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The role of cardiac resynchronization therapy in permanent atrial fibrillation patients: current indications to treat heart failure

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Abstract

The aim of this article is a comprehensive review of the publications during the last decade in order to evaluate current indications for cardiac resynchronization therapy (CRT) in patients with heart failure (HF) and atrial fibrillation (AF). Clinical studies show that CRT not only improves HF symptoms and quality of life but also reduces morbidity in New York Heart Association (NYHA) class III or IV patients with reduced left ventricular ejection fraction (LVEF) and wide QRS. The loss of atrioventricular synchrony and difficulty to ensure an adequate biventricular pacing worsens these patients response to CRT. According to the latest guidelines CRT should be considered for patients to reduce all-cause mortality in patients with chronic HF, QRS ≥ 120 ms and LVEF ≤ 35% who remain in NYHA functional class III/ambualtory class IV despite at least 3 months of optimal pharmacological theraphy who are expected to survive at least 1 year with good functional status, provided that biventricular pacing as close as possible to 100% can be achieved (class IIa, level B). Despite the fact that there is a general agreement on the indication for CRT in AF patients, their optimal management strategy still remains a matter of discussion.

Keywords

Cardiac resynchronization therapy, Heart failure, Atrial fibrillation, Atrioventricular junction ablation

Imprint

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Introduction

Cardiac resynchronization therapy (CRT) is an effective non pharmacological heart failure (HF) treatment method, which has been introduced into the clinical practice since 1990. The aim is to ensure the electrical and mechanical ventricular synchrony and thus improve cardiac function [1]. CRT changes the natural course of HF: it stimulates the physiological changes that lead to ventricular remodeling and improves clinical outcomes. After the publication of the COMPANION [2] and the CARE-HF [3] study results, CRT has been recognized as an effective HF treatment method in combination with optimal medical therapy.

There is no doubt that CRT is an effective treatment method in patients with HF III or IV NYHA functional class despite optimal drug therapy, left ventricle ejection fraction (LVEF) ≤ 35%, QRS ≥ 120 ms in sinus rythm (SR) [4]. CRT not only improves HF symptoms and quality of life, but also reduces morbidity in patients with moderate to severe HF, reduced LVEF and wide QRS [5-6].

Despite the good results using CRT in SR, its use in atrial fibrillation (AF) still remains quite controversial [7].

Heart failure and atrial fibrillation

AF and HF often goes together. In Europe, the prevalence of HF in AF patients was found to be 34% and the prevalence of AF in HF patients 42% [8]. AF rates among patients with HF depends on the severity of the disease: 5% in patients with NYHA class I, in comparison with 25–50% in NYHA III/IV class patients [8]. On the other hand, approximately every third patient with permanent AF also has III or IV NYHA functional class HF and left bundle branch block (LBBB) [4]. According to Baldasseroni et al. [9] out of 5517 HF patients included in the analysis, 185 (3.3%) had complete LBBB associated with permanent AF. These two electrical abnormalities have a cumulative negative effect on the prognosis of patients with HF. According to the European Heart Rhythm Association (EHRA, 2008), American Heart Association (AHA, 2008), European Society of Cardiology (ESC, 2010, 2012, and 2015) and Heart Failure Society of America (HFSA, 2011) guidelines, patients with HF and AF may benefit from biventricular pacing [4, 10-12].

Current European CRT registry (survey) has shown that approximately 22% of patients receiving CRTs in Europe have permanent AF [13]. A total of 2438 patients were enrolled, and 474 (22%) of them were patients with AF. Patients with AF had a worse outcome on both unadjusted and multivariable analyses. Information on the percentage of cumulative biventricular pacing, the extent of atrioventricular junction (AVJ) ablation post-device implantation or up-titration of medical treatment to ensure adequate pacing was not captured in this survey, which can potentially explain the observation of poorer outcome of patients with AF [13].

Clinical research – evidences from CRT observational and randomized trials in AF and HF

Etienne et al. one of the first, in 1999, published the results of a small observational study, which included 28 patients (17 in AF and 11 in SR) with HF NYHA functional class III or IV, LVEF ≤ 35% and LBBB [1]. It was noted that hemodynamic parameters (systolic blood pressure, cardiac index) improved similarly in SR and AF. In addition, the improvement was independent of the length of PR interval in patients with SR.

In 2000 Leclerq et al. [1] published the long-term observational study, in which biventricular pacing was applied in 22 patients with SR and 15 patients with permanent AF who underwent AVJ ablation. Their data in HF functional class, oxygen consumption and LVEF were similar or greater in patients with AF (14 ± 9.4 months of follow-up) [1].

The majority of randomized CRT studies have been almost restricted to patients in SR (REVERSE, MADIT-CRT, COMPANION, CARE-HF) [2-3, 6]. MUSTIC AF, OPSITE, PAVE, APAF, and RAFT are the only published small randomized trials that were designed to assess the efficacy of CRT in patients with HF and AF [14-18].

MUSTIC AF sub-study with 59 patients in refractory HF with NYHA functional class III, and permanent AF, who had LV systolic dysfunction and wide QRS (above 200 ms duration) during right ventricle (RV) pacing, were randomly assigned to 3 months of RV stimulation vs 3 months of biventricular pacing in a crossover study design [14]. For more than 85 percent of patients with biventricular pacing to whom AVJ ablation was performed symptoms decreased, exercise tolerance and LVEF improved, the number of rehospitalizations was reduced within one year follow-up. Thus, according to this randomized trial, the dual electric therapy – AVJ ablation and biventricular stimulation – provides long-term clinical benefits for patients in refractory HF and AF [14].

OPSITE (The Optimal Pacing SITE) study showed that heart rate control by AVJ ablation improves the clinical condition of the patient: reduces symptoms and improves exercise capacity [15]. PAVE (Left ventricular based cardiac stimuliation Post AtrioVentricular nodal ablation Evaluation) study compared biventricular pacing (n = 103) with RV stimulation (n = 81) in patients with HF and permanent AF after AVJ ablation. In six-month period biventricular pacing significantly improved LVEF and exercise capacity (measured in 6-min walk test) [16].

The meta-analysis of these three small randomised studies showed that mortality (regardless of cause) was 7.1% for patients treated with CRT, while in the control group was twice higher [1]. It should be noted that all these studies involved patients who underwent AVJ ablation or bradysystolic AF was diagnosed.

RAFT (The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial) a multicenter, double-blind, randomized, controlled study, included 229 patients with NYHA class II or III symptoms despite optimal medical therapy, with a LVEF 30% or less, at least intrinsic QRS duration of 120 msec or a paced QRS duration of at least 200 msec, permanent AF with a controlled ventricular rate (≤60 b.p.m. at rest and ≤90 b.p.m. during a 6-min walk test) or with planned AVJ ablation. RAFT investigators concluded permanently that AF patients who are otherwise candidates for CRT appear to gain minimal benefit (improved relative survival and decrease in HF symptoms) from CRT-D compared to standard implantable cardioverter defibrillator.

Over the past years numerous observational studies [19-21] have compared CRT effects in SR and AF groups. No significant differences in HF functional class, improvement in quality of life, 6-minute walking test, oxygen consumption and LVEF was found between these groups. However, those trials presented rather controversial echocardiographic parameters (left ventricular end diastolic and systolic diameters, mitral regurgitation) and hospitalizations for HF and mortality results. Meta-analysis (1164 patients) which included four prospective cohort studies and one randomized study (797 in SR and 367 in AF) showed that clinical response to CRT does not differ in patients with SR compared to AF [1].

Only 2 percents of all patients in CRT randomized trials, which demonstrated the positive effects of CRT, have had AF. On one hand, patients with AF generally have more comorbidities, and are less likely to be included in a randomized study. On the other, AF patients often fail to reach required biventricular pacing frequency. Moreover, with high ventricular rate it is difficult to ensure that a sequence of ventricular contraction is appropriate considering the possibility of fusion beats. Atrioventricular synchrony, as one of the main positive benefits, is lost as well [1].

Current indications for cardiac resynchronisation therapy in HF patients with AF

The ESC 2007 guidelines for cardiac pacing and cardiac resynchronisation therapy were the first guidelines which mentioned patients with AF among the candidates for CRT. Three years later, in 2010 ESC gudelines on device therapy in heart failure were two recommendations for this patient group: a CRT-P/CRT-D posibility should be considered in patients with III or IV NYHA functional class, LVEF ≤ 35%, QRS ≥ 130 ms and pacemaker dependency induced by AV nodal ablation (class IIa, level of evidence B), if slow ventricular rate and frequent pacing is achieved using medications (class IIa, level of evedence C) [4].

ESC 2012 guidelines on acute and chronic heart failure updated only one: CRT-P/CRT-D may be considered in patients in NYHA functional class III or ambulatory class IV with a QRS duration ≥120 ms and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF worsening if: (i) the patient requires pacing because of an intrinsically slow ventricular rate, (ii) the patient is pacemaker dependent as a re-

sult of AV nodal ablation or the patient's ventricular rate is ≤60 b.p.m. at rest and ≤90 b.p.m. on exercise (class IIb, level of evedence C) [11].

In 2015 ESC published guidelines on ventricular arrythmias and the prevention of sudden cardiac death. It is stated that: 1) CRT should be considered for patients to reduce all-cause mortality in patients with chronic HF, QRS ≥ 120 ms and LVEF ≤ 35% who remain in NYHA functional class III/ambulatory class IV despite at least 3 months of optimal pharmacological theraphy who are expected to survive at least 1 year with good functional status, provided that biventricular pacing as close as possible to 100% can be achieved (class IIa, level B); 2) AVJ ablation should be considered in case of incomplete biventricular pacing (class IIa, level B) [12].

Atrioventricular junction ablation – is it needed?

AVJ ablation, by slowing and regularizing ventricular rate, has been shown to improve symptoms, quality of life, and cardiac function, as judged by both physiological and structural measurements [22]. Over the past several years, lots of small observational trials tried to compare patients in AF after biventricular pacemaker implantation, depending on whether they have undergone AVJ ablation or not. The results show that biventricular pacing of at least 85% is essential to reach positive effect of CRT [23]. Long term registry data confirm this trend [24] suggesting that CRT combination with AVJ ablation when 100% effective biventricular stimulation is achieved, leads to an improvement of LV function and exercise capacity in patients with AF, and results are similar to results of patients who remain in SR [23]. However, Ousdigian et al. state that high biventricular stimulation is not achieved in greater part of permanent AF patients that leads to increased risk of death [25].

The meta-analysis by Ganesan et al. included 768 AF patients of whom 339 had additional AVJ ablation and 429 patients who were treated with rate-controlling medication alone. The most important finding focuses on the dramatic reduction of total cardiovascular mortality conferred by AVJ ablation [26-27]. The mortality rate in non-ablated patients was about 14% per year, whereas in AVJ-ablated patients a three-fold reduction was observed. Authors indicated that only three studies reported LVEF change after AVJ ablation: the increase of LVEF in the AVJ ablation group was not statistically superior even if the change of LVEF in ablated patients seems to be remarkable (10.3 % vs. 4.2%). The short follow-up after AVJ ablation (from 6 to 25 months) and the limited number of "nonablated survivors" might explain the non-significant increase of EF in ablated patients [26-27].

Data from 1812 CRT patients included in two registries (CRT RENEWAL and REFLEx) [28] showed that the greatest magnitude of reduction in HF hospitalization and mortality was observed when biventricular pacing was > 92%. Boriani et al. published the results of observational study of 1404 patients with CRT, of which 443 had AF. It was concluded that uncontrolled ventricular rates were related to more HF hospitalizations and mortality of all cause [29].

Recent systematic review and meta-analysis that included 1256 patients with permanent AF found that insufficient biventricular pacing (<90%) in patients who have not undergone AVJ abliation had resulted in numerically higher all-cause mortality and significantly higher nonresponse to CRT [30]. Similarly Lopes et al. state in their meta-analysis that though AF patients have greater all-cause mortality compared to patients in SR, AVJ ablation reduces all-cause and cardiovascular mortality, improves response to CRT [31]. Another study showed that patients who have had AVJ abliation had three-fold lower 2-year mortality than patients who have not had this procedure [32].

Two approaches are available to control the ventricular rate in patients with AF. It could be AVJ ablation vs. pharmacological rate control. Nearly one-third of patients heart rate is not sufficiently controled conservatively [33]. AVJ ablation is usually a safe procedure, while it is often presented as a potentially harmful therapy because it leads to pacemaker dependency. Benefits seem to overweight possible risks which are asociated with pacemaker dependency in some AF patients subgroups [34].

In 2012 Tolosana et al. [35] reported the results of the small Spanish Atrial Resynchronization Study II. Results show that only 28% of the AF patients had less than 85% biventricular pacing and required AVJ ablation. After one year follow-up, a similar CRT response rate among the SR and AF patients was observed. It was also noted that the rate control method did not provide differences between two patients groups. It might seem that there is a need to start with pharmacological therapy, reserving AVJ ablation for patients with poor heart rate control. In 2013 Gasparini et al. published a study comparing rate control with AVJ ablation and pharmacological approach. The median follow-up was 37 months. It was found that the AVJ ablation group had similar total and cardiac mortality compared to the SR group. However, the pharmacological control group had higher total and cardial mortality than both the SR and the AVJ ablation groups [36].

The other important conclusion which had been made by Tolosana et al., despite the beneficial effects of CRT, the overall mortality was higher in this patient group. Basal NYHA functional class IV, higher creatinine levels and AF were independent predictors of mortality. It seems that AF per se may pose an increased mortality risk in non-responders, because the percentage of responders were similar in the SR and the AF groups [35].

AVJ ablation role in SR restoration

AVAVJ ablation of AF in patients with HF can also be particularly beneficial in restoration of SR leading to improvement in LV function and quality-of-life even in patients with adequate rate control prior to ablation [37]. In the study reported by Hsu et al. [38] the presence of concurrent structural heart disease in patients with impaired LV function did not significantly affect the outcome of ablation with regard to restoration and maintenance of SR, but a marked increase in LVEF (by at least 20% increase or to a value of 55% or more). In conclusion, the limited data currently available indicate the safety of ablation to treat AF in patients with HF and its efficacy with regard to both restoration of SR and improvement of HF symptoms [37]. Randomized prospective trials on larger patient populations and with longer follow-up durations are required to confirm the AVJ ablation role in SR maintenance.

Right ventricular pacing in patients with severe HF – is CRT better than right ventricular pacing?

In AF patients with refractory HF symptoms AVJ ablation with pacing is an important therapeutic option. The „ablate and pace“ strategy for severe symptomic AF has been available for many years. It gives a posibility to control ventricular rate as well as regularization of the R-R interval [39]. In numerous small studies it has been shown that this therapy helps to provide significant symptoms relief and improve quality of life in selected AF patients [40]. However, the situation becomes more complicated in patients with AF and advanced HF.

APAF — The Ablate and Pace in Atrial Fibrillation [18] was one of the first prospective, randomized, parallel, active-control, multi-centre clinical trial designed to test the hypothesis that CRT is superior to normal RV pacing in reducing clinical events in patients undergoing AVJ ablation. The primary composite endpoint of death from HF, hospitalization due to HF or worsening HF occurred in 11 (11%) patients in the CRT group and 23 (26%) in the RV pacing group. CRT pacing caused 9.2% increase in the EF, 6.8% decrease in LV systolic diameter, 17.3% decrease in mitral regurgitation area, and 59% reduction of LV dyssynchrony compared with RV pacing [17-18].

In 2012 Chatterjee et al., published their meta-analysis assesing the efficacy of biventricular stimulation vs RV pacing in patients with AF [41]. According to this meta-analysis, biventricular pacing was not associated with significantly improved survival when compared with RV pacing. On the other hand, CRT demonstrated modest, but significant increases of LVEF at a short term follow-up (mean follow-up 6 months), although it was associated with a trend to increase procedure morbidity. Currently available data suggest that RV pacing strategy is reasonable as initial treatment option for patients with refractory HF and AF.

Small number of prospective, randomized studies, short follow-up, heterogenity of ventricular function and selection of endpoints are the biggest limitations of this meta-analysis and give the frame to future studies [40].

„Responders“ and „non-responders“

Effective CRT treatment criteria according to performed studies and clinical practice can be divided into two categories: clinical factors (NYHA functional class, 6-min walk test, quality of life changes, number of hospitalizations for HF, incidence of adverse cardiac events and deaths) and echocardiographic parameters (LV volume, LVEF and ventricular end diastolic and systolic diameters, and etc.). They can be analysed in various combinations. However, it is important to emphasize that the clinical improvement („responders“) do not correspond and is not equal to echocardiographic [43].

Approximately 18-30% patients do not respond to CRTs. Moreover, some of them feel worse than prior to biventricular pacemaker implantation. They are referred to as „non-responders“. Understanding the barriers of response to CRT among AF patients is critical. Probably one of the reason could be the wrong stimulation site which leads to dyssinchrony. Stimulation at the latest electrically activated region of the LV is necessary for electrical resynchronization. It could be the posterior or posterolater-basal wall, because these LV stimulation areas lead to rapid contraction and increase of functional capacity as compared with anterior LV wall stimulation [44]. Several above mentioned randomized clinical trials (OPSITE, PAVE) [15-16] showed that posterior or postero-lateral LV wall is stimulated only in 67-77% of patients. Tough there is still controversy on ideal stimulation site, because MADIT CRT [6] showed benefit on basal wall compared to apical locations, but failed to show benefit between posterolater and anterior walls. „Non-responders“ can be observed in both the SR and the AF patient groups. CRT may be also non effective in AF patients because of insufficient biventricular pacing.

Gabrieli et al. suggest an echocardiographic marker – septal flash (SF - early septal inward/outward motion within the sovolumic contraction period/QRS duration). In the study that included 94 AF patients baseline SF was an independent predictor of response to CRT [45].

Conclusion

The prevalence of AF among the patients with HF is increasing. Biventricular pacing changes the natural course of HF, exerting its physiological impact through favourable ventricular remodelling, with a reduction in LV volumes and improvement in systolic function. This leads to long-term clinical benefits such as improved quality of life and functional capacity with a concomitant reduction in hospitalization for HF and overall mortality. Despite the fact that there is a general agreement on the indication for the CRT in the AF patients, their optimal management strategy still remains a matter of further investigations due to the heterogeneity of HF status, etiologies, pharmacological therapies, lead implantation site, and resynchronization results.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and interna-tional ethical standards.

Conflict of interest

None declared.

Author contributions

All authors prepared the manuscript and analyzed the data, R.E. drafted the manuscript. All authors read the ICMJE criteria for authorship and approved the final manuscript.

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