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# Atrioventricular Nodal Catheter Ablation in Atrial Fibrillation Complicating Congestive Heart Failure

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**Abstract**

**The development of atrial fibrillation (AF) during the course of the evolution of heart failure (HF) worsens the clinical outcomes and the prognosis accounting for an enormous economic burden on healthcare. AF is considered to be an independent predictor of morbidity and mortality increasing the risk of death and hospitalization in 76% in HF patients. Despite the good clinical results obtained with conventional pharmacological agents and different new drugs, the optimal medical treatment can fail in the intention to improve symptoms and quality of life of HF patients with severe left ventricular dysfunction and AF with uncontrolled ventricular rate. Therefore, the necessity to utilize cardiac devices to perform cardiac resynchronization therapy (CRT), or the need to use catheter ablation, or both, emerges facing the failure of optimal medical treatment in order to achieve hemodynamic improvement. Some of these AF patients will require atrio-ventricular nodal (AVN) catheter ablation in order to restore 100% CRT functionality and improvements in clinical outcomes. It is hard to imagine that the deliberate destruction of a natural and normally functional specialized tissue of the main conduction system of the heart would do any good. However, in the presence of AF with rapid ventricular response due to normal conduction through the AV node in HF patients, the fast ventricular rate can cause deleterious consequences in the clinical outcome. Moreover, there are interesting published data which will be analyzed in this manuscript documenting significant acute and long-term improvement in left ventricular function, symptoms, exercise tolerance, clinical outcomes, and quality of life in selected HF patients with paroxysmal and persistent drug-refractory AF who have undergone AVN ablation and permanent pacemaker implantation.**

## Introduction

Atrial fibrillation (AF) and heart failure (HF) are common cardiovascular entities with high comorbidities and mortality and severe prognostic implications. The development of AF during the course of the evolution of HF worsens the clinical outcomes and the prognosis accounting for an enormous economic burden on healthcare[1-5]. Once AF develops, it generates rapid ventricular response, irregularity of ventricular rhythm, loss of organized atrial contribution to cardiac output, and in some cases, tachycardia-induced cardiomyopathy[6-13]. It has been shown that aging has a profound impact on the histological and thus, electrophysiological changes in the human atrial myocardium which contribute to the higher prevalence of AF in the elderly[14-20]. The prevalence of AF in patients with advanced HF reaches up to 40%. AF is considered to be an independent predictor of morbidity and mortality increasing the risk of death and hospitalization in 76% in HF patients[11-13].

Despite the good clinical results obtained with conventional pharmacological agents and different new drugs, the optimal medical treatment can fail in the intention to improve symptoms and quality of life of HF patients with severe left ventricular dysfunction and AF with uncontrolled ventricular rate[21-24]. Therefore, the necessity to utilize cardiac devices to perform biventricular pacing, or the need to use catheter ablation, or both, emerges facing the failure of optimal medical treatment in order to achieve hemodynamic improvement and correction of the physio-pathological alterations. Several clinical studies with cardiac devices performing biventricular pacing demonstrated structural and functional ventricular improvement. In addition, there are beneficial effects of this so called cardiac resynchronization therapy (CRT) in left ventricular remodeling. There was a significant improvement in left ventricular ejection fraction, and a significant decrease in end systolic and end diastolic volumes at 3 months of follow-up[25,26]. Importantly, these beneficial effects are dependent on continuous bi-ventricular stimulation since interruption of electric stimulation produce a progressive but not immediate loss of effect. However, CRT may be interrupted in over one-third of patients after successful implantation of a device and the most common reason for CRT interruption is the development of AF (18%). Indeed, almost one fifth of patients who undergo successful implantation of a defibrillator capable of delivering CRT experience an AF with a rapid ventricular response, which at least temporarily results in the inability to deliver CRT[25-27]. Some of these patients will require atrioventricular nodal (AVN) catheter ablation in order to restore 100% CRT functionality and improvements in clinical outcomes. Therefore, it is the aim of this manuscript to analyze the interesting published data documenting significant acute and long-

## Key Words

AVN Ablation, Atrial Fibrillation, Heart Failure, Pacemaker Implantation.

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term improvement in left ventricular function, cardiac performance, symptoms, exercise tolerance, clinical outcomes, and quality of life in selected HF patients with paroxysmal and persistent drug-refractory AF who have undergone AVN ablation and permanent pacemaker implantation.

## Atrioventricular Nodal Catheter Ablation

In 1982, way before the existence of current techniques for catheter ablation of atrial fibrillation, Gallagher JJ et al described the percutaneous catheter technique for the ablation of the atrioventricular conduction system[28]. It is hard to imagine that the deliberate destruction of a natural and normally functional specialized tissue of the main conduction system of the heart would do any good. However, in the presence of AF with rapid ventricular response due to normal conduction through the AV node, the fast ventricular rate can cause deleterious consequences in the clinical scenario. There is a further frank deterioration in the outcome if the left ventricle is dysfunctional. Therefore, catheter ablation of the AV node was utilized to create complete AV conduction block in order to control the ventricular rate in AF patients[28]. In order to preserve a junctional escape rhythm, catheter ablation of the proximal AV junction is performed. Hence, ablation is usually targeted at the atrial side of the annulus in the region of the compact AV node in the vicinity to the anterior border of the coronary sinus ostium [Figure 1]. Ablation of the AV node does not restore physiologic atrial systole and associated atrial transport. Therefore, the beneficial effects of catheter AVN ablation are mediated primarily by restoration of physiologic rate and possibly by regularization of the ventricular response to concomitant AF[29-33]. Although those symptoms that result from a fast and irregular ventricular rate may show dramatic improvement, the symptoms that occur from the loss of atrial contraction and AV synchrony are unlikely to improve. This procedure leads to rate control but not rhythm control, hence, the atria will keep on fibrillating, and the ventricular response will dependent on the implanted permanent pacemaker [34-39].

## Clinical Outcomes in AVN Ablation Studies

In general, several retrospective studies, randomized control studies, and meta-analysis reported beneficial evidence that AVN catheter ablation followed by permanent pacemaker implantation are a valuable palliative therapy for highly symptomatic, drug-refractory AF patients. Many retrospective studies have documented significant acute and long-term improvement in left ventricular function, symptoms, cardiac performance, exercise tolerance, clinical outcomes, and quality of life in selected patients with paroxysmal and persistent drug-refractory AF who have undergone AVN ablation and permanent pacemaker implantation[30-37].

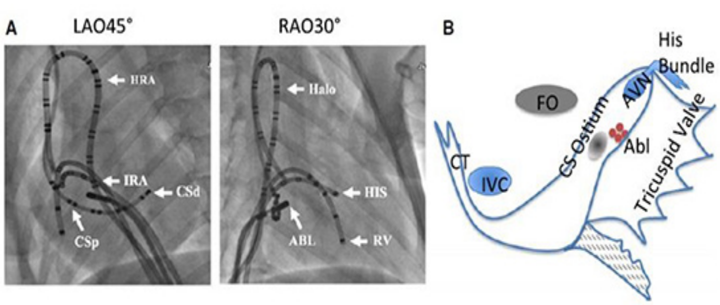


**Figure 1: This figure depicts radiofrequency AVN ablation at the bottom of Koch's triangle. A: Catheter position. B: Koch's triangle and ablation sites.**

ABL: indicates radiofrequency ablation sites. CSd: distal coronary sinus. CSp: proximal coronary sinus. CT: crista terminalis. FO: fossa ovalis. Halo: Halo catheter. HIS: His bundles. HRA: high right atrium. IRA: inferior right atrium. IVC: inferior vena cava. LAO: left anterior oblique. RAO: right anterior oblique. RV: right ventricle. Reprinted with permission from Yin X, et al. Atrioventricular Node Slow-Pathway Ablation Reduces Atrial Fibrillation Inducibility: A Neuronal Mechanism. J Am Heart Assoc. 2016;5:e003083 doi:10.1161/JAHA.115.003083.

There have also been several randomized controlled trials comparing AVN ablation followed by pacemaker insertion strategy with medical therapy[40-43]. Brignole M et al observed that ablation and placement of a DDDR mode-switching pacemaker were highly effective and superior to drug therapy in controlling symptoms and improving quality of life in patients with intolerable paroxysmal AF not controlled with antiarrhythmic drugs[43]. The same authors found similar finding in patients with chronic AF who had clinically manifest HF and underwent VVIR pacemaker implantation after AVN ablation[42]. Like these two mentioned studies by Brignole et al, which all together had only 109 patients, many of the randomized studies had small number of patient and could have been affected by patient selection bias. On the other hand, those clinical studies examining patients with paroxysmal AF may not have demonstrated improvements in exercise tolerance because of the intermittent nature of the tachyarrhythmia. Additionally, hemodynamic improvements may be subjected to the etiology of the left ventricular dysfunction and may only happen in patients with tachycardia cardiomyopathy, which is known to be mostly a reversible entity[37,39,42,44].

Some meta-analysis reported also beneficial evidence in favor of AVN catheter ablation followed by permanent pacemaker implantation in symptomatic, drug-refractory AF patients. Wood MA et al.[45] examined 1181 patients from 21 different studies and found that exercise duration, ejection fraction, quality of life, symptoms, and hospital admissions improved significantly. In their meta-analysis they observed that the only parameter that did not reach statistical significance was LV fractional shortening. However, this last parameter showed a tendency towards improvement. Chatterjee NA et al.[46] analyzed a total of 5 randomized or prospective trials with a total of 314 patients for efficacy review, another 11 studies (810 patients) for effectiveness review, and 47 studies (5632 patients) for safety review. These authors found in their meta-analysis that in the therapeutic management of refractory AF, AVN catheter ablation is associated with improvement in symptoms and quality of life, with a low incidence of procedure morbidity[46]. In addition, in patients with reduced systolic function, AVN ablation demonstrated also significantly improved echocardiographic outcomes relative to medical therapy alone. However, their results demonstrated also that there was no statistical difference in all-cause mortality, exercise duration, and left ventricular ejection fraction between AVN ablation and medical therapy groups[46].

## Permanent Pacing After AVN Catheter Ablation

In order to avoid the deleterious effects of long-term right ventricular pacing on left ventricular function after AVN catheter ablation[47], biventricular pacing, to implement cardiac resynchronization therapy, has been proposed as an alternative to right ventricular pacing. CRT significantly reduces hospitalizations for HF, and significantly improves functional capacity, and left ventricular function, volumes and diameter in comparison with

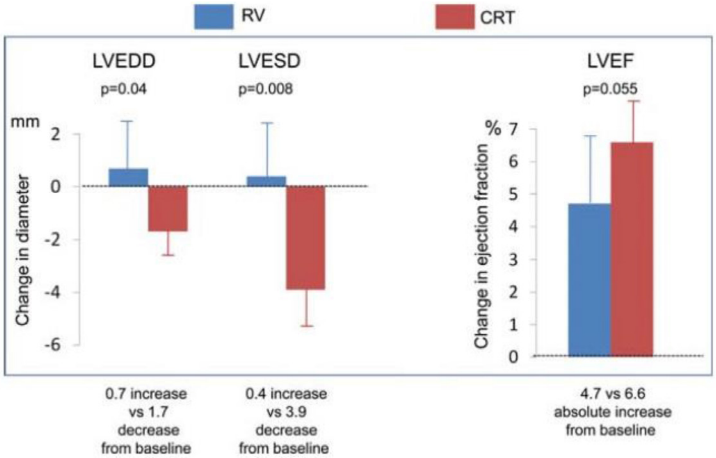


Figure 2: **Mean changes in echocardiographic left ventricular diastolic and systolic diameters and ejection fraction between baseline and 6-month follow-up.**

RV: right ventricular pacing. CRT: cardiac resynchronization therapy. LVEDD: Left ventricular end diastolic diameter. LVESD: Left ventricular end systolic diameter. LVEF: Left ventricular ejection fraction. Reprinted with permission from Brignole M, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. Eur Heart J 2011;32:2420-2429.

right ventricular pacing only [Figure 2][48-50]. Therefore, the current guidelines recommend CRT in patients with AF and left ventricular dysfunction who are candidates for AVN catheter ablation with an indication IIa level of evidence B[51,52]. Indeed, AVN ablation followed by CRT is an established strategy for improving symptoms and morbidity in patients with permanent AF, reduced left ventricular ejection fraction, and uncontrolled ventricular rate.

Patients with AVN ablation become totally pacemaker dependent with iatrogenic chronotropic incompetence. They lose the ability to increase their heart rate appropriately during physical activity. However, this condition may be corrected by the use of rate-adaptive pacing. In this context, Palmisano P et al[53] performed a prospective, randomized, single-blind, multicenter study that was designed as an intra-patient comparison and enrolled 60 patients with refractory AF and reduced left ventricular ejection fraction treated with AVN ablation and biventricular pacing. They compared the clinical effects on exercise capacity of rate-responsive pacing versus fixed-rate pacing in CRT. They found that rate-responsive pacing yields a significant gain in exercise capacity, which seems to be related to the induced increased heart rate during physical exercise [Figure 3A&B]. However, these good results with CRT were not observed with right ventricular pacing alone in another smaller study in patients with preserved left ventricular systolic function[54]. We have to keep in mind that while rate-responsive pacing can help these patients to adapt their cardiac output to increasing metabolic requirements during exercise, it can also elicit an inappropriate and excessive increment in heart rate with possible deleterious effects[55]. This is especially true in pacemakers based on motion sensors in patients with AF and left ventricular dysfunction. An excessive increase in heart rate could further worsen the left ventricular diastolic function, which is already compromised by reduced compliance, and the absence of the atrial systole[56-59].

## Collateral Adverse Effects of the Ablate and Pace Approach

Probably the main concern with this "ablate and pace" approach is sudden cardiac death. Twenty years ago Geelen P, et al[60] roused some concern about AVN catheter ablation and permanent pacemaker implantation. They stated that this approach may predispose patients to an increased risk of sudden cardiac death[60]. Early studies are conflicting however, with 1 year sudden death rates varying from 0 to 9%[45,61]. It is important to note that the vast majority of those who experienced sudden cardiac death in the early studies had a significant number of risk factors, including reduced left ventricular function, advanced HF, and a history of ventricular arrhythmias[62,63]. Since the probable mechanism of sudden cardiac death is bradycardia-dependent prolongation of the QT interval, this may be counteracted by incrementing the pacemaker frequency[60,64]. It was recommended to set the pacemaker at a ventricular pacing rate of minimum of 90 bpm for the first 1 to 2 months following the ablation, and then reducing it to a conventional 60 to 70 bpm [60,65]. This latter approach was corroborated by large studies with long-term follow-up which demonstrated a low incidence of sudden cardiac death[66,67]. Bradley DJ et al.[68] demonstrated an all-cause mortality of 3.5% with AVN ablation and 3.3% with drug therapy at 1 year of follow-up in their

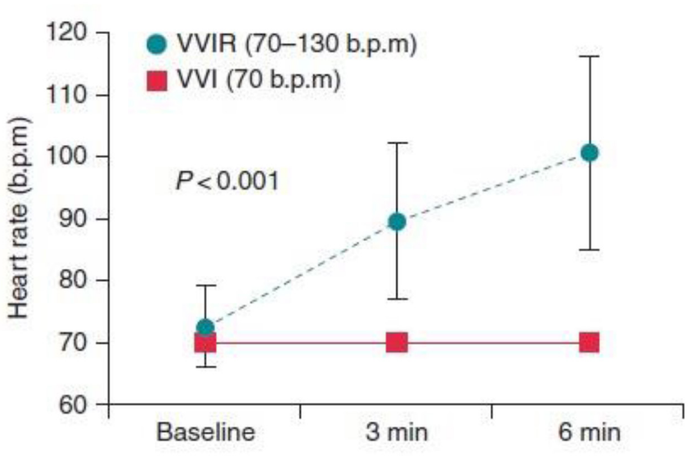


Figure 3A: **A-Mean heart rate during six-minute walking test in VVI pacing mode (solid line) and in VVIR pacing mode (dotted line).**

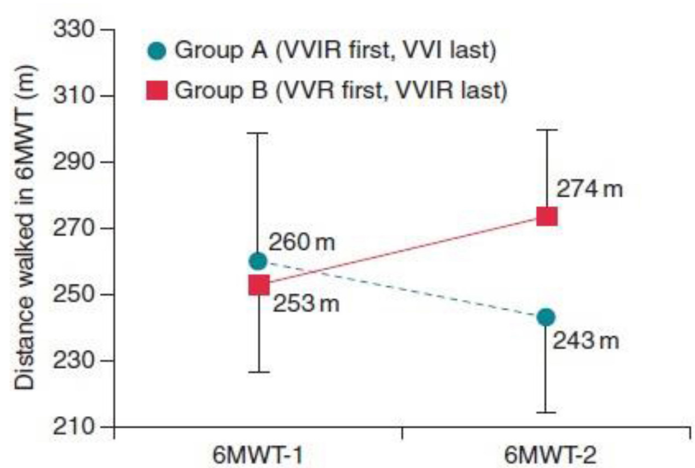


Figure 3B: **B-Mean distance walked during six-minute walking test-1 and 2 by Group A and Group B patients.**

Group A began exercising with VVIR pacing mode first, and then VVI pacing mode last. Group B began exercising with VVI pacing mode first, and then VVIR pacing mode last. Reprinted with permission from Palmisano P, et al. Effect of fixed-rate vs. rate-RESPONSIve pacing on exercise capacity in patients with permanent, refractory atrial fibrillation and left ventricular dysfunction treated with atrioventricular junction aBLation and bivEntricular pacing (RESPONSIBLE): a prospective, multicentre, randomized, single-blind study. Europace 2017;19:414-420.

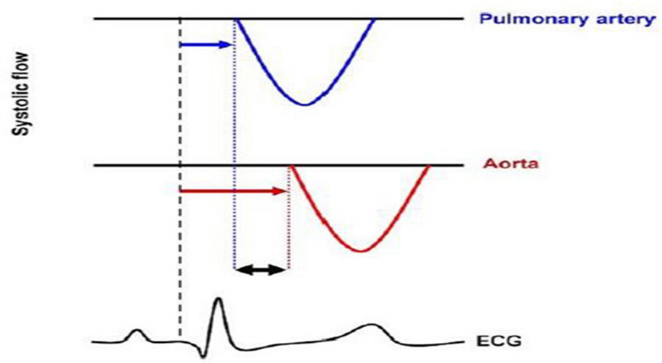


Figure 4A: Schematic representation of interventricular dyssynchrony during RV apical pacing for assessment of interventricular dyssynchrony. The electrocardiogram (ECG) and systolic flow through the pulmonary artery and aorta assessed with Doppler echocardiography are typically used. Both the right ventricular (RV) and left ventricular (LV) electromechanical delay are measured from the onset of the QRS complex (dashed line). The RV electromechanical delay is the time from the onset of QRS interval to the onset of pulmonary systolic flow (blue arrow). The LV electromechanical delay is the time from the onset of QRS complex to the onset of aortic systolic flow (red arrow). Subsequently, the interventricular dyssynchrony can be calculated as the difference between the RV and the LV electromechanical delays (black arrow).

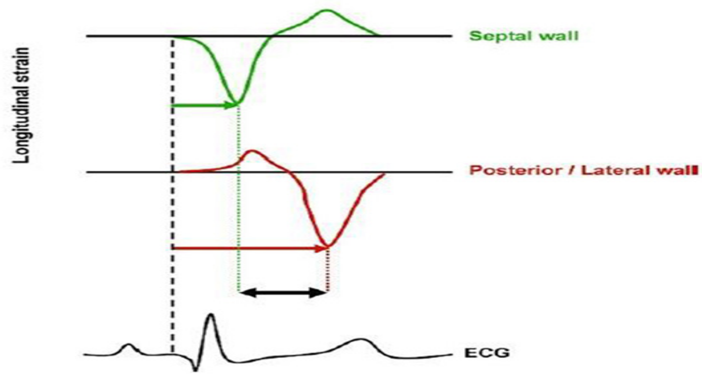


Figure 4B: Schematic representation of intraventricular dyssynchrony during RV apical pacing. Intraventricular dyssynchrony is represented by the delay in mechanical activation between different segments within the LV. In this example, longitudinal strain curves of the septum and the posterior or lateral wall are demonstrated. The time from onset of the QRS complex to peak systolic strain for the septum (green arrow) and the posterior or lateral wall (red arrow) is indicated. The difference in time-to-peak strain for the various segments is the delay in mechanical activation, or LV intraventricular dyssynchrony (indicated by the black arrow). Reprinted with permission from Tops LF, et al. The effects of right ventricular apical pacing on ventricular function and dyssynchrony: implications for therapy. J Am Coll Cardiol 2009;54:754-776.

meta-analysis of randomized trials comparing AVN catheter ablation with permanent pacemaker implantation and drug therapy. In a recent meta-analysis, Chatterjee et al.[46] reported that the incidence of procedure-related mortality within 30 days of AVN ablation was 0.27% among 4886 patients from 42 studies. At a mean follow-up of 26.5 months, the incidence of sudden cardiac death after AVN catheter ablation was 2.1%.

The heart rate post-AVN catheter ablation plays an important role in sudden cardiac death[46]. Ozcan C et al.[63] observed an overall rate of sudden death after AVN ablation and permanent pacemaker implantation of 2.1% when pacing at a lower rate limit of 60 bpm. On the other hand, Wang RX et al.[69] found that the rate of sudden death decreased to 0.2% when pacing at an initial lower rate of 90 bpm. These results suggested that AVN catheter ablation predisposed patients to bradycardia dependent pro-arrhythmia. Therefore, it is necessary to utilize this pacing rate algorithm in order to improved clinical outcomes and survival[69].

There are uncertainties about the exact mechanism underlying sudden cardiac death after AVN catheter ablation. It has been reported that long-term right ventricular pacing can induce electrical and mechanical LV inter-ventricular and intra-ventricular dyssynchrony in almost 50% of patients[70-[73] [Figure 4]. Yan et al.[73] reported that ventricular dyssynchrony is associated with pro-arrhythmic repolarization dispersion. Chronic dyssynchrony leads to chamber remodeling of both early- and late-activated segments[74]. Experimental studies have shown that LV pacing via the coronary sinus promotes arrhythmogenesis due to a pacing-induced increase in QTc and QT dispersion with increased transmural dispersion of repolarization involving the mid-myocardial M cells[75]. Medina-Ravel VA et al.[76] suggested that CRT may enhance arrhythmogenicity by reversing the normal depolarization pattern from endocardium to epicardium, which enhances transmural dispersion of repolarization and propagation of early afterdepolarizations[76]. In addition, pacing-induced changes in QTc and QT dispersion may be related to the risk of sudden cardiac death in patients undergoing CRT[77,78]. Nowadays, sudden cardiac death is not a subject of concern in the "ablate and pace" approach[79,80] [Figure 5]. The 1 year total mortality is 6.3% and the rate of sudden cardiac death is only 2%, which is similar to that of control patients with atrial fibrillation who remain on drug therapy [45,66].

Another concern with this "ablate and pace" approach is the subsequent alteration of the left ventricular function due to permanent right ventricular apical pacing. Some studies asserted conceived concern about rendering a patient dependent upon right ventricular apical pacing following AVN catheter ablation stating that it may lead to further deterioration in left ventricular function[44,81-83]. Right ventricular apical pacing can cause harmful effects due to ventricular dyssynchrony, remodeling, and prolonged QRS durations[81]. It has been observed that constant right ventricular apical pacing may lead to increased mortality, and hospital admissions due to HF, especially in patients who already have significantly impaired left ventricular function[82]. However, there is an interesting controversy on this subject in the published studies. Indeed, the effect on left ventricular function and clinical outcomes of HF are not consistent in the literature, with some studies showing some degree of deterioration [44,83] with others showing no significant change[37,42], and several other studies demonstrating an overall improvement[34,37,39,45]. This important discrepancy may be related to the high proportion of patients with normal left ventricular function included in the majority of studies. In addition, it may also be associated to the initial mechanism of left ventricular dysfunction and HF symptoms. For example, patients with tachycardia cardiomyopathy, show reversible changes when appropriate rate control is achieved. Ozcan C et al.[66] showed that long-term survival after AVN catheter ablation was comparable with that in AF patients with pharmacological therapy. Moreover, when adjusted for underlying heart disease, survival

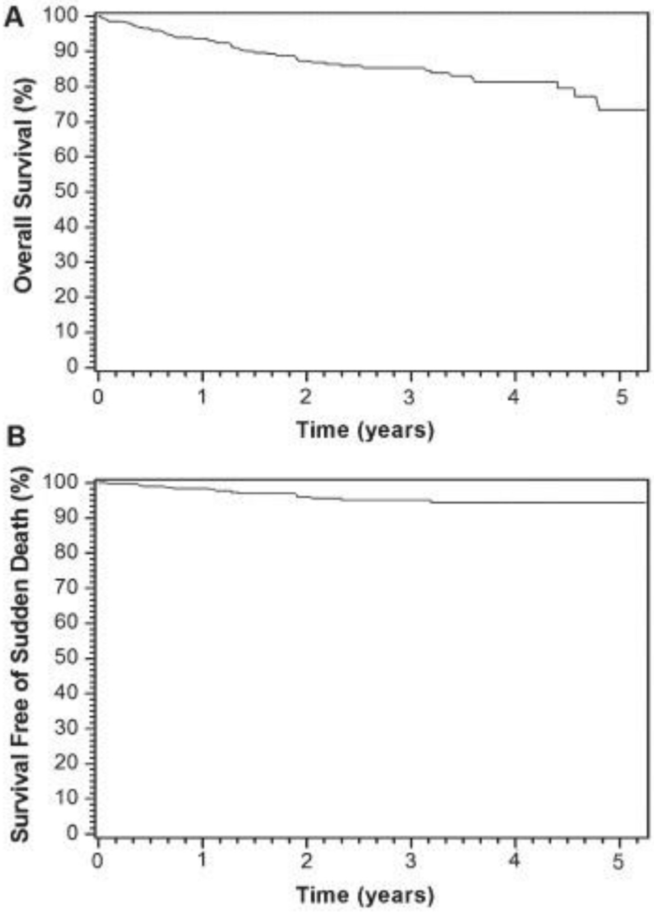


Figure 5: Kaplan-Meier estimated (A) overall survival and (B) survival free of sudden death in patients who underwent atrioventricular junction ablation and device implantation. Reprinted with permission from Wang RX, et al. Sudden death and its risk factors after atrioventricular junction ablation and pacemaker implantation in patients with atrial fibrillation. Clin Cardiol 2017;40(1):18-25.

was similar to the expected survival in the general population. Bjorkenheim A. et al.[83] showed that long-term right ventricular pacing was not harmful in the majority of AF patients after AVN catheter ablation. They identified hypertension and previous HF as independent predictors of all-cause mortality, and prolonged QRS duration and left atrial diameter as predictors of hospitalization for HF during long-term follow-up[83]. They also found that all-cause mortality occurred in 22%, which is similar to the 26% in the study of Tan ES et al[84]. This latter study had a slightly shorter follow-up period[84]. The PAVE study[49]randomized 184 patients with a mean left ventricular ejection fraction of 46% to biventricular pacing or right ventricular pacing. In 83% of the patients, class II or III heart failure was present. Both groups showed an improvement in 6 min walk distance compared with baseline. Of interest is that the two pacing modalities did not differ until 6 months after the procedure, when a small deterioration in the right ventricular pacing group resulted in a significant difference between the two groups. The right ventricular pacing group showed a significant fall in left ventricular ejection fraction within 6 weeks which persisted at 6 months[49]. On the other hand, the ejection fraction in the biventricular pacing group did not change from baseline values. Patients with impaired left ventricular function at baseline who underwent biventricular pacing showed the greatest improvement. Furthermore, patients with class II or III heart failure who received biventricular pacing improved significantly more than those who received right ventricular pacing. There was a 14% failure of left ventricular lead implantation[49].

## Alternative Pacing Modalities

Besides CRT, several pacing techniques have been used to subside the potential alterations of right ventricular apical pacing, including right septal, right ventricular outflow tract, para-Hisian, and direct His bundle pacing. Direct His bundle pacing produces an activation sequence closest to normal physiological activation, and in dilated cardiomyopathy, patients can avoid further deterioration in left ventricular ejection fraction[85-87]. Occhetta E, et al.[88] in a crossover, blinded, randomized study demonstrated good results in the prevention of ventricular desynchronization by permanent para-Hisian pacing after AVN catheter ablation in chronic AF patients. They found that in those HF patients with cardiac co-morbidities and reasonably better left ventricular function, para-Hisian pacing produces improvements in functional status and exercise capacity when comparing to those patients with right ventricular apical pacing[88]. Huang W, et al.[89] demonstrated that permanent His bundle pacing is safe and stable in HF patients with AF who had narrow QRS and underwent AVN catheter ablation. They observed a significant improvement in functional class, and echocardiographic left ventricular ejection fraction, and reduction in the utilization of diuretics in the HF therapeutic management. The success of the His bundle pacing depends upon several factors. The distal portion of the His-Purkinje system to the pacing site should be normal. In addition, the AVN catheter ablation should be performed at the atrial site of the AV node rather than at the site of the His bundle. Considering that patients are rendered pacing dependent permanently, there are also concerns about the stability of an active fixation lead at a site so close to the tricuspid valve. The results of septal and outflow tract pacing are inconclusive [90,91]. Twidale N, et al. in a comparative trial in patients with congestive HF and uncontrolled AF demonstrated that complete AV node ablation and pacemaker permanent implantation delivers a more substantial improvement in exercise capacity, quality of life, and left ventricular ejection fraction than AVN modification [61].

## Conclusions

There is significant acute and long-term improvement in left ventricular function, cardiac performance, symptoms, exercise tolerance, clinical outcomes, and quality of life in selected HF patients with paroxysmal and persistent drug-refractory AF who have undergone AVN ablation and permanent pacemaker implantation. In this context, biventricular pacing is superior to right ventricular apical pacing, and even better with rate-responsive pacing modality which yields a significant gain in exercise capacity due to the induced increased heart rate during physical effort. Current guidelines recommend CRT in patients with AF and left ventricular dysfunction, whom are candidates for AVN catheter ablation with an indication IIa level of evidence B. Caution should be exerted since there is serious concern and controversial results with alternative pacing modalities.

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