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A review on atrioventricular junction ablation and pacing for heart rate control of atrial fibrillation

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Abstract

Atrioventricular junction ablation with permanent pacemaker implantation is a highly effective treatment approach in patients with atrial fibrillation and high ventricular rates resistant to other treatment modalities, especially in the elderly or those with severe comorbidities. Compared with pharmacological therapy alone, the so-called "ablate and pace" approach offers the potential for more robust control of ventricular rate. Atrioventricular junction ablation and pacing strategy is associated with improvement in symptoms, quality of life, and exercise capacity. Given the close relationship between atrial fibrillation and heart failure, there is a particular benefit of such a rate control in patients with atrial fibrillation and reduced systolic function. There is increasing evidence that cardiac resynchronization therapy devices may be beneficial in selected populations after atrioventricular junction ablation. The present review article focuses on the current recommendations for atrioventricular junction ablation and pacing for heart rate control in patients with atrial fibrillation. The technique, the optimal implantation time, and the proper device selection after atrioventricular junction ablation are also discussed.

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1 Introduction

Atrial fibrillation (AF) has been associated with an increased all-cause mortality, long-term stroke risk, heart failure, and impaired quality of life (QoL).[1–3] In particular, AF and heart failure are inextricably linked, sharing common risk factors while each adversely affects the other.[3] An uncontrolled rate-control therapy may lead to severe systolic dysfunction and heart failure.[3] Several mechanisms of tachycardia-induced left ventricular dysfunction have been proposed, including myocardial ischemia with depressed contractility, depletion of high energy phosphate stores, activation of the sympathetic nervous system renin-angiotensin system and depletion of atrial natriuretic factor and oxidative stress and oxidative damage.[4–7] Symptoms referable to AF are often severe and difficult to control with drugs. Randomized controlled trials have shown that rate-control therapy is not inferior to rhythm-control therapy.[8,9] Non-pharmacologic options include atrioventricular junction ablation (AVJA) with permanent pacemaker implantation and catheter left atrial ablation to maintain sinus rhythm, respectively. AVJA with permanent pacemaker implantation is a highly effective treatment approach in AF patients with high ventricular rates resistant to other treatment modalities, especially in the elderly or those with severe comorbidities. AVJA aims to modify the atrioventricular conduction or to perform complete atrioventricular block.[10,11] Compared with pharmacological therapy alone, the so-called "ablate and pace" approach offers the potential for more robust control of ventricular rate as well as regularization of the R-R intervals. Given the relationship between AF and HF, there may be a particular benefit of such a rate and interval control in patients with AF and reduced systolic function. There are increasing evidences that cardiac resynchronization therapy (CRT) devices may be beneficial in selected populations after AVJA.[12,13] The present review focuses on the current recommendations for AVJA and

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pacing for heart rate control of AF. The technique and the optimal implantation time are also described.

2 Current recommendations for AVJA and pacing

ACC/AHA/HRS atrial fibrillation practice guidelines[12,13] recommend that AVJA with permanent ventricular pacing is a reasonable strategy to control the heart rate in AF, when pharmacological therapy is inadequate and rhythm control cannot be achieved (Class IIa, level of evidence B).

ESC guidelines[14] recommend that AVJA should be considered when the rate cannot be controlled with pharmacological agents and when AF cannot be prevented by anti-arrhythmic therapy or is associated with intolerable side effects, and direct catheter-based or surgical ablation of AF is not indicated, has failed, or is rejected (Class IIA, level of evidence B). AVJA should be considered for patients with permanent AF and an indication for CRT [NYHA functional class III or ambulatory class IV symptoms despite optimal medical therapy, left ventricular ejection fraction (LVEF) < 35%, QRS width > 130 ms] (Class IIA, level of evidence B). In patients with any type of AF and severely depressed LV function (LVEF < 35%) and severe heart failure symptoms (NYHA III or IV), biventricular stimulation should be considered after AVJA (Class IIA, level of evidence C). AVJA should be considered for CRT non-responders in whom AF prevents effective biventricular stimulation and amiodarone is contraindicated (Class IIA, level of evidence C). AVJA is useful for optimal rates of biventricular pacing. Ablation of the AV node to control heart rate may be considered when tachycardia-mediated cardiomyopathy is suspected and the rate cannot be controlled with pharmacological agents, and direct ablation of AF is not indicated, has failed, or is rejected (Class IIB, level of evidence C). AVJA with consecutive implantation of a CRT device may be considered in patients with permanent AF, LVEF < 35%, and NYHA functional class I or II symptoms on optimal medical therapy to control heart rate when pharmacological therapy is insufficient or associated with side effects (Class IIB, level of evidence C). CRT should be considered in patients with reduced LVEF who are candidates for AVJA for rate control (Class IIA, level of evidence B).[15] AVJA should not be attempted without a prior trial of medication, or catheter ablation for AF, to control the AF and/or ventricular rate in patients with AF.[12–15]

3 Catheter ablation of the AV junction

In the 1998 NASPE Prospective Catheter Ablation Registry, AVJA was acutely successful in 97.4% of cases, while 3.5% had recurrence of AV conduction during follow up.[16] In a report from the prospective Ablate and Pace trial, the procedure was successful in all but one of 156 patients who underwent RFA of the AV node.[17] From 2008 until 2014, we performed 90 AVJA procedures. The acute success rate of the method was 97.8%. A left-sided approach was attempted in two cases. Recurrent AV conduction during follow-up was seen in 3% of cases.

Ideally, the objective of AVJA is to ablate the compact AV node leaving a stable ideally junctional escape rhythm. This is usually performed using radiofrequency energy in the right atrium near the AV node but it may also be achieved through the left ventricle via a retrograde aortic approach.[18,19] The most common approach is the right-sided with access via the femoral vein. Two venous punctures and catheters are required: one to perform the ablation and one to pace the right ventricle temporarily once heart block has been achieved and the patient is awaiting permanent pacemaker implant. Some patients may already have permanent ventricular pacemakers in place. In this case, the device should be programmed to VVI or VOO modes at 40 beats/min. The positions of the AV node and His bundle are identified by using fluoroscopic landmarks and electrogram recordings (Figure 1). In a left anterior oblique view, clockwise rotation of the ablation catheter will ensure its septal placement at the tricuspid annulus. An annular electrogram signal will demonstrate an atrial component and a ventricular component. When positioned correctly (1 o'clock on the tricuspid valve annulus on the left anterior oblique view), a His bundle electrogram will be seen in between the atrial and ventricular signals. The AV node is localized to the atrial tissue at the apex of the Triangle of Koch. Ablation of the AV node may produce a slightly faster, more stable escape rhythm from the His bundle which has often narrow complex, whereas ablation lower at the His bundle is likely to result in a slower, broad complex ventricular escape rhythm which may be less reliable. An atrial-to-ventricular electrogram ratio of 1: 1 indicates an atrial position that favours AV node ablation, while a ratio of 1: 2 to 1: 5 suggests an annular position favouring the His bundle ablation. The presence of atrial fibrillation can make the electrograms difficult to interpret due to the presence of high frequency, small amplitude atrial potentials. Application of radiofrequency energy is usually causing a transient accelerated junctional rhythm and then heart block develops. It is essential to wait for at least 30 min before moving on to pacemaker implant in order to ensure that heart block is permanent. A left-sided approach via the retrograde transaortic approach is used if the approach from the right side of the

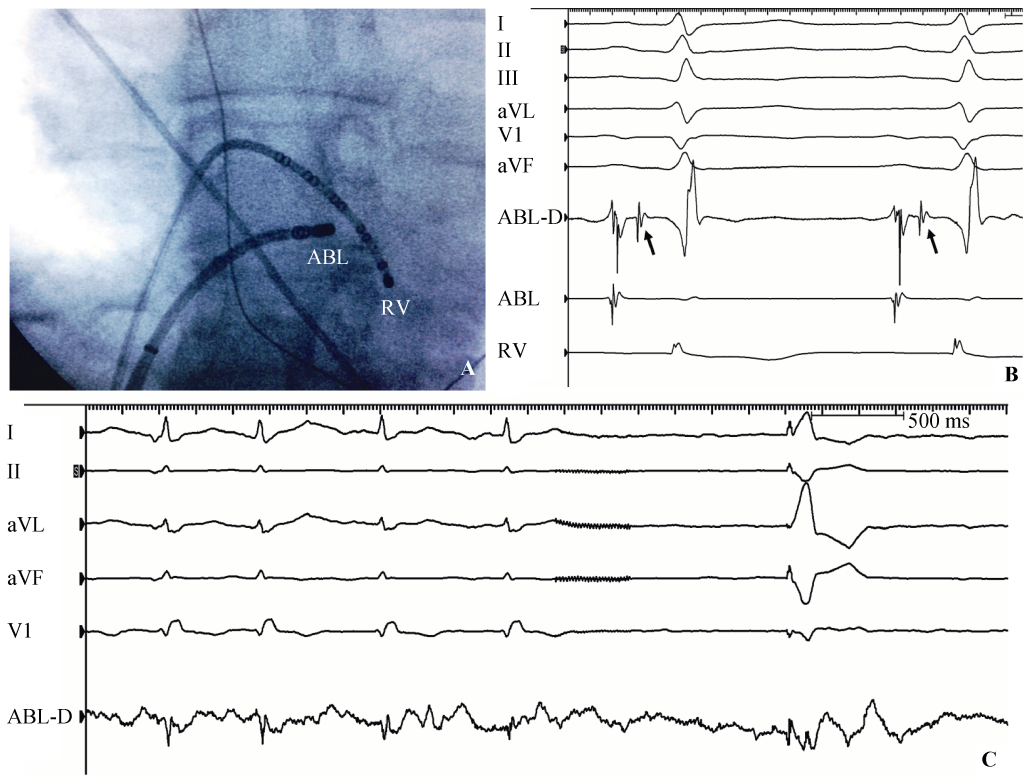

Figure 1. The positions of the AV node and His bundle in a case. (A): posterior-anterior fluoroscopic projection showing the position of the ABL at the AV junction as well as a temporary pacing catheter positioned in the RV; (B): intracardiac electrograms recorded at the distal bipole of the ablation catheter (ABL-D) during sinus rhythm showing a large atrial component, a His bundle electrogram (arrows), and a ventricular component; and (C): successful AVJA in patient with AF leading to AV block and paced-rhythm. The presence of AF makes the electrograms difficult to interpret due to the presence of high frequency, small amplitude atrial potentials. ABL: ablation catheter; AF: atrial fibrillation; AV: atrioventricular; AVJA: AV junction ablation; RV: right ventricle.

heart is undesirable or unsuccessful, which occurs in about 5% of patients.[18,20] The left-sided portion of the His bundle emerges on the septum just below the aortic valve. It is helpful to maintain a catheter at the His position in the right side of the heart as an anatomic reference while mapping on the left side of the septum. The His potential must be differentiated from the left bundle branch recording. In older patients with aortic disease or peripheral arterial disease, the AV node can be approached through a transseptal puncture from the right atrium. The left-sided His activation should occur essentially at the same sight as the right-sided His. The left bundle branch is typically recorded 1 to 1.5 cm inferior to the optimal His bundle recording site. The left bundle branch recording is identified by a potential-to-ventricular electrogram interval of 20 ms or less and A/V ratio of 1: 10 or less. In patients with aortic stenosis, prosthetic aortic or mitral valves or peripheral vascular disease, it may be better to insist on a right-sided approach. On the other hand, a left-sided approach may be preferred for patients with recently implanted LV pacing leads for cardiac resynchronization therapy to minimize the risk of lead displacement.

Overall, it is conventional to start a case with the right-sided approach, as there is a much greater familiarity and probably a lower incidence of complications using a venous rather than arterial route. One concern with left-sided approaches is the need for intravenous heparin leading to an increased risk of pacemaker haematoma. The pacemaker implant either needs to be performed in advance of the ablation or 24 h after. In rare circumstances where standard right- and left-sided approaches are both unsuccessful, energy delivery in the non-coronary or right aortic cusp where the His bundle potential is recorded may lead to complete AV block. In patients with preexisting complete bundle branch block, ablation of the contralateral bundle branch results in complete heart block. Complete heart block can also result from ablation of both fast and slow pathway inputs to the AV node. For patients with chronically elevated ventricular rates, abrupt normalization of the heart rate by ablation and pacing may produce repolarization abnormalities and fatal polymorphic ventricular tachycardia.[20–24] This phenomenon resulted in a significant incidence of sudden death after AVJA before it was appreciated in the early ex-

perience. Currently, the risk of postprocedural polymorphic ventricular arrhythmias has been essentially eliminated by programming the permanent pacemaker lower rate limit to 80–90 beats/min immediately after ablation.[20–24] The lower rate limit is then reduced by 10 beats/min each month until the desired lower rate limit is achieved.

4 Modification of the AV junction

Accumulating evidence suggests that selective ablation of the slow pathway of the AV node results in an increase in AV refractoriness and therefore decreases the ventricular rate.[25–32] Initially, ablation is performed in the slow pathway region of the low posteroseptal right atrium during AF. Specifically, it is delivered at sites with A/V ratios of 1: 2 to 1: 4. While the ventricular response is monitored, radiofrequency energy applications are delivered in incremental steps superiorly toward the midseptal area. Ablation is not applied at sites where a His potential is recorded or in those that exceed 0.02 mV.[26] An acceptable end point is the reduction of the ventricular response to less than 100 beats/ min , and ideally to 60 and 80 beats/ min. At this point, isoproterenol or atropine challenge may be administered and ablation continued until a heart rate < 120 beats/min achieved. Of note, the patient should be monitored for 24 to 72 h after the procedure for recurrences of rapid ventricular rates, excessively slow rates and AV block or polymorphic ventricular arrhythmias. Especially, AV junction modification leads to satisfactory ventricular rate control in 25%–85 % of patients.[25–32] Lee, *et al*.[33] randomly assigned 60 patients with medically refractory AF to receive complete AVJA with permanent pacing or AV junction modification. Subjective perception of QoL was assessed by a semiquantitative questionnaire before and 1 and 6 month after ablation. Patients after complete AVJA had a significantly greater improvement in general QoL than those undergoing AV junction modification. Overall, AVJA with permanent pacing, as compared with AV junction modification, had a significantly greater ability to decrease the frequency of attacks and the extent of symptoms of AF, while the patients who received this procedure were more satisfied with their general well being. Thus, AV junction modification has been largely abandoned because of its limited efficacy.

5 The time of pacemaker implantation

Implantation of a single chamber pacemaker for chronic atrial fibrillation or dual chamber device for paroxysmal or persistent atrial fibrillation is recommended. The timing of the AVJA in relation to pacemaker implantation is controversial with pros and cons for each of the timing strategy. Implantation of a permanent device before the ablation has the advantage of proving reliable pacing but carries the risk of lead dislodgement during manipulation of the ablation catheter. For this reason, many electrophysiologists wait for 30–40 days after the device implantation and then perform AVJA.[34] The followers of this approach believe that a combined procedure is prolonged and there is a great risk of infection. In addition, they prefer active fixation leads. Others choose a combined procedure with AVJA followed by permanent pacemaker insertion.[35]

6 Long term efficacy

Case series and randomized trials of AVJA with permanent pacemaker implantation have proven to be an effective therapeutic option for improving symptoms and QoL in AF patients with high ventricular rates resistant to other treatment modalities. Kay *et al*.[36] first reported that QoL could be improved in 12 consecutive patients with PAF after catheter ablation using direct current. Brignole, *et al*.[37] showed that radiofrequency AVJA with permanent pacing significantly improved QoL and activities of daily life scores in 23 patients with permanent AF and flutter. Similarly, Fitzpatrick *et al*.[38] recently reported positive outcomes in terms of QOL, activities of daily life and consumption of health care resources after radiofrequency AVJA with permanent pacing in 107 patients who had established permanent or paroxysmal AF. The Ablate and Pace Trial prospectively evaluated the efficacy of AVJA and permanent pacemaker implantation on health-treated quality of life, survival, exercise capacity, and ventricular function in 156 patients with highly symptomatic atrial fibrillation.[39] Survival at one year was 85.3%, with 5 out of 23 deaths characterized as sudden cardiac deaths. The patients reported improved QoL; however, LVEF and exercise capacity were not statistically significantly changed from baseline. An escape rhythm was noted after ablation in 67% of patients. Ozcan, *et al*.[22] investigated the long-term survival after the "ablate and pace" approach. The survival was compared with age and sex-matched controls of the Minnesota population and consecutive patients with AF who received drug therapy. After adjustment for the underlying heart disease, the survival was similar to the expected survival in the general population. The observed survival rate was also similar to the controls with atrial fibrillation who received drug therapy. Wood and colleagues performed a meta-analysis of 21 studies published between 1989 and 1998 that included 1,181 patients who underwent radiofrequency AVJA and permanent pacing for symptomatic relief

of medically refractory atrial fibrillation.[10] All patients had medically refractory atrial tachy-arrhythmias, primarily atrial fibrillation (97%). A broad range of clinical outcomes encompassing QoL, ventricular function, exercise duration, and healthcare use were derived from the studies. The meta-analysis demonstrated significant improvement after ablation and pacing therapy in all outcome measures except fractional shortening. Of note, ejection fraction did show significant improvement. The calculated 1-year total and sudden death mortality rates after ablation and pacing therapy were 6.3% and 2.0%, respectively. In a recent meta-analysis, the all-cause mortality was similar between AVJA and medical therapy (3.1% vs. 3.3%).[11] There was no significant difference in exercise duration or ejection fraction with AVJA relative to pharmacotherapy. Compared with pharmacotherapy, AVJA was associated with significant improvement in several symptoms (palpitations, dyspnea). The incidence of procedure-related mortality (0.27%) and malignant arrhythmia (0.57%) was low.

7 Device selection after AVJA

Patients with permanent AF undergoing AVJA require a pacing device that can be a conventional single-chamber or a biventricular pacing system. In patients who still display periods of sinus rhythm, an atrial electrode may be additionally implanted. In the early experience with AVJA, single-site right ventricular pacing was the standard treatment. However, long-term right ventricular pacing is not free from complications. Right ventricular pacing leads to negative inotropic effects, abnormal histologic changes with thinning of the myocardial wall, and fibrosis.[40,41] Several clinical studies have suggested that long-term right ventricular pacing can also be detrimental due to ventricular dyssynchrony and hemodynamic abnormalities. Large studies including ICD patients (DAVID trial, MADIT II trial)[42,43] have demonstrated the adverse effects of long term right ventricular pacing. However, these studies were carried out in patients without AVJA, while most of these patients had underlying ischemic disease and impaired left ventricular systolic function. However, Chen, *et al*.[44] showed the long-term effects of right ventricular pacing in patients who had AVJA were evaluated in 286 patients. No change after a mean follow up of 36 months followed was evident. Moreover, there was no significant change in heart failure hospitalizations after initiation of right ventricular pacing. On the other hand, biventricular pacing has proven efficacy in patients with severe left ventricular systolic dysfunction and increased QRS duration.[45–51] It could therefore be speculated that this mode of pacing may exert favorable effects in patients with AF following AVJA. The impact of biventricular pacing after AVJA was first studied by Doshi and colleagues in the Post AV Nodal ablation Evaluation (PAVE) study.[52] In this study, 184 patients with medically refractory AF and who underwent AVJA were randomized to either biventricular pacing or RV pacing. At 6 months after ablation, there was an overall improvement in the primary end point of 6-min walk test in both study groups. Remarkably, the mean LVEF at the end of 6 months remained stable in the CRT group and whereas it was reduced in the right ventricular pacing group (ejection fraction of 46% *vs*. 41%, $P = 0.03$). A recent meta-analysis evaluating the outcomes of biventricular versus right ventricular pacing after AVJA in 534 patients reported increased LVEF and improved symptoms with CRT among patients with a depressed LVEF.[11] The favorable effect of biventricular pacing in terms of 6-min walk test, was prominent in patients with LVEF < 45%.

The role of an "ablate and pace" strategy, as an alternative to classic rhythm control or rate control strategies, has been of considerable interest in CRT trials. AVJA is attractive because it affords the opportunity to guarantee essentially 100% biventricular capture.[53–58] In a large prospective observational cohort study of 673 patients, 162 (24%) of whom were in permanent AF. Gasparini, *et al*.[54] reported that only those patients who underwent AVJA showed significant improvement in ventricular volumes, exercise capacity, and clinical response to CRT. The same group conducted a more extensive multicenter observational study of 1285 consecutive patients, 243 (19%) of whom were in permanent AF, and found that AVJA was associated with a survival benefit driven by reduction in HF-associated mortality.[56] These results have been replicated by Ferreira, *et al*.[57] and Dong, *et al*.[58] who found significantly improved clinical outcome and survival among CRT patients with AF who received AVJA versus those who did not. However, other investigators have argued that sufficiently high degrees of ventricular capture can be achieved with the use of medications alone, thus avoiding the risk associated with AVJA.[59–61] A further criticism of this approach is that patient selection has not been random, because CRT studies usually restrict the procedure to patients in permanent AF with severe symptoms.

8 New technology

Complications regarding pacemaker implantation include lead displacement, haematoma, infection, pneumothorax, and pericardial effusion. Furthermore, battery replacement is quite critical following AVJA. An important advance in pacemaker's technology eliminating many of these compli-

cations is the advent of the leadless pacing system. In the LEADLESS trial, a self-contained leadless cardiac pacemaker device was implanted in 33 patients and followed for 90 days.[62] This was the first study of a permanent, completely self-contained, leadless cardiac pacemaker in humans. Based on these findings, leadless pacing is feasible and safe in a consecutive series of patients with an indication for single-chamber ventricular pacing. The device was designed to address poor clinical outcomes associated with complications, including fractures and erosions associated with conventional leads used in current pacemakers. The overall complication-free rate in this nonrandomized prospective trial was 94%. At 90 months, adequate sensing and pacing thresholds were met in all patients. A leadless pacing system may become part of the "ablate and pace" strategy for patients with AF.

9 Conclusions

AVJA and pacemaker implantation is indicated for patients who have failed rhythm control and medical rate control strategies for AF. It is a safe and effective approach to reduce symptoms and to improve QOL in this population. An increase of ejection fraction in patients with systolic dysfunction has been additionally observed following the "ablate and pace" approach. A survival benefit has been reported in patients with heart failure who undergo AVJA and receive a CRT device. In patients with heart failure and AF who undergo implantation of a biventricular pacing system, AVJA leads to maximal biventricular pacing.

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