reasons. A reasonable and 'up-dated' approach to investigate the effects of CRT in this group involves using device-based surrogates of major clinical events. Device-based remote continuous patient monitoring may provide information on a daily basis of the patients' functional and clinical status, before the onset of an overt clinical event becomes manifest.<sup>37,38</sup> But before these parameters may be validated as surrogates for strong endpoints of major cardiovascular events, better definition of their accuracy is needed.

## Conclusions

Atrial fibrillation and other atrial rhythm disturbances in patients with HF may have an important negative impact on the clinical benefit conveyed by CRT, if these are not appropriately managed. Careful overall evaluation is mandatory to define precisely the AT/AF burden in order to articulate tailored diagnostic and therapeutic strategies. On the basis of recent observational data, in patients presenting intermediate or elevated AT/AF burden, AVJ ablation may represent a fundamental tool to achieve full CRT delivery and, thus, confer marked improvements in global cardiac function, and, further, in survival. More studies are necessary to further support the recourse to AVJ ablation in this situation. Efforts should also be dedicated towards establishing tailored treatment approaches to adequately manage different atrial rhythm issues in HF patients treated with CRT.

**Conflict of interest:** none declared.

## Funding

Funding to pay the Open Access publication charges for this article was provided by Electrophysiology and Pacing Unit, IRCCS Istituto Clinico Humanitas, Rozzano, Milano.

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