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## Role of Atrio-Ventricular Junction Ablation in Symptomatic Atrial Fibrillation for Optimization of Cardiac Resynchronization Therapy

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#### Abstract

Cardiac resynchronization (CRT) therapy is indicated in patients with at least mildly symptomatic heart failure, left ventricular ejection fraction  $\leq$ 35% and wide QRS, and has been associated with decreased morbidity and mortality. Unfortunately, approximately 30% of the patients appropriately selected for therapy do not respond to CRT. Among the reasons for non-response, atrial fibrillation (AF) plays a prominent role. AF limits the degree of biventricular pacing during CRT, not only when the ventricular rate is fast and highly irregular, but also during periods of of relatively constant rate, by causing fusion and pseudo-fusion complexes. Importantly, achievement of nearly 100% biventricular pacing is necessary to derive benefit from CRT. A simple, albeit irreversible, method to maximize biventricular pacing in patients with AF who are otherwise eligible for CRT is atrioventricular junction (AVJ) ablation. In this review, we discuss the role of AVJ ablation in CRT optimization in patients with AF. The available evidence from observational non-randomized studies suggests that AVJ ablation in patients with AF qualifying for CRT may offer improvement in heart failure symptoms, better survival, and better cardiac function. In light of the inherent limitations of non-randomized studies, further randomized studies are needed to support this treatment option.

#### Introduction

Heart failure (HF) is a significant cause of mortality and morbidity in the United States. In 2010, the estimated prevalence in adults over 18 years of age was 2.8%, and by 2030 the prevalence is projected to grow by 25% <sup>1</sup> While optimal pharmacologic therapy has been shown to reduce HF symptoms and mortality, many patients still remain symptomatic and need additional interventions.<sup>2</sup> In patients with at least mildly symptomatic HF (New York Heart Association [NYHA] class II to IV), left ventricular (LV) ejection fraction  $\leq$ 35%, wide QRS with a left bundle branch block (LBBB) morphology and sinus rhythm, cardiac resynchronization therapy (CRT) is indicated<sup>3</sup> CRT has been shown to improve functional status, increase exercise capacity, decrease hospitalizations, and reduce mortality in HF patients that meet implant criteria. <sup>4-8</sup>

Unfortunately, about 30% of patients who are appropriately selected for therapy, do not respond to CRT.<sup>9</sup> Several predictors of non-response have

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been identified, including male gender, ischemic cardiomyopathy, QRS duration <150ms and non-LBBB pattern.<sup>10-13</sup> Other studies have identified apical LV lead position ,<sup>14</sup> presence of lateral LV scar<sup>15</sup> and impaired renal function<sup>16</sup> as reasons for a lack of response to CRT. Atrial fibrillation (AF) is another possible cause of poor response to CRT,<sup>17</sup>as patients with AF do not derive as large a benefit as patients with sinus rhythm do. This is unfortunate for several reasons. First, at least 25% of patients eligible for CRT have AF.18,19 Furthermore, since HF and AF share similar risk factors, about 40% of patients with AF or HF will develop the other condition 1, and the prevalence of AF is related to worsening NYHA class.18 The lack of a definitive benefit of CRT in patients with AF is reflected in the current ACCF/AHA/HRS guidelines, which require the presence of sinus rhythm for a class I indication .3

#### Atrial Fibrillation and CRT Response

Achievement of nearly 100% biventricular pacing has been the holy grail of CRT. In a study of more than 36,000 patients (most of whom were in sinus rhythm) who underwent CRT implantation and were enrolled in a remote monitoring program, there was a direct relationship between the percentage of biventricular pacing and mortality, with incremental increases in mortality benefit observed with an increasing percentage of biventricular pacing, whereas AF limited the degree of biventricular pacing.<sup>20</sup> In another study, the presence of atrial arrhythmias was associated with a less-than-optimal degree of biventricular pacing, which in turn limits the efficacy of CRT.<sup>21</sup> AF limits the degree of biventricular pacing, not only when the rate is fast and highly irregular, but also during periods of relatively constant rate, by causing fusion and pseudo-fusion complexes .<sup>22</sup> While slower ventricular rates help increase the degree of biventricular pacing, even modest increases in ventricular rates have been shown to reduce the benefit of CRT .23 Moreover, the absence of regular, organized atrial activity, and the loss of atrioventricular synchrony in the presence of AF, may adversely influence the response to CRT .17,23

Most of the randomized controlled CRT trials included only patients with sinus rhythm.<sup>3</sup> Therefore, evidence for the benefit of CRT in patients with AF has been derived from mostly observa-

tional studies,<sup>24-32</sup> whereas only two randomized controlled trials included patients with AF.5,33 An acute hemodynamic study of biventricular pacing in patients with HF and LBBB, in either sinus rhythm or AF, revealed a similar degree of improvement in pulmonary capillary wedge pressure, V-wave amplitude and systolic blood pressure in both groups, suggesting that biventricular pacing may be beneficial in patients with HF regardless of whether or not they are in sinus rhythm.<sup>34</sup> A few small preliminary studies indicated that CRT may improve symptoms and exercise tolerance 35,36 and induce reverse LV remodeling <sup>36</sup> at 1 year in patients with HF and wide QRS, regardless of the presence of AF. However, despite aggressive rate control to ensure adequate biventricular pacing, reverse LV remodeling was less prominent in the AF group in the latter study <sup>36</sup>, whereas in the former study, atrioventricular junction (AVJ) ablation was performed systematically in all patients with AF, in order to achieve complete and permanent biventricular pacing.<sup>35</sup> Of note, AF was associated with an increased risk of death at follow-up in both studies.<sup>35,36</sup>

In the first randomized controlled trial to include patients with AF, the Multisite Stimulation in Cardiomyopathy (MUSTIC) study, the benefit of CRT in surrogate markers, including exercise tolerance, peak oxygen uptake, quality of life and NYHA class was observed equally in the AF and sinus rhythm groups at 12 months follow up.<sup>33</sup> However this study did not offer definitive evidence as the sample size was small and it was not powered to examine differences between subgroups. In a pre-specified secondary analysis of the Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT), the effect of CRT was examined in a subgroup of patients with permanent atrial fibrillation who received either an implantable cardioverter defibrillator (ICD) or CRT-ICD. In this analysis, there was no clear improvement in any clinical or surrogate outcome in the CRT-ICD group compared to the ICD group. AF was associated with a higher risk of death, but there was a trend towards reduced HF hospitalizations in the CRT-ICD group. 37 However, the trial was underpowered to detect moderate treatment effect differences, and only one third of patients received more than 95% biventricular pacing, suggesting that the effect of CRT was not maximized.

To summarize the available evidence on the efficacy of CRT in patients with AF compared to those in SR, Wilton et al.<sup>38</sup> conducted a meta-analysis on 23 observational studies, including 7,495 CRT recipients (25.5% with AF). In five of the included studies, clinical response was defined as improvement in one functional class and survival over 6 to 12 months. The remainder of the studies used a 10% improvement in 6-minute walk distance or a 15% improvement in quality of life score. Patients with AF had a significantly higher risk of non-response to CRT and all-cause mortality compared to those in sinus rhythm.<sup>38</sup> Likewise, AF was associated with an attenuated improvement in 6 minute walk distance, quality of life and LV end-systolic volume. Importantly, among patients with AF, AVJ ablation was associated with a lower risk of CRT non-response, as well as improved survival. In another meta-analysis of prospective cohort studies, Upadhyay et al.<sup>39</sup> examined the differential impact of CRT for patients in AF and sinus rhythm. Five studies met their inclusion criteria, four of which were prospective cohort studies and one was a subgroup of a randomized clinical trial. The use of AVJ ablation in this meta-analysis varied from 22% 24 to 100%.35 Only two of the studies mentioned biventricular capture rates. Specifically, Gasparini et al. 28 reported a 75% biventricular capture rate and Molhoek et al. 31 reported 82% capture rate. They concluded that while patients with AF derive benefit from CRT, they have smaller functional improvements compared to thise in sinus rhythm. Specifically, while both groups had improvement in the 6-minute walk test, those in sinus rhythm patients walked 11.6 m farther on average. Similarly, both groups showed improvement in the quality of life as measured by the Minnesota Living with HF questionnaire, but those in in sinus rhythm showed more relative improvement. In summary, the presence of AF is associated with an attenuated response to CRT, in part because of the inability to achieve almost complete biventricular pacing. A simple, albeit irreversible, method to maximize biventricular pacing is AVJ ablation.

# AVJ Ablation to Maximize CRT Response In Patients with AF

The importance of biventricular capture in patients with CRT cannot be overstated. Current evidence suggests that a high degree of biventricular pacing is necessary in order to derive benefit from CRT. Analysis of the LATITUDE remote monitoring network ,which followed more than 36,000 CRT patients, showed a 27% reduction in mortality compared to all other groups when biventricular pacing was achieved in excess of 98% .<sup>20</sup> Most of these patients, however, were predominantly in sinus rhythm. In a subgroup analysis of patients with atrial arrhythmias from the RENEWAL and REFLEX trials, those with biventricular pacing percentages more than 92% had a reduced hazard ratio of heart failure events compared to those with less than 92% biventricular pacing.<sup>21</sup>

As described above, fast and irregular AF poses a significant challenge to achieving effective CRT by reducing the degree of biventricular pacing. Another challenge, which is often overlooked, arises when the percentage of biventricular pacing taken directly from the device counter does not accurately represent effective CRT. Kamath et al.40 placed Holter monitors on AF patients with CRT devices. In this analysis, a high percentage of pseudo-fusion and fusion beats in patients with AF were seen that the device counters labeled as biventricular paced beats. These beats likely do not deliver the true mechanical benefit of a biventricular paced beat, which further advocates for more complete resynchronization in AF patients with CRT.

AVJ ablation was reported as a successful procedure with a low incidence of complications in 1991 by Yeun-Lai-Wah et al. 41 for the treatment of supraventricular tachycardias, around the same time that radiofrequency catheter ablation started to be used for mapping and ablation of Wolff-Parkinson-White syndrome.<sup>42</sup> AVJ ablation continues to be used for the maintenance of appropriate ventricular rate control in AF patients, but usually only as a final option, 43-45 mostly because of the irreversible nature of the procedure and the possible long-term consequences. Inappropriate ICD therapies may not be resolved completely after AVJ ablation, but since inappropriate therapies compose about 30% of all ICD interventions, this secondary benefit may have more long term quality of life improvements.<sup>46</sup>

A recent meta-analysis by Ganesan et al.<sup>47</sup> systematically examined the role of AVJ ablation inpatients with coexistent AF and HF undergoing

CRT. Six observational non-randomized cohort studies, including 768 patients (339 patients who underwent AVJ ablation and 429 who received medical therapy aimed at rate control alone) were included in the analysis. AVJ ablation was associated with a significant reduction in all-cause and cardiovascular mortality, as well as improvement in NYHA Class when compared to medical management alone.<sup>47</sup> In another meta-analysis, Wilton et al. reviewed five studies comparing CRT outcomes by use of AVJ ablation in AF patients with HF, low LV ejection fraction (<35%) and wide QRS (>120ms). In these studies, patients were selected for AVJ ablation based on inability to achieve at least 85% to 90% biventricular pacing, while the timing of AVJ ablation varied from either before or after CRT implantation. AVJ ablation was associated with a lower risk of CRT non-response. Moreover, improved survival with AVJ ablation was seen in two studies, independent of other factors.<sup>38</sup>

Notwithstanding the limitations of non-randomized trials, these analyses suggest that AVJ ablation is associated with improved outcomes in patients with AF who otherwise meet criteria for CRT. Further randomized trials are warranted to confirm these findings. Importantly, the degree of biventricular pacing in the two groups should be systematically assessed and correlated with clinical outcomes in a pre-specified analysis. Evidence from non-randomized trials supports the notion that the benefit of CRT may be equal in patients with sinus rhythm and those with AF who undergo AVJ ablation. Tolosana et al.<sup>19</sup> performed an observational prospective multicenter study in 202 patients who received CRT for symptomatic heart failure despite optimal drug therapy, LV ejection fraction less than 35%, and a QRS duration more than 120ms. Patients were grouped according to their intrinsic rhythm. If biventricular pacing was ≤85% in the first 2 months, AVJ ablation was recommended for patients in AF. In the group of patients with AF, 28% required AVJ ablation after maximizing negative chronotropic drug therapy. After one year of therapy, the percentage of biventricular pacing was similar in all three groups (sinus rhythm, AF, AF/AVJ ablation). , Importantly, there was no difference in the percentage of response, defined as  $\geq 10\%$  reduction in left ventricular end-systolic volume at 12 months

between patients in sinus rhythm and AF. Nonetheless, the mortality was higher in patients with AF .<sup>19</sup> These results are consistent with those of a previous trial, in which CRT resulted in a similar benefit among patients with sinus rhythm and AF, when AVJ ablation was performed systematically in all patients in the latter group, in order to maximize biventricular pacing.<sup>35</sup>

The above information taken together seems to suggest that the benefit of AVJ ablation by maximizing effective CRT outweighs the risk of pacemaker dependency. Hopefully, continued advancements in bipolar pacing strategies will reduce this fear in patients who may benefit the most from this strategy. The importance of effective delivery of CRT in patients with AF is reflected in the current ACCF/AHA/HRS guidelines, which indicate that CRT can be useful in patients with AF and low LV ejection fraction who otherwise meet CRT criteria, only if AVJ ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT (class IIa).<sup>3</sup>

#### CRT Use After AVJ Ablation For Refactory AF

As previously mentioned, AVJ ablation with permanent pacing has been used in patients with symptomatic AF with difficult to control high ventricular rates. The optimal pacing modality in these patients is still a matter of debate. In this subgroup of patients, a few studies have compared RV pacing versus CRT in patients undergoing AVJ ablation for refractory AF.48-52 Some studies suggested that CRT might be more beneficial than RV pacing in such patients,<sup>48,50-52</sup> whereas some failed to show an additional benefit of CRT beyond that conferred by rate regularization.49 Since most studies evaluated surrogate endpoints and were underpowered to evaluate major clinical endpoints, the optimal pacing modality after AVJ ablation remains unclear.

Our group performed a meta-analysis on this subject and found 5 randomized controlled trials 48-52 meeting our inclusion criteria.<sup>53</sup> The majority of the patients included in these studies had at least mildly depressed LV ejection fraction (<45%) and 50% had a QRS duration of >120ms. Our results suggested that CRT for permanent AF

after AVJ ablation may be superior to RV pacing. Specifically, CRT decreased hospitalization for heart failure and provided a favorable, albeit non-significant, trend in mortality, compared to RV pacing. Based on this meta-analysis, we hypothesized that the beneficial effect of CRT was a result of reverse LV remodeling, as indicated by the significant improvement in LV ejection fraction, LV end-systolic and end-diastolic diameters compared to RV pacing. These findings are consistent with previous studies, showing that the beneficial effects of CRT are associated with improvement of cardiac structure and function through reverse LV remodeling <sup>54,55</sup> Although these results are encouraging, they cannot be considered definitive. Importantly, the evidence supporting use of CRT after AVJ ablation in patients with normal LV ejection fraction is sparse, even though the benefit of CRT was seen irrespective of LV ejection fraction or NYHA class in one study.<sup>52</sup> Therefore, a randomized clinical trial, adequately powered to detect clinical outcomes and specifically examining patients with normal LV ejection fraction, is urgently needed. Based on our calculations, a sample size of 1310 patients would need to be recruited over a 3-year period with a total study duration of 5 years (minimum of 2 years follow-up for all patients) to provide adequate power to detect a difference in mortality between the two groups.<sup>53</sup>

**Figure 1:** Recommended strategy for atrioventricular junction (AVJ) ablation in patients with atrial fibrillation (AF) for optimization of cardiac resynchronization therapy (CRT) based on available evidence.



### Conclusions

CRT is a well-studied non-pharmacologic treatment for HF, a disease that is only increasing in prevalence. Atrial fibrillation, among other factors, may have a negative impact on the clinical benefit of CRT by reducing the degree of biventricular pacing. Based on the knowledge that maximizing bi-

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ventricular pacing reduces mortality, AVJ ablation may be an important treatment in this patient population. Based on the available evidence, we recommend the following algorithm for the use of AVJ ablation in patients with AF for optimization of CRT (Figure 1). In patients who otherwise meet criteria for CRT (NYHA class II to IV, LV ejection fraction ≤35%, QRS duration ≥150ms with left bundle branch morphology), <sup>3</sup>aggressive medical therapy to achieve rate control may be tried first. If the degree of biventricular pacing is <95% at follow-up, we recommend considering AVJ ablation to maximize the response to CRT. In patients with symptomatic AF, in whom a decision was made to perform AVJ ablation, the decision to implant a CRT device may be reserved for those who have HF with a low LV ejection fraction ≤35%. Given the uncertainty of the value of CRT in patients with normal ejection fraction and without HF, no firm recommendations can be made at this time and the decision to implant a CRT in these patients should be individualized.

In conclusion, the available evidence from observational non-randomized studies suggests that AVJ ablation in patients with AF qualifying for CRT may offer improvement in HF symptoms, better survival, and better cardiac function. In light of the inherent limitations of non-randomized studies, further randomized studies are needed to support this treatment option.

#### Disclosures

No disclosures relevant to this article were made by the authors.

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