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Enhancing Cardiac Resynchronization Therapy for Patients with Atrial Fibrillation: The Role of AV Node Ablation

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Abstract

Cardiac resynchronization therapy (CRT) has evolved as an effective therapy for patients with congestive heart failure (CHF) and ventricular dyssynchrony, currently defined as a wide QRS on the electrocardiogram. While multiple randomized controlled trials have confirmed the favorable effects of CRT on mortality and heart failure symptoms for patients in sinus rhythm, only recently observational studies have begun to suggest a similar benefit for patients with atrial fibrillation (AF) and dyssynchrony. Yet, implementing effective biventricular pacing in patients with AF can be problematic due to competing intrinsic AV conduction. For patients with depressed ejection fractions needing AV node (AVN) ablation to control fast ventricular rates, biventricular pacing has been shown to be superior to right ventricular pacing alone. When consistent pacing (over 90% of the time) cannot be achieved in AF patients due to a rapid ventricular response despite pharmacological therapy, AVN ablation should be considered. The additional benefit of performing AVN ablation to promote biventricular pacing in patients without rapid ventricular rates remains uncertain. A randomized controlled trial is needed to test the incremental benefit of AVN ablation to promote biventricular pacing in heart failure patients with AF and wide QRS.

Introduction

Congestive heart failure (CHF) remains a major public health burden affecting an estimated 5.7 million people in the United States, and accounting for over 250,000 deaths annually[1]. Over the past few decades, data from randomized trials have led to a dramatic increase in the use of pharmacological therapies that improve outcomes for patients with heart failure due to systolic dysfunction.[2-7] In addition to these medical therapies, implantable cardiac devices provide additional therapeutic benefits for patients with congestive heart failure and depressed left ventricular systolic function.[8,9]

Cardiac resynchronization therapy (CRT) has been shown to improve quality of life, prevent hospitalizations, and reduce mortality for patients in sinus rhythm with congestive heart failure and a wide QRS on the surface electrocardiogram.[10-12] Emerging evidence suggests that patients with atrial fibrillation (AF) and ventricular dyssynchrony derive similar benefits from CRT.[13-18] Yet, although implementation of CRT in patients with sinus rhythm is readily feasible, the presence of AF can interfere with effective CRT as rapid and irregular intrinsic conduction, frequently seen in AF, often inhibits pacing.

For CRT to be effective, a high percentage of paced beats must capture the ventricles on a consistent basis (over 90 to 92% of the time). [19,20] Therefore, in the presence of persistent or permanent AF, seen in up to 20% of CRT recipients,[21,22]

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achieving effective biventricular pacing can be challenging. The use of rate-controlling medications or programming higher pacing rates may be ineffective or result in undesired side effects. As such, AV node (AVN) ablation has become an important therapeutic option to eliminate intrinsic AV conduction and ensure a high percentage of biventricular-paced beats. Here we review the data relevant to CRT in patients with AF and the potential role of AVN ablation in improving outcomes for these patients.

Atrial Fibrillation and Heart Failure

AF and CHF often coexist together, and each portends a worse prognosis for patients with heart disease. The prevalence of AF varies with the severity of heart failure, from less than 10% of those with class I symptoms to as high as 50% of those with class IV symptoms.[23] In a community-based cohort study, 17% of patients with CHF were subsequently diagnosed with AF over a mean follow-up of 4.2 years,[24] which is associated with an increased risk of death or hospitalizations.[24,25] AF contribution to worsening heart failure can be secondary to loss of AV synchrony, faster ventricular rates,[26] or more ventricular rate irregularity.[27] It is also possible that AF is simply a marker of a worse disease process in this patient population.

The presence of structural heart disease and CHF complicates the management of AF. Options for antiarrhythmic medications for rhythm control are limited due to potential toxicities of these drugs. Most recent guidelines recommend only dofetilide or amiodarone as antiarrhythmic options in this population,[28,29] yet limitations still exist, such as limited efficacy, exclusion due to comorbidities, potential harmful drug interactions, and concern about long-term side effects. Finally, pulmonary vein isolation for AF has developed as an important therapy and is highly effective,[30] yet procedural success may be lower in the presence of severe structural heart disease.

In view of the limited efficacy of antiarrhythmic agents, clarity on optimal therapeutic strategies was necessary. The AF-CHF study, a large randomized multicenter study that enrolled 1376 patients, found no significant difference in outcomes for patients randomized to a rate-control versus rhythm-control strategy.[31] However, it may be difficult to achieve acceptable rate-control for all patients with AF and heart failure using medications alone.

For patients unable to achieve adequate rate-control, AVN ablation and implantation of a pacemaker may be performed. However, when pacing is required, patients with structural heart disease tend to do poorly over the long term as a consequence of the detrimental effects of RV apical pacing. In the DAVID trial, 506 patients with standard ICD indications were randomized to backup VVI pacing at 40 bpm, or DDD pacing at 70 bpm. The trial was designed with the hope of demonstrating that DDD pacing was superior, as it would allow up titration of CHF medications, mainly beta-blockers, and therefore improve outcomes. Yet the opposite was observed, as the group randomized to the DDD arm had a significant increase in mortality and hospitalizations for CHF, prompting for the early termination of the study.[32] Since then, and after analysis of other prior studies, RV apical pacing is considered detrimental to patients with CHF due to systolic dysfunction and is best avoided.

CRT for Patients with Atrial Fibrillation and Heart Failure

Cardiac resynchronization therapy has been shown to improve quality of life and survival for patients in sinus rhythm with depressed left ventricular systolic function, wide QRS, and class III or IV heart failure symptoms.[10-12] Left ventricular reverse remodeling was evident with CRT including improved ejection fraction, decreased left ventricular volume, and diminished mitral regurgitation.[33] The initial randomized trials of CRT tended to exclude patients with AF, but emerging data now suggests that heart failure patients with AF also benefit.

Leclerq, et al. first observed an improvement in left ventricular ejection fraction and exercise tolerance in a small group of patients with AF and wide QRS who received a CRT device.[13] In an observational study including 60 patients, the response to CRT was noted to be similar in patients with AF compared to those with sinus rhythm.[14] Subsequently, multiple observational studies, some that included several hundred patients, have found similar outcomes after CRT

for patients with AF compared to those in sinus rhythm,[15,16,18] although one study noted worse survival for those with AF.[17] The improvement in heart failure outcomes was even observed in one study in which no AVN ablation was performed.[16]

The mechanism of improvement in cardiac function in patients with AF is likely multifactorial. For patients in sinus rhythm, CRT may enhance atrio-ventricular synchrony, interventricular synchrony, and intraventricular synchrony leading to reverse remodeling. In addition to the aforementioned benefits, in patients with AF, CRT might also allow for optimal ventricular rate control. Implantation of a CRT device may allow more aggressive rate-controlling drugs to be administered to prevent rapid ventricular rates. Also, a number of patients in these studies were noted to have undergone AV node ablation.

AV Node Ablation as a Rate-Controlling Strategy

A major potential contributor to heart failure symptoms for patients with AF and wide QRS may be uncontrolled ventricular rates. AV node ablation and permanent ventricular pacing have shown to improve symptoms of heart failure in patients with AF regardless of ejection fraction.[34] This "ablate and pace" strategy appears to be highly effective in relieving symptoms from rapid AF with no significant detrimental effect on mortality compared to pharmacological rate control, even when right ventricular pacing is utilized.[35] However, these short term benefits are tempered by the potential detrimental effects of right ventricular apical pacing over the long term, especially in the presence of underlying structural heart disease, mainly systolic dysfunction, as demonstrated in the DAVID trial.

More recent data suggest that biventricular pacing with a CRT device is superior to right ventricular pacing after AVN ablation, especially in patients with structural heart disease. In the PAVE study, randomization to biventricular pacing resulted in greater improvements in six minute walk test, especially for those patients with depressed left ventricular ejection fraction.[36] Furthermore, in patients with AVN ablation who have documented CHF and low systolic function, upgrading from a right ventricular to a biventricular pacing device leads to reduced heart failure symptoms and improved left ventricular ejection fraction.[37-39] More recently, Brignole and colleagues reported their results of a randomized study they conducted involving 186 patients assigned to CRT or RV apical pacing alone after AVN ablation. After a median follow up of 20 months, biventricular pacing resulted in fewer hospitalizations or worsening heart failure symptoms, regardless of ejection fraction and QRS width before the procedure.[40]

These data support the use of AVN ablation and biventricular pacing for patients with palpitations and heart failure symptoms that are attributed to uncontrolled rapid or irregular ventricular rates. Yet, not all patients deteriorate with RV apical pacing, especially those with no evidence of structural heart disease at baseline. Since CRT therapy is associated with higher costs and complication rates than RV apical pacing alone, additional data is required in order to understand who would be the best candidates for CRT after AVN ablation when the ejection fraction is preserved as the outcome after AVN ablation might not be only dependent on ejection fraction but also other mechanisms, such as the autonomic tone. When the ejection fraction is impaired, CRT therapy appears to be superior. Alternatively, not all heart failure patients with AF suffer from rapid ventricular rates, yet they may have ventricular dyssynchrony as evident by a wide QRS, for which cardiac resynchronization may be beneficial.

Assessment of Effective Cardiac Resynchronization

A concern for CRT recipients with AF is whether effective biventricular pacing is being delivered. Rapid or irregularly conducted beats may inhibit pacing such that ventricular dyssynchrony persists. A commonly used measure of the amount of CRT delivered is the percentage of biventricular pacing recorded by the CRT device counter. However, these counters can be misleading as they are unable to assess whether paced beats are fully captured because there is often fusion with intrinsic AV conduction.

Kamath and colleagues used 12-lead Holter monitoring to evaluate patients with AF and CRT.

They demonstrated that the CRT device pacing counters do not accurately quantify the amount of effective biventricular pacing administered to patients with AF; it was often the case that many of the paced beats did not capture or only partially captured due to fusion with the conducted intrinsic complex.[20] In fact, nonresponders to CRT demonstrated a higher percentage of fusion and pseudofusion beats, while responders had a higher percentage of fully paced beats (over 90%). These data suggest that ineffective biventricular pacing due to intrinsic AV conduction may be an important cause for lack of response to CRT in AF patients. Furthermore, the presence of ineffective biventricular pacing may be unapparent from device interrogation alone, and Holter evaluation would be required.

The CRT device may be programmed to a faster pacing rate to ensure biventricular pacing, but these faster rates may be undesirable in some patients, such as those with coronary artery disease and angina. Rate-controlling medications such as beta-blockers, calcium channel blockers, digoxin, or even amiodarone could be administered, but these might be ineffective or the side effects not tolerated. AVN ablation therefore is often considered, as the creation of heart block is naturally the most effective tool in preventing intrinsic AV conduction and augmenting the percentage of effective biventricular pacing in those who require it.

AV Node Ablation to Promote Biventricular Pacing

There are no randomized trials that test the effect of AVN ablation on outcomes for heart failure patients with AF who are receiving CRT for wide QRS. Several recently published observational studies provide some insight into the potential role of AVN ablation for these patients (Table).

Gasparini, et al. described the outcomes of consecutive patients with AF and heart failure with a wide QRS who received CRT devices at two centers in Europe.[15] Those patients who had less than 85% biventricular pacing on device interrogation underwent AVN ablation. Compared to patients in sinus rhythm with CRT devices, those in AF who underwent AVN ablation had similar improvements in echocardiographic parameters and functional capacity. Interestingly, those who did not have AVN ablation performed were significantly less likely to respond to CRT with no significant change in left ventricular ejection fraction. In a subsequent analysis of mulitcenter registry data, similar results were observed.[41] Those heart failure patients with a CRT device and AF who were treated with negative chronotropic drugs had a higher mortality rate compared to patients who underwent AVN ablation.

Consistent with the above results, Ferriera, et al. found that AVN ablation performed after CRT in patients with AF was associated with lower mortality and a higher CRT response rate.[42] There was also a higher rate of hospitalization for heart failure for those patients who did not have AVN ablation performed. Most recently, Dong et al. analyzed the outcomes after CRT-D implant in 154 patients with heart failure, QRS greater than 120 msec, AF and depressed ejection fraction.[43] They observed improved survival and greater improvement in NYHA class for those patients who received AVN ablation compared to those who did not have ablation performed. It is noted that in this study, those patients who did not receive AVN ablation still had a median percentage of biventricular pacing of 96%, although only device counters were used. More effective biventricular pacing in this group might account for the similar improvement in echocardiographic parameters that was observed for AF patients after AVN ablation compared to those in normal sinus rhythm in this study. The observational nature of these studies limits the interpretation of the results, as selection bias or unmeasured confounding variables may have influenced the differences in outcomes between those who did or did not have AVN ablation performed. Specifically, patients who did not receive AVN ablation in the multicenter registry tended to have lower ejection fraction and wider QRS duration at baseline, suggesting they had more severe cardiac disease.[41] Also, the effectiveness of biventricular pacing in AF patients was generally measured using the CRT device counters, which have been shown to overestimate the percentage of effective biventricular pacing.[20] Those patients with less effective biventricular pacing would be expected to more likely benefit from AVN ablation. Furthermore, large-scale randomized trials are necessary to reproduce the effect of the procedure on global outcome over the long-term for

Table 1: Observational studies of CRT patients with atrial fibrillation for whom AVN ablation was or was not performed

Reference	Number of patients	Findings associated with AVN ablation compared to no AVN ablation
Molhoek et al. 2004[14]	17	Similar improvement in NYHA class NYHA class Similar improvement in LVEF
Gasparini et al. 2006[15]	114	Improved LVEF Improved NYHA class improved functional capacity score
Delnoy et al. 2007[18]	21	Not reported
Gasparini et al. 2008[41]	117	Improved survival
Ferreira et al. 2008[42]	26	Greater improvement in NYHA class Fewer HF hospitalizations
Tolosana et al. 2008 [17]	19	Fewer HF hospitalizations
Dong et al. 2010[43]	45	Improved survival greater improvement in NYHA class (No difference in improvement in LVEF)

+AVN Abl, AVN ablation was performed; -AVN Abl, AVN ablation was not performed; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HF, heart failure; CRT, cardiac resynchronization therapy

this population.

Potential Limitations

The disadvantages of AVN ablation should be considered before pursuing this procedure on all patients. The procedure itself carries a small risk of complications at the venous access site or damage to cardiac or vascular structures. Ventricular fibrillation and sudden death have been observed following AVN ablation, although this complication may be prevented by initially programming the pacemaker to a higher pacing rate.[44] In fact, sympathetic nerve activity increases after AVN ablation, which might contribute to the incidence of post-ablation arrhythmia. Interestingly, sympathetic nerve activity is decreased if patients are programmed to faster rates after the ablation.[45] Patients are generally rendered pacemaker dependent after AVN ablation, and as such there is the potential for life-threatening bradyarrhythmia to occur in the event of pacemaker malfunction. Oversensing of diaphragmatic myopotentials has been observed in pacemaker-dependent patients with CRT devices, notably with integrated bipolar right ventricular leads, which has resulted in inhibition of pacing, inappropriate shocks, and potentially death.[46] As such, dedicated bipolar lead systems should be considered in these instances. When AVN ablation results in a slower ventricular escape rhythm, this was associated with worse outcomes in one study.[47] In the event of device complications or infections, prolonged hospitalizations may be required for treatment before a new device can be implanted.

Not all patients with heart failure and electrical dyssynchrony benefit with CRT, and some patients may become worse. By promoting more biventricular pacing, AVN ablation could be detrimental for these nonresponders. Suboptimal left ventricular lead positions, notably anterior or apical positions, are associated with worsening heart failure in CRT recipients.[48,49] An increase in ventricular tachyarrhythmia has been reported with biventricular pacing and may be a significant problem in patients who do not respond to CRT.[50-52] In addition, some patients in AF may return to sinus rhythm after CRT is implemented such that AVN ablation is no longer required.[53]

An important question that remains is what is the optimal percentage of pacing that leads to clinical benefits? Although there is consensus that at least 90% capture on Holter should be achieved, it is not clear whether an even higher number (such as over 95%) would be superior and therefore considered as a target. Additional data would be required to answer this and other questions.

Conclusions

Cardiac resynchronization therapy remains an effective treatment for patients with heart failure and wide QRS whether they are in sinus rhythm or AF. The presence of AF may prove to be an obstacle to effective biventricular pacing in these patients, as intrinsic conduction can preclude

the patient from achieving the high percentage of pacing required to achieve full benefit from CRT. An accurate assessment of the effectiveness of CRT may not be apparent from the device interrogation alone, as fusion and pseudofusion would not be detected. AVN ablation is effective in ensuring a high percentage of biventricular pacing in most patients with AF. Observational studies have shown that the performance of AVN ablation in patients with heart failure and AF with a CRT device is associated with improved survival and a higher CRT response rate, although selection bias and unmeasured confounding variables may limit the interpretation of these results. A randomized controlled trial testing the effect of AVN ablation on clinical outcomes for patients with AF who are candidates for CRT is indicated. Until the results of such trial are available, the decision to perform AVN ablation must be made on an individual basis, but strong consideration must be given to patients with AF and CHF who fail to respond to CRT and who have less than optimal percentage of biventricular pacing as demonstrated by Holter monitoring.

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