VIA MEDICA
REVIEW ARTICLE
Cardiology Journal
2009, Vol. 16, No. 1, pp. 4–10

ISSN 1897–5593

Cardiac resynchronization therapy and atrial fibrillation

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Abstract

Cardiac resynchronization therapy (CRT) is an important advance for the treatment of end-stage heart failure (HF). About 15–50% of HF is complicated by atrial fibrillation (AF), associated with worsened outcomes. The presence of AF may interfere with optimal delivery of CRT due to competition with biventricular (BiV) capture by conducted beats. Pacing algorithms in newer devices may not ensure consistent CRT delivery during periods of rapid ventricular rates. Atrioventricular junction ablation with permanent pacing eliminates interference by conducted beats and provides complete BiV capture and is associated with improved outcomes. Catheter ablation of AF is another promising alternative to maintain sinus rhythm in patients with AF and HF. However, the optimal indications for CRT delivery for patients in this complex cohort remain to be assessed in randomized clinical trials. (Cardiol J 2009; 16: 4–10)

Key words: atrial fibrillation, cardiac resynchronization therapy

Introduction

Atrial fibrillation (AF) frequently coexists with heart failure (HF); the two conditions may directly predispose to each other. The prevalence of AF is closely related to New York Heart Association (NYHA) class. In approximate terms, the prevalence is 5% for NYHA functional class I, 10% to 25% for class II to III, and as high as 50% for class IV [1, 2]. The permanent form of AF [3] is present in 10% to 30% of patients with HF [4] and is associated with increased morbidity and mortality [5, 6]. The development of AF in the HF patient often heralds a worse prognosis [6, 7]. For example, in the Framingham study, the risk of death approximately doubled in HF patients who experienced AF [7].

Cardiac resynchronization therapy (CRT) has emerged as an important therapeutic modality for patients with end-stage drug refractory HF [8, 9]. Currently, CRT therapy is employed to treat patients who have ejection fraction (EF) ≤ 35%, ventricular dyssynchrony (QRS duration ≥ 120 ms), and NYHA class III to IV HF. Several clinical trials have demonstrated the efficacy of CRT; however, all major trials have included patients in sinus rhythm [9–11].

Clinical trials of atrial fibrillation and cardiac resynchronization therapy

Data for the efficacy of CRT in AF patients has been obtained from observational studies and 1 randomized trial that included AF patients. Leon et al. [12] studied the effect of biventricular pacing (BiV) on the functional status, quality of life, and hospitalization in patients with HF and AF. Twenty consecutive patients with severe HF (EF ≤ 35%, NYHA class III /IV) prior atrioventricular junction (AVJ) ablation and right ventricular (RV) pacing performed for permanent AF of at least six months

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duration were studied. The investigators studied only patients that underwent AVJ ablation, as it forced BiV pacing to be delivered effectively without other interference. There was a significant improvement in NYHA class and EF, a decrease in the number of hospitalizations, and improved quality of life scores.

The MUSTIC (MUltisite STimulation in Cardiomyopathies) trial was a randomized cross-over study of 131 patients including 67 in sinus rhythm and 64 in AF [13]. The trial demonstrated a similar improvement in the 6-minute walk test in class III HF patients following CRT, whether they were in sinus rhythm or in AF. Of the 64 AF patients, only 37 patients completed both crossover phases, greatly limiting the impact of the results. In addition, all patients in AF had a slow ventricular rate trial achieved through either spontaneous or induced atrioventricular (AV) block; this criterion is important because it probably distinguished a subset of patients that were most likely to have a high degree of BiV capture.

Molhoek et al. [14] evaluated the clinical response and long-term survival of CRT in 60 patients with NYHA class III/IV HF and decreased EF (< 35%), of whom 30 were in sinus rhythm and 30 had chronic AF. The study showed that the improvement in clinical parameters (NYHA class, exercise capacity, and quality of life score) was comparable between patients who had sinus rhythm and those who had AF. In addition, 2-year survival rate was similar in the 2 groups. Interestingly, 17 of the 30 AF patients had AVJ ablation.

Delnoy et al. [15] compared the efficacy of CRT in 96 patients with chronic AF and 167 patients with sinus rhythm. Echocardiographic and clinical parameters were evaluated at baseline and at 3 and 12 months. HF hospitalizations were compared the year before and the year after CRT implantation. Overall mortality and rates of hospitalization were similar in both groups. However, among patients with chronic AF, 22% had AVJ ablation and nearly 50% the patients were in spontaneous or cardioverted sinus rhythm. Among the AF patients, > 90% pacing was achieved in > 90% of the patients at follow-up.

An underlying issue for all these studies is the consistent and complete delivery of CRT. This is important since the delivery of CRT is dependent on effective and complete BiV capture. In patients with AF, there is no AV synchrony, and thus an inability to establish coordinated AV pacing; BiV capture is difficult to assure. Furthermore, patients with AF often have intermittent or consistent accelerated ventricular rates. Even when pacing rates are well programmed, the high intrinsic ventricular rates seen in some AF patients may inhibit consistent pacing and capture [16]. Fusion and pseudo-fusion beats resulting from an interaction between intrinsically conducted and paced beats may be responsible for ineffective pacing, despite the apparent delivery of CRT. This leads to inaccuracy and overestimation of the effective pacing capture. Thus it is imperative that in AF patients who undergo CRT, close follow-up is necessary to ensure close to 100% BiV capture [2].

Cardiac resynchronization therapy pacing algorithms: Ventricular capture

Irregular heart rate is itself associated with worsened cardiac function in patients with AF and HF [17]. Ventricular rate control has been considered to be an important component of optimal CRT delivery during rapid ventricular rates. Modern CRT devices employ algorithms designed to maximize ventricular pacing during potentially disruptive events such as rapidly conducted atrial arrhythmias. Both Medtronic and Boston Scientific CRT systems include algorithms that temporarily shorten the post-ventricular atrial refractory period to regain atrial tracking and restore resynchronization after premature ventricular complexes or during sinus tachycardia faster than the nominal upper rate limit. For Medtronic devices, the Ventricular Sense Response™ feature triggers pacing in one or both ventricles after each RV-sensed event. Medtronic's Conducted AF Response™ resynchronizes conducted beats in AF up to a minimum R-R interval without increasing ventricular rate. Boston Scientifics Ventricular Rate Regularization™ algorithm is intended to restore resynchronization and ventricular regularity by pacing the ventricle during irregular conduction of AF [18].

It is important to emphasize that the percentage of BiV pacing alone, as recorded by the CRT device, may be an ineffective surrogate of complete and consistent BiV capture. Fusion and pseudo-fusion beats resulting from an interaction between intrinsically conducted and paced beats may be responsible for ineffective pacing, despite the apparent delivery of CRT as assessed by a high percentage of BiV pacing. We studied 18 patients with permanent AF who underwent CRT [19]. All patients received medical therapy with digoxin, beta-blockers, and amiodarone for rate control, and device interrogation showed > 90% BiV pacing. At a median of 12 months after device implant, the patients were instructed to wear an ambulatory 12-lead Holter for 24 hours. Effective pacing was

defined by the presence of more than 90% fully paced beats with complete ventricular capture as confirmed in all 12 leads. In all CRT devices, device specific special pacing algorithms were activated. Despite advanced pacing algorithms and CRT device counters showing > 90% pacing, in reality only 44% of patients had effective pacing (> 90% fully paced beats/24 h). The remaining 56% of patients met criteria for ineffective pacing; in these patients, nearly 40% of pacing was accounted by fusion and pseudo-fusion. Only patients with effective pacing demonstrated response to CRT (≥ 1 NYHA improvement) and had evidence of reverse remodelling. These results emphasize the importance of effective BiV capture to ensure clinical response from CRT, rather than using simple counts of pacing delivery. It further underlies that, despite the CRT counters showing a high degree of BiV pacing, complete BiV capture may still be less than optimal.

Atrial pacing prevention algorithms

A vicious cycle exists between AF and HF; thus interruption or prevention may be a worthwhile therapeutic strategy. CRT combined with a refined atrial tachyarrhythmia prevention pacing algorithm appears to be an important addition in the management of AF. The Atrial Dynamic Overdrive Pacing Trial (ADOPT), designed to assess the clinical efficacy and safety of the AF suppression algorithm™ (St. Jude Medical) in patients with permanent pacemaker with prior history of AF, demonstrated that the overdrive atrial pacing algorithm was safe and decreased the symptomatic AF burden [20]. However, all patients had normal EF and the primary outcome was symptomatic AF burden. The Management of Atrial fibrillation Suppression in AF-HF COmorbidity Therapy (MASCOT) study evaluated whether the addition of atrial overdrive pacing (AOP) to CRT could reduce the incidence of permanent AF in patients with HF [21]. The study randomized 394 patients with NYHA class III/IV HF to either "AOP ON" or "AOP OFF", following CRT implantation. The overall incidence of permanent AF was low and was similar for the two treatment groups (n = 6 for "AOP OFF" and n = 7 for "AOP ON"). It is likely that the advanced atrial remodelling in the setting of HF and AF may preclude benefit from atrial algorithms in this altered milieu.

Atrioventricular junction ablation

Destruction of AVJ and placement of a permanent pacemaker has been used in patients with AF with uncontrolled ventricular rates. However, in patients with AF who undergo CRT therapy, AVJ ablation is increasingly being viewed as an important adjunct to ensure adequate CRT delivery. The Post AV Nodal Ablation evaluation (PAVE) study was a prospective, randomized trial comparing BiV to RV pacing in patients with chronic atrial fibrillation undergoing AV node ablation [22]. The study randomized 184 patients requiring AVJ to BiV (n = = 103) or RV pacing system (n = 81). The study endpoints were changes in the 6-minute walk test, quality of life, and left ventricular ejection fraction. At 6 months post-ablation, patients treated with BiV pacing had significant improvement in 6-minute walk distance in comparison to patients receiving right ventricular pacing. There was a decrease in EF in the RV paced group while EF remained stable in the BiV group.

Gasparini et al. [23] presented data on 673 consecutive patients (162 in AF, 511 in sinus rhythm). Of the 162 AF patients, 114 patients underwent AVJ ablation for inadequate BiV capture during follow-up, i.e. < 85% BiV capture. Patients in the sinus rhythm and AF groups showed significant and sustained improvement in functional capacity, left ventricular (LV) systolic function, and NYHA class. However, within the AF group, only patients who underwent ablation showed a significant increase of EF, reverse remodelling, and improved exercise tolerance. No improvements were observed in AF patients who did not undergo ablation. The long-term effect on mortality and hospitalization was subsequently assessed in the follow-up of 1285 consecutive patients (1042 in sinus rhythm, 243 in AF) who underwent CRT therapy [24]. In the AF group, an arbitrary cut-off of more than 85% BiV pacing was considered evidence of sufficient CRT delivery. Patients with > 85% BiV pacing were continued on rate control regimen while AVJ was performed if ≤ 85% BiV pacing. At nearly 3 years of follow-up, all-cause mortality and cardiac mortality was similar in the sinus rhythm group and the AF group. Within the AF group, total mortality was significantly better in the AVJ-ablation group compared to the AF drug-treated group (Fig. 1, 2). Ferreira et al. [25] also conducted a retrospective analysis of 131 consecutive HF patients who underwent CRT implantation. The patients in 3 groups were considered: sinus rhythm (n = 78), AF with AVJ ablation (n = = 26), and AF without AVJ ablation (n = 27). The primary outcomes were occurrence of cardiac death, hospitalization for HF, and improvement in NYHA class. There was a significant improvement in the NYHA class in all 3 groups. However, the

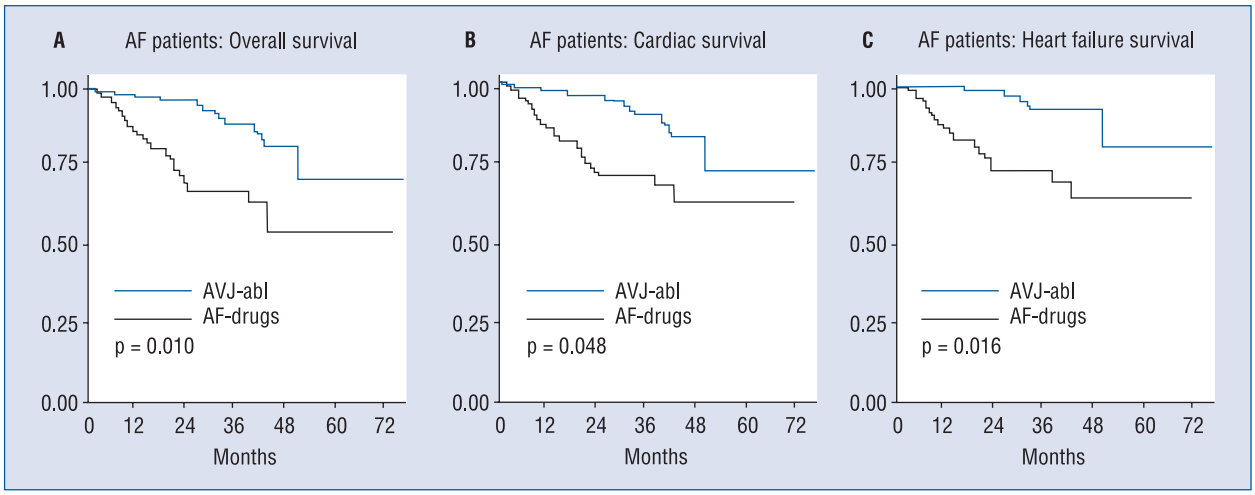

Figure 1. Comparison of Kaplan-Meier estimates of overall (**A**), cardiac (**B**), and heart failure (**C**) survival between atrial fibrillation (AF) patients who underwent atrioventricular junction ablation (AVJ-abl) and AF patients treated only with negative chronotropic drugs (AF-drugs); the p values presented derive from the adjusted hazards ratio analysis stratified according to the corresponding cause of death [24].

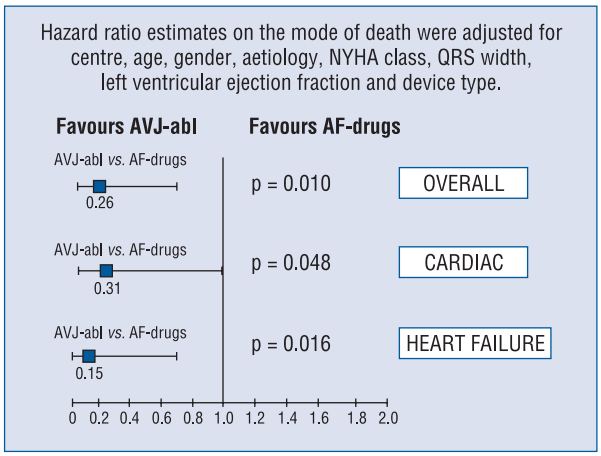

Figure 2. Hazard ratio estimates on the mode of death were adjusted for centre, age, gender, aetiology, NYHA class, QRS width, left ventricular ejection fraction and device type. Hazard ratio estimates stratified according to cause of death between atrial fibrillation (AF) patients who underwent atrioventricular junction ablation (AVJ-abl) and patients treated with negative chronotropic drugs (AF-drugs); hazard ratio estimates were adjusted for centre, age, gender, aetiology, NYHA class, QRS width, left ventricular ejection fraction and device type. Corresponding hazard ratio values for each cause of death are indicated with a square, the bar represents 95% confidence interval range, and the p value for each estimate is presented on the right of the figure [24].

proportion of responders was significantly lower in AF patients without AVJ ablation (52 *vs*. 79% in sinus rhythm and 85% in AF with AVJ ablation). AF without AVJ ablation was independently associated with five-fold increase in mortality and six-fold risk of hospitalization for HF during the first 12 months. The outcomes of AF with AVJ ablation patients were similar to the outcomes of patients in sinus rhythm. The authors concluded that AF patients display similar survival as sinus rhythm patients provided that AVJ ablation is performed.

These data suggest that patients with AF and HF may do better with the 'ablate and pace' strategy. The AVJ ablation with placement of permanent BiV pacemaker renders the patient pacemaker dependent and ensures complete and consistent BiV capture. CRT is delivered without fusion or pseudofusion thus ensuring high quality BiV capture. However, data from larger randomized clinical trials will be needed before utilizing this as a standard practice since this would create a large number of pacemaker-dependent HF patients. In addition, a small but variable rate of spontaneous conversion of AF to sinus rhythm has been reported after CRT [26, 27].

Catheter ablation of atrial fibrillation

In patients with permanent AF who undergo CRT without AVJ ablation, a few studies have suggested that cardioversion and aggressive rhythm control result in better clinical outcomes [28, 29]. However, currently available antiarrhythmic drugs (AAD) are only partially effective in maintaining sinus rhythm, and this is achieved at the cost of potential risk. In the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM)

Table 1. Clinical trials of catheter ablation in atrial fibrillation and left ventricular dysfunction.

Study	Study population	Results
Chen et al. [34] Retrospective case series	94 patients with LVEF < 40% *vs*. 283 patients with normal EF	73% of patients with decreased EF and 87% of patients with normal EF were free of AF 4.6% increase in LVEF, significant improvement in QoL
Hsu et al. [35] Prospective study	58 consecutive patients with HF and LVEF < 45% *vs*. 58 matched patients without HF	78% of the patients with CHF and 84% of controls were free of AF Significant improvement in LVEF of 21 ± 13%, exercise capacity, symptoms scores, and QoL scores
Tondo et al. [36] Prospective study	40 patients with LVEF < 40% *vs*. 65 patients with normal ventricular function	87% of patients with decreased EF and 92% of patients with normal EF were free of AF Improvement in LVEF from 33% to 47%
Gentlesk et al. [37] Prospective study	Patients with reduced LVEF (≤ 50%) *vs*. patients with normal LVEF	86% of patients in decreased LVEF and 87% of patients in normal EF were free of AF LVEF increased from 42% to 56% after ablation
Choi et al. [38] Retrospective case-control analysis	15 patients with AF and LVEF ≤ 45% referred for catheter ablation *vs*. 15 matched patients treated with medical therapy	Significant improvement in EF from 37% to 50%

AF — atrial fibrillation; EF — ejection fraction; LVEF — left ventricular ejection fraction; QoL — quality of life; HF — heart failure; CHF — congestive heart failure

trial, the use of AAD was associated with an almost 50% increase in mortality, which offset the potential benefit of maintaining sinus rhythm [30]. Furthermore, maintenance of sinus rhythm using AAD in the setting of AF and HF does not improve survival or other important endpoints [31, 32]. In contrast, catheter ablation may offer another approach for achieving sinus rhythm in these patients [32, 33]. Several clinical trials have demonstrated catheter ablation as a promising alternative (Table 1). Chen et al. [34] studied 94 patients with decreased EF (LVEF = 36%) who underwent catheter ablation. The control group consisted of 283 patients who had normal EF. At 14 months of follow-up there was a 5% improvement in EF, and 73% of the patients were free from AF recurrence in the decreased EF group. Hsu et al. [35] studied 58 consecutive patients with HF and LVEF < 45% who underwent catheter ablation for AF and compared their outcomes to a matched control group without HF. Sinus rhythm was achieved in 78% of patients with HF and in 84% of controls. In addition, patients with HF had significant improvements in EF, LV dimensions, exercise capacity, and quality of life (Fig. 3). Tondo et al. [36] evaluated 40 patients with LV dysfunction with EF < 40% and compared them to 65 patients with normal ventricular function. Outcomes included changes in LV function, maintenance of sinus rhythm, and quality of life during follow-up. After a mean follow-up of 14 months, 87% of patients with impaired LV function and 92% of patients with normal ventricular function were in sinus rhythm, with or without antiarrhythmic therapy. A significant improvement in LVEF was seen in patients with HF (33% to 47%). More recently, Choi et al. [38] evaluated 15 patients with AF and symptomatic LV dysfunction (EF ≤ 45%) referred for ablation. These patients were compared to a matched cohort treated medically for AF and LV dysfunction. Baseline EF in the study group was 37%, and for the controls it was 34%. The groups were similar in all respects. During the 16 months after ablation, EF improved to 50% ± 13% along with a significant improvement in NYHA class. In the medically treated group, no improvement in EF (36 ± 12%) or NYHA class was seen. Thus, compared to pharmacologic therapy, ablation significantly improved LV function and NYHA class in patients with AF and symptomatic LV dysfunction. The results of these nonrandomized series provide a potent rationale for a randomized clinical trial comparing ablation to pharmacologic therapy.

Conclusions

Current evidence suggests that CRT is effective in patients with AF and HF. However, there is no possibility of response to CRT if ventricular capture does not occur during BiV pacing. In patients with HF and AF, there is no atrioventricular

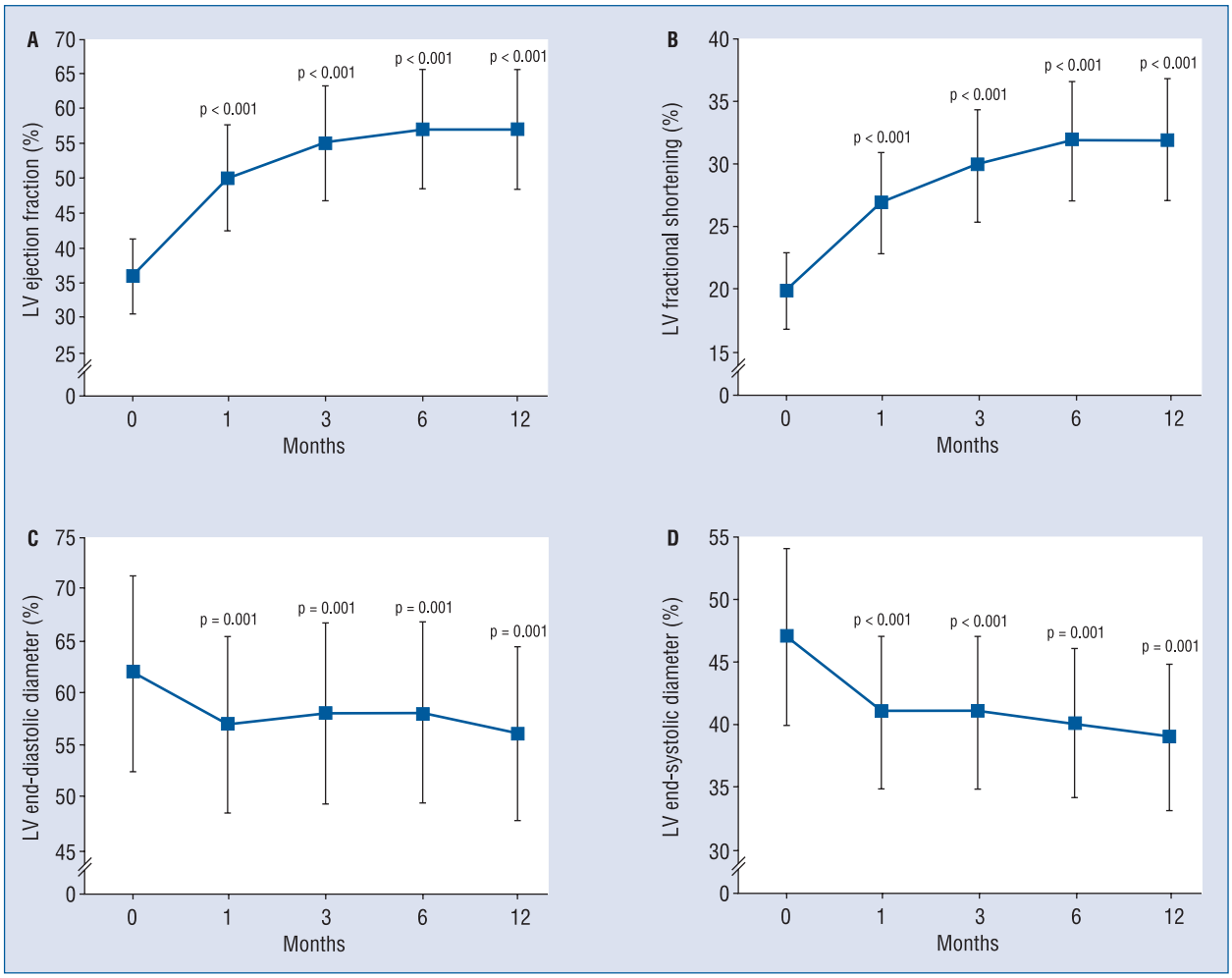

Figure 3. Improvement in left ventricular (LV) function and dimensions after ablation in patients with congestive heart failure; adapted from [35].

synchrony and BiV capture is difficult to assure. The optimal method to ensure complete and consistent BiV capture in patients with AF and CRT remains to be determined. At this time, AVJ ablation or AF ablation appear to be promising adjunctive modalities.

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