DEVICE THERAPY

REVIEW ARTICLE

Maximizing Cardiac Resynchronization Therapy in Patients With Atrial Fibrillation

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ABSTRACT. Atrial fibrillation (AF) and heart failure (HF) commonly coexist and exacerbate each other’s course. Cardiac resynchronization therapy (CRT) is a highly effective therapy for many patients with HF and dyssynchrony of inter- and intraventricular electromechanical activation. Because of the frequent co-occurrence of AF and HF, AF is often present in CRT patients and can have a significant negative impact on the CRT response. This occurs for two reasons: 1) the negative effects that AF has on HF in general; and 2) when conducted to the ventricles with an R-R interval similar or shorter than the lower pacing rate, AF completely or partially precludes biventricular pacing. We will review the current understanding of the extent, pathophysiology, and potential solutions to this significant and increasingly widespread clinical problem.

KEYWORDS. atrial fibrillation, atrioventricular junction ablation, cardiac resynchronization therapy, percentage biventricular pacing.

Introduction

More than 2.2 million people in the United States are affected by atrial fibrillation (AF).1 The prevalence of AF in industrialized and semi-industrialized countries is rising to epidemic proportions. The number of affected individuals is projected to more than double over the next 50 years, such that by 2050, it is estimated that more than five million people in the United States will be affected.2 From 1996 to 2001, hospitalizations with AF as the first-listed diagnosis increased by 34%, and the number of AF-related hospital admissions in the past 20 years has doubled.1,3–5

Heart failure (HF) is the leading cause of morbidity and mortality in the United States, with a prevalence of five million and an annual incidence of 500,000. It results in two million hospitalizations annually and is the main cause of hospitalization in patients 65 years and older. HF is the single largest Medicare expenditure, accounting for approximately $4 billion annually. Most estimates suggest that the incidence of HF will continue to rise.6–8

Cardiac resynchronization therapy (CRT), achieved by biventricular (BiV) pacing, is a highly effective therapy for patients with HF, a depressed ejection fraction (EF), and electrocardiographic (ECG) evidence of electrical dyssynchrony, in particular left bundle-branch block. Over 20% of individuals treated with CRT have evidence of AF, and this often worsens HF treatment, as well as interfering with BiV pacing.9 The aim of this review is to: 1) summarize the epidemiology and pathophysiology of the interaction between AF and CRT delivery, and the techniques for monitoring this effect; 2) review current device algorithms targeted at promoting maximal BiV pacing in the presence of rapidly conducted AF; and 3) review the pharmacologic and invasive techniques for rate and rhythm control of AF in order to achieve maximal BiV pacing and an improved CRT response.

Epidemiology and pathophysiology of AF in CRT

Epidemiology of AF in CRT recipients

Many predisposing clinical factors and echocardiographic features are shared between AF and HF, including hypertension, increased alcohol consumption,
diabetes mellitus, coronary artery disease, reduced left ventricular (LV) systolic function, LV hypertrophy, and left atrial (LA) enlargement.

Since AF is the most common arrhythmia in patients with HF, it stands to reason that AF is present in many patients with an indication for CRT.\(^\text{10,11}\) The prevalence of AF rises as the severity of HF increases. In patients with mild HF symptoms, the prevalence of AF is \(\approx 5\%\), whereas almost 50% of those with the most severe forms of HF have AF.\(^\text{2,12,13}\) Patients with New York Heart Association (NYHA) Class III or IV HF symptoms, a QRS duration of \(\geq 120\) ms, an EF of \(\leq 35\%\), and who are in AF have a Class IIa indication for CRT, combined with an implantable cardioverter-defibrillator (ICD), whereas their counterparts in sinus rhythm (SR) have a Class I indication.\(^\text{10}\) Although in some patients, CRT reduces the burden of AF, in general AF remains common in the CRT population, with a reported annual incidence of 16% per year,\(^\text{11,14,15}\) and a prevalence ranging between 20% and 45% in various studies.\(^\text{9,11,16,17}\) A recent European survey indicated that approximately one-fifth of CRT recipients are in permanent AF.\(^\text{18}\)

**Impact of AF on the response to CRT**

Although some observational studies have suggested that patients in AF may gain equivalent benefit from CRT as those in SR, the vast majority of data indicates that AF results in a significant reduction in CRT response.\(^\text{11,15-17,19-25}\) A recent study examined 1,193 subjects who were in SR at the time of BiV ICD implantation and showed that even a small burden of atrial arrhythmias was associated with a worse response to CRT and a higher rate of HF hospitalization and death.\(^\text{26}\) Caldwell et al.\(^\text{19}\) analyzed data collected from HF patients undergoing CRT who were thought to be free of AF, and found that 27% had paroxysms of atrial arrhythmias, and that this was associated with a trend towards increased mortality. In a prospective study comparing CRT recipients in permanent AF with those in SR, Gasparini et al.\(^\text{27}\) demonstrated that the response to CRT was significantly better for those patients in SR than in AF. As will be discussed later, atrioventricular junction (AVJ) ablation in the AF group resulted in a CRT response comparable to those in SR. A meta-analysis comparing CRT recipients in permanent AF with those in SR demonstrated that although both groups of patients benefit significantly from CRT in terms of mortality and improvement in NYHA class, AF patients had diminished improvement in the 6-min walk distance and the Minnesota quality of life score (QOL).\(^\text{23}\) Similarly, a recent meta-analysis that included 23 studies and 7,495 CRT recipients, found that AF is associated with an attenuated CRT response and an increased all-cause mortality.\(^\text{24}\)

**Mechanisms by which AF worsens response to CRT**

AF interferes with CRT response via two mechanisms: 1) the deleterious effects of AF on the course of HF in general; and 2) interference with effective BiV pacing.

**General effects of AF in HF**

AF has a significant negative effect on HF. In a study on 390 patients with severe HF and EF of 20%, Middlekauf et al.\(^\text{27}\) demonstrated a survival of 52% in the presence of AF and 71% when SR was present at 1-year follow-up. Similarly in mild and moderate HF, AF imparts a negative prognosis. In patients with either symptomatic or asymptomatic HF in the SOLVD (Studies of Left Ventricle Dysfunction) trials, AF was associated with an increase in all-cause mortality.\(^\text{28}\) AF worsens HF and results in a 15–25% reduction in cardiac output (CO) via several mechanisms (Figure 1), including rapid ventricular rate (RVR); irregularity of the ventricular response; tachycardia-induced cardiomyopathy (TIC); and loss of atrial contribution to CO.\(^\text{29-31}\)

RVR acutely interferes with diastolic filling, leading to potential HF decompensation in susceptible patients. Chronically, RVR can cause a reduction in intrinsic ventricular function and TIC (see below).\(^\text{32}\) The irregular ventricular response (R-R irregularity) in AF decreases CO and elevates both right and LA pressures independent from the effects of RVR.\(^\text{33,34}\) Irregularity of ventricular rhythm has been linked to increased sympathetic nerve activity (SNA), which has many undesirable effects in HF.\(^\text{35}\) In one study, it was estimated that for roughly every approximate 1% increase in ventricular irregularity, there was a 6% increase in SNA.\(^\text{36}\) This autonomic disturbance can promote ventricular arrhythmia, perpetuate AF, and worsen the clinical course of HF through toxic effects on cardiomyocytes.\(^\text{37}\) Furthermore, R-R irregularity may cause a worsening of mitral regurgitation.\(^\text{31}\)

Moderately rapid arrhythmias, i.e. 100–120 bpm, are more likely to result in TIC, because they may cause
minimal symptoms of palpitation and tend to stabilize. Thus, they may remain undetected and untreated for months or years. In order for TIC to develop as a direct result of AF, chronic exposure to a resting heart rate consistently >100 bpm and/or >150 bpm with mild exercise is thought to be necessary. Improvement in symptoms, exercise capacity, and even partial or complete resolution of TIC with improvement in EF can be achieved by effective rate or rhythm control.38–40

Finally, the atria function as reservoirs, conduits, and as boosters of CO. Atrial contribution to CO in SR is 10–15%, and thus the loss of coordinated atrial mechanical function can exacerbate HF.41 The degree to which the atria contribute to the overall CO varies among patients with different cardiac disease states and also depends on the individual volume status. For instance, patients with diastolic LV dysfunction are particularly dependent on the atrial contribution to LV filling.

**Interference with effective biventricular pacing**

In order for CRT to be effective, it is imperative that native conduction through the atrioventricular (AV) node is completely pre-empted, with the ventricles being exclusively activated by BiV pacing. Failure to achieve this results in dyssynchronous ventricular activation as a result of bundle-branch block. An R-R interval in AF shorter than the programmed R-R interval for that beat will prevent complete BiV capture for that beat since BiV capture competes with conducted AF, leading to intrinsic, fusion, or pseudo-fusion beats.20 Fusion occurs when a paced beat collides with an intrinsic event and is variable depending on the relative contribution of intrinsic and BiV-paced ventricular activation (Figure 2). Pseudo-fusion occurs when the output occurs simultaneously with intrinsic activation. The ECG shows a pacing artifact while all conduction is native.

Intrinsic, fusion, and pseudo-fusion beats are undesirable, as exclusive BiV pacing is required to ameliorate electrical and mechanical dyssynchrony. In AF patients, a significant proportion of AF beats conduct faster to the ventricles than the BiV pacing can pre-empt; thus, AF reduces the global effective “CRT dose” and interferes with CRT delivery. An Italian study examined 1,404 HF patients who received CRT-ICD devices. Using device data, 443 of 1,404 patients (32%) were estimated to be in AF, and 34% of this subgroup had uncontrolled ventricular rate during AF. BiV pacing was inversely correlated with ventricular rate, decreasing by 7% for each 10-bpm increase in rate. RVR was associated with increased HF hospitalizations, suboptimal CRT (<95% BiV pacing), and death (Figure 3).25,32

**Target percentage biventricular pacing goal in CRT**

To derive benefit from CRT, percentage BiV pacing must be maximized. Gasparrini et al.22 chose an arbitrary cutoff rate of greater than 85% BiV pacing to evaluate the efficacy of CRT in permanent AF patients with and without AVJ ablation. Another study proposed that in order for CRT to be as effective in AF as in SR, the percentage of BiV pacing needed to be greater than 90%.42 In a post hoc study consisting of >1,800 patients, Koplan et al.43 concluded that to achieve the greatest magnitude of benefit from CRT in terms of HF hospitalization and mortality, >92% BiV pacing must be accomplished. Most recently, Hayes et al.44 examined a large cohort of 36,935 patients enrolled in a CRT remote-monitoring network. BiV pacing of >98% was associated with a reduction in mortality (Figure 4). Caution must be applied when using the percentage BiV pacing counters from cardiac implantable electronic devices (CIEDs), as they can overestimate the percentage of BiV pacing, as discussed below.

**Monitoring for rapidly conducting AF in CRT patients**

Detection of AF that is conducted rapidly enough to preclude effective BiV pacing can be achieved by a variety of methods, including 12-lead ECG, Holter and event monitoring, and from the CIED itself. Resting 12-lead ECG gives very limited information and significantly underestimates the true prevalence of AF. As discussed previously, a retrospective study using data downloaded from CRT devices showed that 27% of patients previously thought to be free of AF were in fact found to have a significant AF burden.19 Information obtained from CIED interrogation can give estimates of both AF burden and the percentage of BiV pacing: a) estimates of number and duration of atrial tachyarrhythmia episodes are reported by these devices; b) information regarding ventricular rate during AF is also available from many devices; c) stored electrograms (EGMs) from the atrial lead of CIEDs may contain important information regarding the nature of the atrial arrhythmia (e.g. AF versus atrial flutter versus atrial tachycardia) and initiation/termination of the arrhythmia; and d) counters indicating percentage BiV pacing.

It is important understand the limitations of these approaches. For example, not all “mode switches” are necessarily due to AF. Oversensing can cause overestimation of AF episodes, whereas undersensing of AF may cause underestimation. Similarly, reported percentage BiV pacing may be inaccurate. In an important study, Kamath et al.45 studied 19 patients with permanent AF and severely depressed LVEF who underwent BiV implantation. Device interrogations on study subjects all showed >90% BiV pacing on the device counters. However, using a 12-lead Holter monitor, only 47% of the subjects had true effective BiV pacing. Over half of the subjects had fusion and pseudo-fusion beats that were reported as BiV-paced beats by the device. In this study, lack of true effective BiV pacing as demonstrated by a high percentage of fused and pseudo-fused beats correlated with CRT non-response.45 Therefore, even if...
the device counters record a high percentage of BiV pacing, it is imperative to examine rhythm strips and EGMs of non-responders to verify that the beats are truly BiV paced. Importantly, certain company algorithms aimed at maximizing BiV pacing in AF patients may also lead to a false sense of reassurance with regards to the percentage of BiV pacing. For example, when an algorithm-like ventricular sense response (VSR) is turned on (discussed in detail below), the first summary page of a device interrogation may report a high BiV pacing percentage. One must look further into the remaining interrogation strips to assess the components that make up this BiV pacing percentage (i.e. truly BiV-paced beats, plus fused beats as a result of VSR).

**Device algorithms aimed at promoting maximal biventricular pacing in AF patients**

LV capture must be achieved to maximize cardiac resynchronization. Devices from most CIED companies have algorithms aimed to help maintain BiV pacing. Medtronic CRT device features include VSR, atrial tracking recovery (ATR), and conducted AF response (CAFR).

In VSR, a sensed right ventricular (RV) event triggers an immediate ventricular pacing pulse (LV pacing), maintaining some CRT in the presence of ventricular sensing. This device algorithm may result in a higher overall heart rate as the BiV device tries to match the

![Figure 2: An intrinsic beat, denoted by a black arrow, conducted through the atrioventricular (AV) node interferes with biventricular (BiV) pacing, depicted as green arrows. (a) 100% BiV-paced beat is achieved when the native conduction is completely preempted. The degree of fusion can be variable, as demonstrated in (b) and (c). Pseudo-fusion occurs when the entire conduction is native, although a pacing artifact is seen (d). Illustration courtesy of St Jude Medical.](image)
intrinsic conduction. Of note, if the ventricular interval measured from the preceding ventricular event is shorter than the programmed maximum rate interval, no VSR pacing pulse is delivered. In addition, because of the close proximity of the ventricular sensed event and the VSR pacing pulse, the BiV annotation is not printed on the ECG strips, but the VSR pacing event is considered as a BiV-paced beat in the device counters on the overall summary page (Figure 5a). Therefore, one must look beyond the first page of a device interrogation to make a distinction between BiV-paced beats versus VSR triggered beats.

ATR helps maintain BiV pacing in select patients with HF and RVR (usually 110–120 bpm) in DDD mode (mode switch may not have occurred due to undersensing). In rapidly conducted AF, atrial sensed events may fall in the post-ventricular atrial refractory period (PVARP), leading to a loss of atrial tracking as the device classifies the event as a refractory event. This can prevent BiV pacing and thus CRT delivery. ATR temporarily shortens PVARP so that sensed atrial events can be tracked to the ventricles, allowing CRT to resume.

CAFR is used in non-tracking modes to promote BiV pacing with little or no increase in the daily average heart rate. With an intact AV conduction, the device can be programmed to increase the pacing rate in concert with the patient’s intrinsic ventricular response to conducted AF. CAFR adjusts the pacing rate to be faster when ventricular sensed events occur and slower when ventricular pacing occurs. The device adds up to 3 bpm in response to a sensed event and subtracts 1 bpm in response to a pacing pulse.

St. Jude Medical CRT devices (St. Jude Medical, St Paul, MN) use ventricular triggered pacing (or BiV trigger mode) to promote BiV pacing. Similar to VSR, ventricular triggered pacing force paces the LV 8 ms after a sensed premature ventricular complex or a sensed RV event. It is used in DDT or VVT modes, which can be permanently programed or set to occur only during mode switch. Histograms and marker channels differentiate a BiV-paced beat from a triggered beat to allow differentiation between true BiV pacing from triggered beats (Figure 5b).

Boston Scientific (Boston, MA) CIEDs use BiV trigger and ventricular rate regulation (VRR). BiV trigger prompts LV to pace after a sensed RV event. VRR is activated during mode switch to reduce irregular ventricular intervals, similar to Medtronic’s (St. Paul,

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**Figure 3:** The percentage of effective biventricular pacing (BiVP%) during atrial fibrillation decreased linearly as a function of the ventricular rate. The faster the ventricular rate, or the shorter the R-R interval, the less biventricular pacing was present.\(^{25}\)

**Figure 4:** High percentage of biventricular (BiV) pacing achieved, specifically \(>98.5\%\), was associated with a reduction in mortality. As expected, patients with atrial fibrillation (AF) had a worse outcome than those without AF. However, this was lessened if the high percentage of BiV pacing could be achieved in the AF population, usually after an atrioventricular junction ablation.\(^{44}\)
Biotronik (Berlin, Germany) CIEDs use a feature named RVsense, similar to VSR, to provide triggered pacing of LV for RV-sensed events. When a patient is in AF, the device can be programmed to provide triggered pacing up to 160 bpm by delivering LV pacing 2.5 ms after an intrinsic RV event. All of the triggered algorithms are likely to result in a fusion beat, rather than a true BiV-paced beat, since the RV septum has already started its depolarization. As discussed above, the algorithms often result in a higher ventricular rate. There are no randomized controlled trials evaluating the effectiveness of these algorithms. However, a study looking at the 4-year efficacy of CRT, disease progression, and the importance of AVJ ablation observed that the device features, specifically VRR, combined with negative chronotropic drugs were not sufficient to improve functional status, EF, or LVESV reduction. Thus, additional measures are required to maximize BiV resynchronization. These include stringent rate control (if necessary by performing AVJ ablation), or rhythm control in which a strategy aimed at curing AF is adopted.

Rate control for promotion of maximal BiV pacing in AF

Rate control: pharmacologic therapy

As discussed previously, RVR worsens HF and hinders effective BiV pacing when the R-R interval of AF is shorter relative to the lower pacing rate. Adequate rate control aims to allow the ventricles to be activated exclusively through BiV pacing and makes native conduction through the AV node irrelevant. Medications used for rate control include AV nodal blocking...
agents (preferably beta-blockers over non-dihydropyridine calcium channel blockers), digoxin, and amiodarone. Beta-blockers are relatively effective rate-controlling agents and provide mortality benefit in HF. Digoxin has a limited effect on heart rate in the setting of high sympathetic tone but is a good adjunct to beta-blockers. The combination of digoxin and beta-blockers has been shown to be more effective than each agent alone. Used acutely, amiodarone acts as a rate-controlling agent; however, it is not used in the long term for this effect because of its marked potential for drug-induced toxicities. Calcium channel blockers may worsen HF because of the negative inotropic effect and should be avoided in patients with HF and depressed EF. Sufficient rate control is often difficult to achieve with medications because of borderline hemodynamics in patients with severe HF. Furthermore, these agents do not regularize the ventricular rhythm.

**Rate control: AVJ ablation**

There are no randomized controlled trials evaluating AVJ ablation versus no AVJ ablation in patients with AF and CRT, although most centers have great experience in promoting maximal BiV pacing and benefit from CRT by AVJ ablation. Ablation of the AVJ creates heart block and ensures that CRT is delivered without fusion or pseudo-fusion beats, regardless of short R-R intervals. AVJ ablation also regularizes ventricular rhythm, eliminates the risk of RVR, and allows for discontinuation of potentially toxic drugs such as calcium channel blockers, digoxin, and amiodarone. Gasparini et al. evaluated the effect of AVJ ablation on CRT delivery in patients with permanent AF. The study showed that despite using negative chronotropic drugs and adjusting the device algorithms, only those who underwent AVJ ablation had significant improvement in EF, LVEF, and exercise capacity. When compared with patients in SR, those with permanent AF had worse outcomes; however, the difference disappeared in those who underwent AVJ ablation. At 12-month follow-up, AVJ ablation enhanced CRT response and improved overall survival by reducing HF death.

A retrospective analysis by Ferreira et al. compared three groups of patients with HF: SR, AF with AVJ ablation, and AF without AVJ ablation. With BiV CIED implantation, there was an overall improvement in the NYHA class; however, there were significantly fewer responders to CRT in the AF patients without AVJ ablation. The authors concluded that AF patients had a similar rate of survival as those in SR, provided that AVJ ablation was performed. Another retrospective study examining 154 HF patients with AF who underwent CRT also found that AVJ ablation for definitive BiV pacing not only provided improvement in NYHA class but also conferred a significant survival benefit when compared with those using pharmacologic rate control strategy alone. A meta-analysis of 23 observational studies, following a total of 7,495 CRT recipients, found that AF was associated with an increased risk of non-response to CRT and all-cause mortality compared with those in SR. However, in this analysis, those who underwent AVJ ablation had reduced risk of death and improved CRT outcomes. On the other hand, some small studies have suggested that AVJ ablation is not a prerequisite for CRT. They showed that patients with AF benefitted from CRT without the need for mandatory AVJ ablation. However, in these studies, rate control was achieved with pharmacological agents.

Limitations of AVJ ablation include the ongoing need for anticoagulation, loss of AV synchrony, and lifelong pacemaker dependency. Polymorphic ventricular tachycardia occurring early after AVJ ablation can lead to ventricular fibrillation and sudden death. Pacing at 90 bpm for 1 month after AVJ ablation can prevent this phenomenon.

**Rhythm control for promotion of maximal BiV pacing in AF**

**Rhythm control: pharmacological therapy**

The most commonly used antiarrhythmic drugs (AADs) in HF are Class III agents, namely amiodarone, sotalol, and dofetilide. Class IC AADs, such as flecainide and propafenone, are absolutely contraindicated in HF because of their predisposition to lethal ventricular arrhythmias. The CHF-STAT (Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy) study demonstrated that amiodarone is effective and did not increase mortality in HF patients; however, a subgroup analysis from SCD-HeFT showed that amiodarone was associated with higher morality in more advanced HF. In general, AADs have increased mortality in HF patients. However, DIAMOND-CHF showed that dofetilide was safe and effective in converting AF back to SR, preventing its recurrence, and reducing hospitalization due to HF. Often AADs are combined with direct-current cardioversion to successfully restore SR in persistent AF.

**Rhythm control: AF ablation**

The success of catheter ablation for AF has largely been shown in patients with paroxysmal AF without HF. Results might not be expected to be as promising in the HF population who often have persistent AF, marked LA enlargement, patient frailty, ventricular dysfunction, and areas of low-voltage atrial scar. Catheter ablation nevertheless is still a reasonable method for maintaining SR in selected patients.

In one study, pulmonary vein isolation was demonstrated to safely improve symptoms and LV function in patients with HF. At these high-volume and experienced centers, SR could be maintained in about 70% of patients at follow-up. However, although AF ablation produces a significant improvement in functional capacity, EF, and QOL with respect to AVJ ablation and BiV
pacing, many HF patients are poor candidates for AF ablation. They are often elderly, frail, in persistent AF, and may require several ablations to achieve rhythm control. Furthermore, stiff LA syndrome, i.e. pulmonary hypertension with LA diastolic dysfunction, has been described as a rare but significant complication of AF ablation. It is associated with LA scarring and an elevated LA pressure. Clinical manifestations include dyspnea and progressive HF. Thus, AVJ ablation remains the most practical method to achieve maximal BiV pacing in a significant proportion of patients with severe HF.

Conclusion

AF has the potential to present a major obstacle to the delivery of CRT. It decreases CO and exacerbates HF via RVR, irregularity, TIC, and loss of atrial transport. It attenuates effective BiV pacing also via RVR and irregularity. The percentage of BiV pacing correlates with LV remodeling, improved LVEF, functional capacity, and mortality. BiV pacing may be maximized via rate control, using nodal-blocking agents or AVJ ablation, rhythm control, using antiarrhythmic agents or AF ablation, and device algorithms aimed at promoting BiV pacing during AF. We propose that at least 95% BiV pacing is necessary to derive benefit from CRT. If the rate control option is selected, the most practical and safest method to achieve this is by AVJ ablation. With the advancement of various mapping systems and innovative catheter techniques, AF ablation will also play an increasingly significant role in the management of these patients.

References


