ATRIAL FIBRILLATION

REVIEW ARTICLE

The Utility of Cardiac Resynchronization Therapy in Patients with Atrial Fibrillation

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ABSTRACT. Since the first documentation of deterioration in cardiac ventricular contraction to the development and implementation of the concept of simultaneous pacing of both ventricles, cardiac resynchronization therapy (CRT), a long road has been travelled. The effects of CRT in heart failure are well documented. Most of the studies have included patients with sinus rhythm, even though a significant number of patients have heart failure and atrial fibrillation (AF) simultaneously. In this review article we have made an attempt to underline the potential impact of CRT in patients with AF and the special treatment considerations for patients with AF who undergo CRT placement; we have also described strategies to maximize the benefit of CRT in patients with AF.

KEYWORDS. atrial fibrillation, cardiac resynchronization therapy.

Introduction

Detrimental effects in cardiac ventricular contraction related to pacing stimulation were first documented by Wiggers in 1925.1 In 1986, Burkhoff et al,2 in a study of canine pacing, noted that left ventricular systolic pressure decreased linearly as QRS duration increased. Other studies elucidated a high prevalence of left bundle branch block (LBBB) or intraventricular conduction delay in chronic heart failure leading to interventricular and intraventricular dyssynchrony.3 With the above findings as background, Lattuca et al4 hypothesized that simultaneous pacing of the left and right ventricles would lead to more synchronous contraction with reduction in QRS duration and mechanical dyssynchrony, leading to the concept of cardiac resynchronization therapy (CRT). Since then, there has been rapid adoption of CRT based on the results of multicenter studies. Interest has picked up in this field in the recent past and it has shown rapid evolution. CRT has shown to be of benefit in patients with left ventricular ejection fraction (LVEF) ≤35%, QRS duration ≥0.12 s for treatment of New York Heart Association (NYHA) class III or IV heart failure (HF) symptoms on optimal recommended medical therapy, and more recently for NYHA class I and II as well. In the CARE-HF (Cardiac Resynchronization Heart Failure) study, CRT was associated with a 40% reduction in all-cause mortality.5 Most of the large randomized studies of CRT have required the presence of sinus rhythm (SR) for enrollment, however.

AF in HF in relation to CRT

Atrial fibrillation (AF) occurs frequently in patients with HF, with its prevalence paralleling the severity of HF—10% in NYHA class II to 50% in NYHA class IV.6 Data from the Framingham Heart Study showed that the relative risk for patients with HF for developing AF is 4.5 in men and 5.9 in women, and also showed that AF is associated with doubling of mortality in patients with or without pre-existing heart disease.7 CRT has been shown to confer significant reduction in left ventricular volumes and improvement of LVEF in HF patients.8,9 In turn these CRT effects are associated with reduction in mortality over a mid-term follow-up in SR patients.10 Even though AF has a high prevalence among HF...
patients and has significant negative impact on survival, most of the large randomized controlled CRT trials have generally excluded patients with AF or included significantly larger number of patients with SR. Hence there is a scarcity of data regarding the impact of CRT in this group of patients.

Role of CRT in AF

Many of the studies describing the effects of CRT in AF patients are observational. Khadjooi et al.\textsuperscript{11} showed that CRT delivers similar prognostic benefits to HF patients in AF or SR. They also documented similar improvements in NYHA class, 6-min walking distance (6MWD) and quality of life (QoL) with additional evidence showing reverse left ventricular remodeling in both groups. Molhoek et al.\textsuperscript{12} in a small study comparing 30 patients each in AF and SR concluded that there was significant improvement in regards to 6MWD, NYHA class and QoL after a follow-up of 2 years in both groups, although the responder rate was lower in the AF group. Kiese et al.\textsuperscript{13} also described similar findings in a follow-up of 6 months. MUSTIC (Multisite Stimulation in Cardiomyopathies) documented similar improvement in peak oxygen uptake, NYHA class, 6MWD and QoL at 12 months in both AF and SR groups of patients.\textsuperscript{14} Similar findings have been reported by Delnoy et al.\textsuperscript{15} Reverse remodeling effects of CRT in AF patients as shown by Kiese et al\textsuperscript{13} have also been described in other studies\textsuperscript{14,16} by documenting a reduction in left ventricular end-diastolic and end-systolic volumes. The molecular bases for these mechanical changes have not been definitively established. Preliminary data from an experimental model suggest that CRT reduces regional and global molecular remodeling, generating more homogeneous activation of stress kinases and reducing apoptosis.\textsuperscript{17}

Meta-analyses of CRT in AF patients

In 2008, Upadhyay et al.\textsuperscript{18} in their meta-analysis of five studies concluded that patients with AF undergoing CRT have similar or slightly greater improvements in LVEF than patients in SR, but have smaller functional benefits as measured by NYHA class, 6MWD and the Minnesota Living with Heart Failure score with similar impact on mortality.

In July 2011, Wilton et al.\textsuperscript{19} published a meta-analysis of 23 studies in which they summarized the relative effectiveness of CRT in patients with and without AF (Figure 1). They reported that patients with AF had significantly higher rates of clinical non-response to CRT and higher mortality rates after CRT placement than patients with SR. They found no consistent difference in LVEF change in studies comparing those with and without AF (pooled absolute weighted mean difference 0.00, 95% CI −0.02 to 0.02). Considering quality of life, those with AF had improved scores in all studies (mean reduction 18.8 points, range 8.0–22.7). The pooled mean improvement was 4.1 points less than in those without AF (95% CI 1.7–6.6, \( p = 0.001 \)). Patients with AF experienced a weighted mean improvement in 6MWD of 63 m (range 8–99 m), which was 14.1 m smaller than those without AF. Patients in AF appeared less likely to respond clinically to CRT and at higher risk for death.

Role of percentage of biventricular pacing in patients with AF

It can be difficult to achieve a high percentage of biventricular (BiV) pacing in patients with AF due to competition from intrinsic conduction of AF. It is likely that the full benefit of CRT might not have been realized in some studies because of difficulty in providing an effectively high percentage of BiV pacing in patients with AF.

![Figure 1](https://example.com/figure1.png)

**Figure 1:** (a) Meta-analysis of the relative risk of clinical non-response to cardiac resynchronization therapy over 6–12 months in patients with atrial fibrillation (AF) versus sinus rhythm (SR) shows increased clinical response in patients with SR. Reproduced with permission from Ref. 19. (b) Meta-analysis of the relative risk of all-cause death in patients with versus those without AF undergoing cardiac resynchronization therapy shows reduced overall mortality in patients with SR. Reproduced with permission from Ref 19.

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AF as a result of non-paced as well as fusion or pseudo-fusion beats. Kamath et al\textsuperscript{20} utilized 12-lead Holter monitoring and reported that patients with CRT on device counters which yielded >90% pacing may have >40% fusion and pseudo-fusion beats, therefore overestimating the degree of complete BiV pacing. Their study further noted that patients with a high percentage of fully paced beats showed a favorable clinical response and evidence of reverse remodeling after CRT compared with those with a lower percentage of fully paced beats (HR 12.0, 95% CI 1.3–111.3, p = 0.03) (Figure 2). In SR, the effect of CRT is achieved by BiV pacing with an atrioventricular (AV) interval shorter than the patient’s intrinsic AV interval. In the setting of AF, as there is no fixed AV interval, it becomes necessary to pace the ventricles faster than the patient’s underlying ventricular rate to deliver effective CRT. This in turn makes it important to slow the intrinsic ventricular rate to a level where a high percentage of BiV pacing can be delivered as it is believed that near maximal BiV pacing is necessary to assure optimal CRT response.\textsuperscript{9,21} Koplan et al\textsuperscript{21} have shown that a BiV pacing percentage less than 92% is a predictor of worse clinical than patients who received 93–100% pacing. A more recent study has suggested a cut-off as high as 98.5% BiV pacing as a criteria for achieving maximal CRT response.\textsuperscript{22} Of note, there are device-based algorithms designed to both pace the left ventricle when the right ventricular lead senses an intrinsic beat and to increase the pacing rate to overdrive intrinsic conduction of AF, but the clinical effects of these algorithms has not been extensively studied and may even produce deleterious effects.

Rate control and AV nodal ablation in CRT patients

To effectively control the ventricular rate in AF patients, AV nodal (AVN) blocking agents (typically beta-blockers, often combined with digitalis) are utilized to help increase the percentage of BiV pacing. If pharmacologic rate control proves ineffective in achieving a high percentage of BiV pacing or is poorly tolerated, then AVN ablation can be performed, which eliminates native AV conduction ensuring almost 100% BiV pacing (in the absence of ventricular ectopy) and hence potentially increasing CRT efficacy. Gasparini et al\textsuperscript{23} compared patients on pharmacologic control versus those with AVN ablation. Their results demonstrated that total mortality was significantly improved in the AVN ablation group compared with the pharmacologic control group (adjusted hazard ratio 0.26, 95% CI 0.09 to 0.73, p = 0.01) with a ninefold lower HF mortality. In a previous study from 2006, it was noted that the benefit of CRT in HF patients with AF was seen only in patients who underwent AVN ablation in addition to CRT placement.\textsuperscript{9} However, it is possible that part of the impact on this group of patients (AVN ablation) could have been related to discontinuation of medications such as digoxin and amiodarone, which may worsen mortality in HF patients,\textsuperscript{24,25} and avoidance of high doses of AVN blocking agents which may be poorly tolerated. Dong et al\textsuperscript{26} in their study found that AVN ablation was an independent predictor of improved all-cause mortality and combined events of death, heart transplant and left ventricular assist device. The PAVE trial compared patients with chronic AF undergoing AVN ablation for medically refractory rapid ventricular rate, randomly assigning them to treatment with right ventricular pacing or CRT.\textsuperscript{27} At an interval of 6 months, patients with CRT were noted to have significantly greater increase in 6MWD, exercise duration and LVEF than the right ventricular pacing group. These results were more prominent if LVEF was less than 45%.

AVN ablation typically creates pacemaker dependency, and there is a theoretical risk of device failure leading to catastrophic outcomes including death in pacemaker-dependent patients, and this must be weighed against the benefit of improving the percentage of BiV pacing in patients with CRT and AF. Given the results above, however, AVN ablation should be strongly considered in patients unable to achieve a high percentage BiV pacing with pharmacologic means alone.

Comparison with catheter ablation of AF

Limited data are available comparing CRT with or without AVN ablation to catheter ablation of AF via pulmonary vein isolation. A small randomized trial suggested that in appropriately selected patients with AF and HF, restoration of SR by pulmonary vein isolation may produce greater improvement in LVEF, 6MWD and QoL than CRT combined with AVN ablation\textsuperscript{28} (Figure 3). It could be possibly because of beneficial effects of atrial transport pumping function and normal sinus node rates at rest and during exertion in SR compared with AF, where atrial pumping function is lacking and heart rates are controlled by a CRT pacing device. Factors such as duration of AF and left atrial size
may be useful to determine the likelihood of success of catheter ablation of AF, and to appropriately select which patients with AF are most likely to benefit from AF ablation as opposed to CRT with or without AVN ablation. Similarly, there are currently no definitive studies to determine which patients with CRT who develop AF (either before or after CRT placement) are most likely to benefit from catheter ablation of AF.

**Effect of CRT on AF**

There are some data to support the hypothesis that CRT may contribute to the maintenance of SR. The rate of AF conversion varies from 7% to 75% with an antiarrhythmic drug regimen. However, it is not clear if CRT reduces the incidence of AF, as large trials have not shown any definite decrease in AF, but AF was not one of the specified trial end-points. A small observational study found a reduced incidence of AF in CRT patients. Gasparini et al in a cohort study of 330 patients found that 1 in every 10 patients with HF and "permanent" AF treated with CRT spontaneously reverted to SR after a median of 4.4 months from implant. Independent predictors of this phenomenon were found to be post CRT QRS duration less than or equal to 150 ms, baseline end-diastolic diameter ≤65 mm, left atrial diameter ≤50 mm and ablation of the AVN. This study described that the presence of three favorable predictors increased the likelihood of resumption of SR by a factor of 3.5 (hazard ratio 3.5, 95% CI 1.52–8.13, p=0.003) compared with 0 to 2 predictors and that the presence of all four factors increased the probability by 5.7 with respect to three predictors.

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**Figure 3:** Composite Primary End Point of Ejection Fraction, 6-Minute Walk Distance, and Score on the Minnesota Living with Heart Failure Questionnaire at 6 Months showed significantly greater improvements with atrial fibrillation ablation with pulmonary vein isolation compared with treatment with atrioventricular node ablation and cardiac resynchronization therapy. Reproduced with permission from Ref 28.
Conclusions

CRT appears to be beneficial in AF patients, although there are far fewer patients with AF in the large randomized CRT studies than patients in SR, and a prospective randomized trial comparing patients in SR and AF with EF <35% and QRS >0.12 ms is needed. It is important to achieve a high percentage of BiV pacing in patients with AF who receive CRT, which can be accomplished by pharmacologic means in many patients, whereas others will require AVN ablation. CRT may re-establish SR in a minority of patients with pre-existing persistent AF. Among carefully selected patients, successful catheter ablation of AF may offer greater benefit than CRT and AVN ablation. Further studies will enhance our understanding of how to maximize the benefit of CRT among patients with AF.

References


