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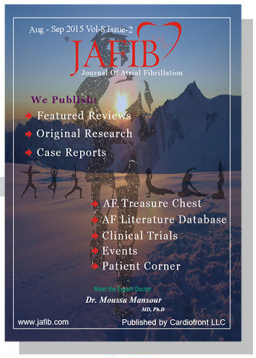


# Atrioventricular Junction Ablation In Atrial Fibrillation: Choosing The Right Patient And Pacing Device

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**Abstract**

**Atrial fibrillation (AF) is the most common cardiac arrhythmia and despite advancements in rhythm control through direct catheter ablation, maintaining sinus rhythm is not possible in a large proportion of AF patients, who therefore are subject to a rate control strategy only. Nonetheless, in some of these patients pharmacological rate control may be ineffective, often leaving the patient highly symptomatic and at risk of developing tachycardia-induced cardiomyopathy and heart failure (HF). Catheter ablation of the atrioventricular junction (AVJ) with subsequent permanent pacemaker implantation provides definite rate control and represents an attractive therapeutic option when pharmacological rate control is not achieved. In patients with reduced ventricular function, cardiac resynchronization therapy (CRT) should be considered over right ventricular apical (RVA) pacing in order to avoid the deleterious effects associated with a high amount of chronic RVA pacing. Another group of patients that may also benefit from AVJ ablation are HF patients with concomitant AF receiving CRT. In this patient cohort AVJ ablation ensures near 100% biventricular pacing, thus allowing optimization of the therapeutic effects of CRT.**

## Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia and has during recent years experienced significant advancements, with pulmonary vein isolation through direct catheter ablation becoming a cornerstone therapy in drug refractory AF.[1,2] Despite this, a significant proportion of AF patients are resistant to rhythm control and in some instances pharmacological rate regulation is also insufficient, often leaving the patient highly symptomatic and at risk of developing tachycardia-induced cardiomyopathy and heart failure (HF).[3] In such patients, catheter ablation of the atrioventricular junction (AVJ) represents an attractive, and often the only, therapeutic option.[4] Since the patient is left with a junctional escape rhythm, implantation of a permanent pacemaker is warranted and when left ventricular (LV) systolic function is reduced cardiac resynchronization therapy (CRT) should be considered in order to avoid the deleterious effects associated with right ventricular apical (RVA) pacing.[5] Another group of patients that may also be eligible for AVJ ablation are those with AF who require CRT as part of their HF therapy and during follow-up present low percentage of biventricular pacing secondary to insufficient rate control and irregular RR intervals.[6,7] In this cohort AVJ ablation ensures near 100% biventricular pacing thereby optimizing the therapeutic effects of CRT.[8] The aim of this review is to discuss the existing evidence regarding the role of AVJ ablation in the two mentioned AF patient groups – AF with rapid ventricular rates and HF patients with concomitant permanent AF receiving CRT – as well as the preferred type of pacing device (RVA pacing vs. CRT) following AVJ ablation.

**Key Words:**
Atrial Fibrillation, AV Junction Ablation, Cardiac Resyncrhonization Therapy, CRT, Pacing.

**Disclosures:**
None.

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## Ablation Technique

On the 9th of April 1981, the first AVJ ablation in humans was carried out, using high-energy direct current shock (300-500 J) from a portable defibrillator which was delivered over a standard electrode catheter, positioned at a site where His bundle potential was recorded.[9] However, given the high complication rates, in particular cardiac perforation, direct current energy was replaced by radiofrequency energy towards the end of the 1980s.[10]

The aim of AVJ ablation is to ablate the compact AV node with resultant AV block and a stable junctional escape rhythm. Normally,

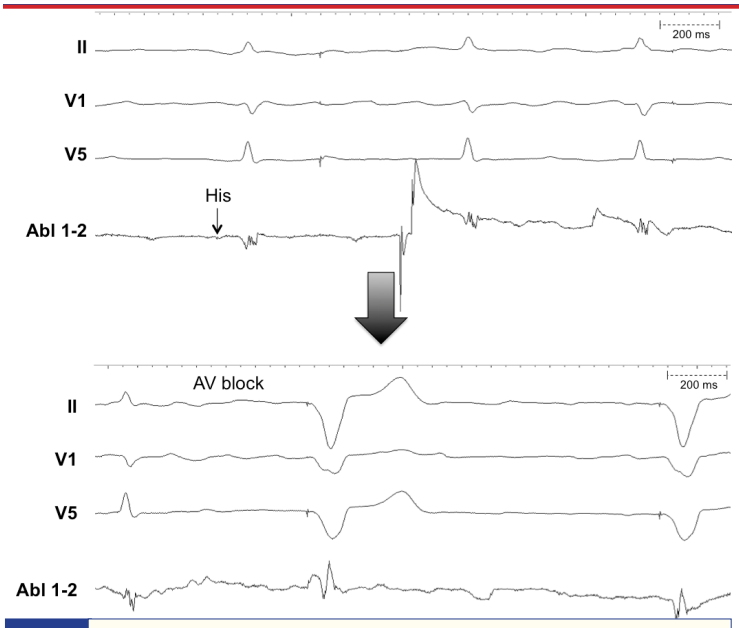


**Figure 1:** Surface electrocardiogram (lead II, V1, and V5) and intracardiac radiofrequency ablation (Abl) catheter electrodes (distal 1-2) of a 78-year-old woman with symptomatic permanent fast atrial fibrillation refractory to pharmacotherapy. Top panel shows recordings at the start of ablation and bottom panel 25 seconds later when atrioventricular (AV) block is achieved. Note the asynchronous ventricular pacing spikes due to the permanent pacemaker programmed in V00 mode at 50 ppm.

radiofrequency ablation is performed in the right atrium through femoral venous access with the ablation catheter advanced across the tricuspid valve annulus and withdrawn until it lies over the compact AV node, typically identified by a definite His signal, and a large atrial and smaller ventricular electrogram. Radiofrequency energy, with maximum power of 60W, is administered for 30-60 seconds at a temperature of 60-70ºC (Figure 1).[11] Overall success rate have been reported over 97%.[12] Occasionally, in patients with cardiomyopathy and ventricular remodeling the recoding of a stable His potential from the right side can be difficult and a left-sided ablation may be necessary. In those instances the ablation catheter is placed across the aortic valve over the upper left ventricular septum where a His bundle potential is recorded, through a retrograde aortic approach.[13] The permanent pacemaker options include a single chamber (VVIR) for permanent AF, dual chamber (DDDR) for paroxysmal AF, and in case of ventricular systolic dysfunction, a CRT device. The device is usually placed 4-6 weeks prior to ablation with the advantage of stable pacing lead(s) at the time of ablation, although a combined procedure, obviating the risk of lead dislodgement during the manipulation of the ablation catheter, is advocated by some.[14]

Complications include those related to femoral venous access, (venous thrombosis, ateriovenous fistula, infection and bleeding), cardiac perforation or tamponade, tricuspid valve regurgitation and death.[11] Specific procedure related complications include hemodynamic deterioration and development of severe mitral regurgitation secondary to mitral valve leaflet apposition due to RVA pacing,[15] and sudden cardiac death (Figure 2).[16] The latter has been described to occur more frequently in patients with certain comorbidities (diabetes mellitus, aortic valve lesions, ventricular rhythm disturbances, and chronic obstructive pulmonary disease).[16] Although the exact mechanisms of sudden death following AVJ ablation is not fully elucidated, several factors that contribute to repolarization disturbances have been identified, creating a substrate for pause-dependent polymorphic ventricular arrhythmia (similar to acquired long QT syndromes). These predisposing factors include decreased heart rate, increased sympathetic activity, hypokalemia, antiarrhythmic drugs and change in myocardial activation sequence from the native conduction system to RV apical pacing. Therefore, in order to minimize the risk of ventricular arrhythmia it is recommend to program a relatively high pacemaker lower rate limit (80-90 ppm) for the first 4-6 weeks following AVJ ablation.[17] More recently, reports of Gerbode defect (LV to right atrium shunt) has been described as a rare complication following AVJ ablation.[18] This is due to unfortunate ablation at the thin superior atrioventricular portion of the membranous septum which separates the right atrium from the LV. Given that a permanent pacemaker is necessary complications related to its placement should also be included. Overall, the incidence of procedure-related complications is around 3%, with the majority being related to femoral venous access.[11] In a European survey from 88 institutions including 900 patients a 3.2% complication rate was reported with major complications of 1.8%.19 The NASPE Prospective Voluntary Registry, which included 646 patients, had a 0.8% severe complication rate.[12] Finally, an observational study of long-term survival of 350 patients with AF undergoing AVJ ablation and permanent pacemaker insertion found that this strategy does not adversely affect patient survival when compared to general population (adjusted for underlying heart disease) or patient with AF who received drug therapy.[20]

## AF With Rapid Ventricular Rates

This represents the largest group of patients with AF who undergo AVJ ablation, which is normally considered as a last resort when both rhythm (direct catheter or surgical ablation and/or pharmacotherapy) and pharmacological rate control have failed and the patient remains symptomatic. Worth mentioning are a subgroup of patients with left atrial flutter following AF ablation, often significantly more symptomatic and more difficult to control pharmacologically than when the patient was suffering AF. Although, in the majority of cases a repeat ablation of the flutter is successful, in some instances ablation is unsuccessful and the only remaining option is AVJ ablation to manage the symptoms.[4]

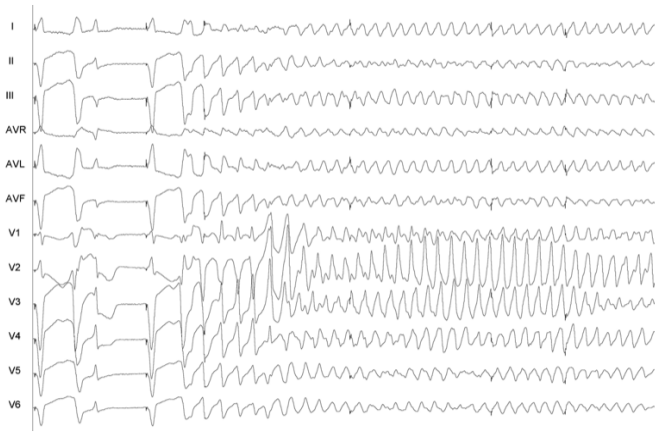


**Figure2:** Ventricular tachycardia (Torsade de Pointes) recorded 60 minutes after atrioventricular junction ablation in a patient with mitral valve disease and atrial fibrillation with rapid ventricular response. Adapted from Rodríguez-Mañero M. et al.[35] with permission.

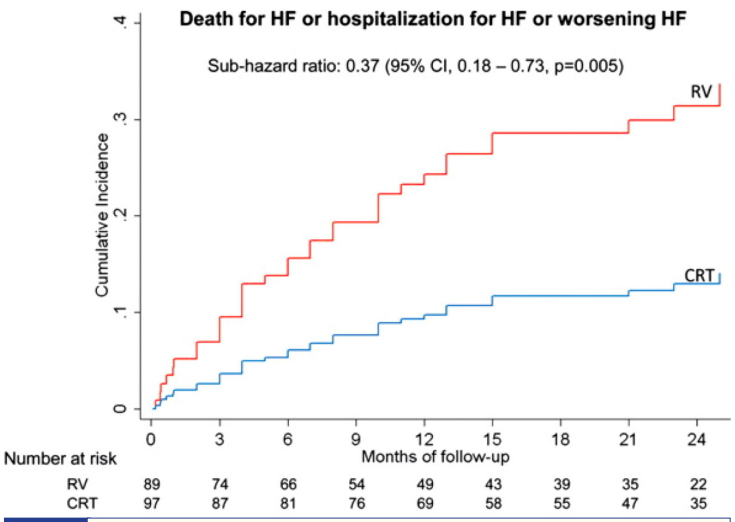


**Figure 3:** Corrected cumulative incidence of the composite primary outcome of death from heart failure, hospitalization due to heart failure, or worsening heart failure, comparing cardiac resynchronization therapy (CRT) vs. right ventricular (RV) pacing following atrioventricular junction ablation for permanent atrial fibrillation in the APAF trial.[44] Reproduced with permission.

**Tachycardia-Induced Cardiomyopathy**

The rapid ventricular rate is the main source of symptoms in this patient group and, if occurring for a prolonged period of time, increases the risk of tachycardia-induced cardiomyopathy, consisting of reversible ventricular dilatation, systolic dysfunction and symptoms of heart failure. The entity may be divided into 2 types: pure (tachycardia being the chief mechanism of LV deterioration); and 2) impure (tachycardia worsens a pre-existing cardiomyopathy of a different cause). Although described in 1913 in a patient with AF, and during the last 3 decades extensively studied in both animal models and in humans, its pathophysiological mechanisms have not been fully elucidated although interplay of several mechanisms clearly exists.[3]

In animal models sustained atrial or ventricular pacing leads to severe biventricular systolic dysfunction which is characterized by increased ventricular filling pressures, diminished cardiac output and increased systemic vascular resistance.[21] At a microscopic level there is myocyte loss, myocyte elongation, effacement of the interface between the basement membrane and sarcolemmal surface, depletion of T-tubules associated with decreased density of L-type calcium channels and beta-adrenergic receptors, resulting in abnormal excitation-contraction coupling which may impair contractile function.[22] Diastolic function is impaired by tachycardia with impaired relaxation secondary to a disproportionate increase in sarcoplasmic reticulum calcium content that manifests as diastolic contracture.[23] Other mechanisms include exhaustion of high energy stores in the myocardium due to augmented metabolism from the tachycardia, mitral regurgitation secondary to annular dilatation, reduced myocardial blood flow, oxidative stress, and neurohormonal changes.[3]

Both in animal and human studies, normalization of the rapid heart rates results in recovery of myocardial function with improvements in LV ejection fraction (LVEF) typically observed after 3 to 4 months. In a metaanalysis of 21 studies with a total of 1181 patients with drug refractory AF, an overall improvement in LVEF of 4.4% was observed as well as in a broad range of clinical outcomes including symptoms, number of hospital admissions and New York Heart Association (NYHA) functional class.[24]

**AVJ Ablation: Symptomatic, Echocardiographic, And Functional Benefits**

As AVJ ablation became a more widespread therapeutic option for drug refractory fast AF during the 1990s, several studies were published evaluating the potential beneficial aspects of this procedure. Initial uncontrolled studies in highly symptomatic patients with drug refractory permanent AF established that AVJ ablation provides symptom relief[25] and improved cardiac function,[26,27] the latter attributed to the reversal of tachycardia-induced cardiomyopathy and the favorable hemodynamic effects of regularization of RR intervals.[28] For example, The Ablate and Pace Trial,[25] a prospective multicenter study including 156 patients with drug refractory fast AF undergoing AVJ ablation and pacemaker implantation, reported after a 12-month follow-up an significant improvement in NYHA class (2.1 to 1.8), quality of life and arrhythmia related symptoms and frequency. The LVEF at 12-month was not different from baseline, however in those with reduced LVEF at baseline a significant improvement was observed (31±2% vs. 41±3%; P=0.0001).

Subsequently, the results of a few randomized trials were reported comparing pharmacological rate control with AVJ ablation in AF patients (Table 1).[29-33] Of note, the patient profile was different to the previous uncontrolled studies, in particular since an acceptable pharmacological heart rate control was a pre-requisite. Brignole et al.[31] studied 66 patients with AF lasting >6 months, clinically manifest heart failure, evidence of structural heart disease, and heart rate >90 bpm, randomized to AVJ ablation and pacemaker implantation or pharmacological treatment. At 12 month the ablation group showed significantly lower scores in palpitations and exertional dyspnea and a non-significant favorable trend for exercise intolerance, Living with Heart Failure Questionnaire, NYHA class, and Activity Scale when compared with the drug group. No difference in echocardiographic parameters between the 2 groups was observed at the end of the study, perhaps due to the presence of structural heart disease having more of an impact on the depressed cardiac function than tachycardia induced cardiomyopathy. In a similar way, The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT)[33] compared AVJ ablation and pacemaker

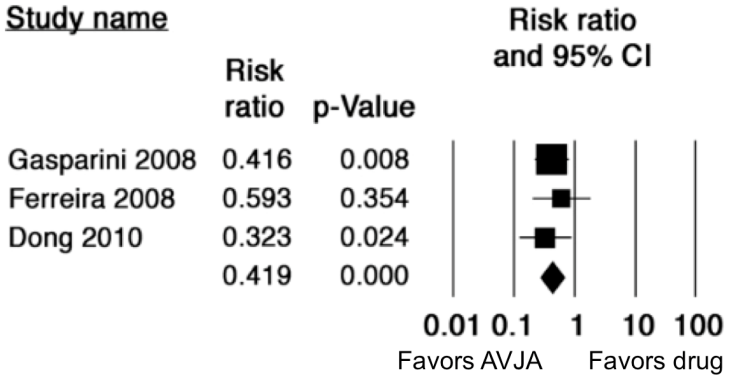


**Figure 4:** All-cause mortality meta-analysis data from 3 studies,[8] comprising 450 patients, comparing pharmacological rate control (drug) vs. atrioventricular junction ablation (AVJA) in heart failure patients with concomitant permanent AF receiving cardiac resynchronization therapy. CI = confidence interval. Figure content under Elsevier user license.

**Table 1:** Randomized controlled trials comparing pharmacological rate control (drug) vs. AVJ ablation + pacemaker implantation (Abl+Pm) in patients with rapid AF

| Study | Patients (n) | Age (y), Abl+Pm/ drug | AF duration (y), Abl+Pm/ drug | Baseline LVEF (%), Abl+Pm/drug | Follow-up (m) | Inclusion criteria | Results |
|---|---|---|---|---|---|---|---|
| Brignole[29] 1997 | 43 | 66±10/ 64±10 | 9±8/ 8±5 | 58±11/60±10 | 6 | -Symptomatic paroxysmal AF -Refractory to 3 AAD | Abl+Pm group showed significantly better scores in LHFQ, palpitations, effort dyspnea, exercise intolerance score, and easy fatigue. -AF was documented in 25% (Abl+Pm group) and 8% (drug group) -No differences in echocardiography parameters |
| Brignole[31] 1998 | 66 | 72±9/ 72±9 | 5.7±6.9/ 4.1±5 | 43±12/44±15 | 12 | -AF duration >6m -HR >90 bpm + clinical HF | - Abl+Pm group showed significantly better scores in palpitations and effort dyspnea - No differences in echocardiography parameters nor exercise test |
| Marschall[30] 1999 | 56 | 65±8/ 60±10 | 7.1±6.3/ 9.8±8.0 | NR | 4 | -Symptomatic paroxysmal AF -Refractory to 2 AAD | -Abl+Pm group showed significantly better scores for overall symptoms, palpitations and dyspnea -DDDR was better than VVIR pacing for overall symptoms and dyspnea -More patients developed persistent AF in the Abl+Pm group |
| Ueng[32] 2001 | 50 | 68±6/ 65±8 | 14±7/ 12±8 | 45±6/45±8 | 12 | -Symptomatic lone AF >6m -Normal HR (60-100 bpm) -LVEF ≤50% | -Abl+Pm group showed significantly better scores for overall symptoms, overall activity scale -Abl+Pm group presented significantly higher LVEF than drug group (49±5% vs. 44±6%) |
| Weerasooryia[33] (AIRCRAFT Study) 2003 | 99 | 68±9/ 68±9 | 4.8±5.5/ 6.5±10.9 | 55±16/57±14 | 12 | -Symptomatic AF >12m -HR controlled by drugs (<80 bpm) | -Abl+Pm group showed significantly improved QoL and less symptoms -No differences in echocardiography parameters nor exercise test |

AAD = antiarrhythmic drugs; AF = atrial fibrillation; AVJ = atrioventricular junction; LHFQ = Living with heart failure questionnaire; LVEF = left ventricular ejection fraction; QoL = Quality of life.

implantation with pharmacological rate control in 99 patients with mild to moderately symptomatic permanent AF, normal LVEF, and a ventricular rates that was adequately controlled by medication (<80 bpm and <150 bpm at rest and exercise, respectively). After 12 month of follow-up no difference in echocardiographic parameters or exercise tolerance was observed, however quality of life was significantly improved in the AVJ ablation group. Finally, Ueng et al.[32] studied 50 patients with permanent symptomatic AF, reduced LVEF and no evidence of structural heart disease, and normal ventricular rates (60 – 100 bpm). Assignment to AVJ ablation and pacemaker implantation was according to patient preference and after 12 months the ablation group showed significant improvements in quality of life, symptoms and LVEF, the latter likely due to the regularization of R-R intervals when compared to the drug group. A metaanalysis of randomized or prospective trials, including the previously commented studies,[31-33] found that AVJ ablation when compared with pharmacotherapy was associated with significant improvement in several symptoms (palpitations, dyspnea) but no significant difference in exercise duration or LVEF.[34] In subgroup analysis of patients with reduced LVEF this parameter was significantly improved after AVJ ablation. Importantly, the same metaanalysis reported a low incidence of procedure-related mortality(0.27%) and malignant arrhythmia (0.57%).

Our group aimed to determine the change in LVEF after AVJ ablation and RV apical pacing and the clinical predictors of LVEF deterioration in a sample of 104 consecutives patients referred for AVJ ablation.[35] After 2 years of follow up there was a decrease in the rate of hospital admission (from 0.9 admission/year to 0.35, P<0.001), an increase in the functional status in at least one NYHA class in 58 patients, and an increase in the global LVEF (from 48.9% to 54,1%; P<0.001). Valvular replacement and LVEF <50% were independently associated with a decrease in the LVEF. Therefore, we hypothesized that the mechanical ventricular dyssynchrony induced by long-term RVA apical pacing may have more impact in patients with mitral disease, which as is known, plays an important role in the cardiac mechanics. Scarce information in this subgroup is currently available and it is our belief that it warrants further investigations

**RVA Pacing vs. CRT After AVJ Ablation**

RVA pacing produces electrical and mechanical ventricular dyssynchrony, similar to left bundle branch block, with subsequent detrimental effects on cardiac structure and function.[36] During the last 2 decades the clinical relevance of the negative effects of long-term RVA pacing has gained recognition following the publication of large pacemaker and implantable cardiac defibrillator (ICD) trials where a high amount of chronic RVA pacing was associated with increased risk of AF, HF and death.[36-38] Subanalyses from these trials suggest that patients with reduced LVEF subject to >40-50% of RVA pacing are at high risk.[39,40] Such findings are also relevant for patients who undergo AVJ ablation and conventional pacemaker implantation since they will receive near 100% of pacing for the rest of their life. Importantly, the vast majority of patients studied (including all studies commented in the previous section) received an RVA pacing system (typically VVIR), and it is therefore likely that some of the benefits associated with the AVJ ablation procedure were offset by the detrimental effects of chronic RVA pacing, especially after years of chronic pacing. This was observed by Tops et al[41] who retrospectively evaluated 55 patients with medically refractory AF and preserved LVEF who had undergone AVJ ablation. After a relatively long follow-up of 3.8±1.7 years, 49% had developed LV dyssynchrony and in this subgroup LVEF was significantly worsened (from 48±7% to 43±7%; P<0.05) as well as NYHA class (from 1.8±0.6 to 2.2±0.7; P<0.05). On the contrary, a retrospective study[42] of 286 patients with baseline LVEF of 48±18% with a shorter follow-up (1.7±1.6 years) than the Tops et al.[41] who had undergone AVJ ablation showed short-term improvement in mean LVEF with no significant change compared to baseline at the end of the study follow-up. Differences in the prevalence of patients with tachycardia-induced cardiomyopathy, duration of exposure to RVA pacing (i.e. study follow-up), and baseline LV dysfunction are possible explanations for the contradictory study results.

During the 2010s several studies compared RVA pacing with

cardiac CRT in patients undergoing AVJ ablation for AF (Table 2). This was first studied in the randomized controlled trial Post AV Nodal ablation Evaluation (PAVE) study[43] where 184 patients with drug refractory AF and baseline LVEF of 46±18%, who had undergone AVJ ablation were randomized to CRT or RVA pacing. At 6 months postablation, the LVEF remained stable in the CRT group but had deteriorated by 3.1% at 6 weeks and 3.7% at 6 months in the RVA pacing group. Similar results were reported in the more recent Ablate and Pace in Atrial Fibrillation (APAF)[44] randomized controlled trial, which included 186 patients with impaired cardiac function (mean LVEF 37.5±14%) and AVJ ablation for symptomatic AF. After a mean follow-up of 20 months, the primary composite endpoint of death from HF, hospitalization due to HF, or worsened HF occurred more frequently in the RVA pacing group than the CRT group (26% vs. 11%; P=0.005), principally driven by the latter 2 endpoints (Figure 3). Of note, 50% of the patients had a QRS duration ≥120ms, however patients benefited equally from CRT independent of QRS duration. A meta-analysis of 5 RCTs[43-47] that compared RVA pacing with CRT following AVJ ablation in patients with drug refractory fast AF and at least mildly depressed LVEF (<45%) found a significant reduction in hospitalization for HF and increase in LVEF but no effect on exercise capacity, quality of life or mortality.[5] Taken together, in patients with reduced LVEF and drug refractory fast AF who undergo AVJ ablation, RVA pacing is associated with deterioration of LV function and increase risk for hospitalization for HF and in this cohort CRT confers significant clinical and cardiac functional benefits. Given the lack of clinical studies, there is currently no evidence to support CRT after AVJ ablation for AF when LV function is normal.

### Clinical Guidelines

Both the North American and the European AF clinical practice guidelines recommend AVJ ablation followed by permanent pacemaker implantation in patients with AF when rate is not controlled pharmacologically and rhythm control is not achievable (when antiarrhythmic therapy is ineffective or associated with intolerable side effects and direct catheter-based or surgical ablation of AF is not indicated, has failed or is rejected) (recommendation Class IIa; Level B).[1,2] When it comes to device selection the European clinical practice guidelines on cardiac pacing recommends CRT in those with reduced LVEF (without a specific cutoff value) (recommendation Class IIa; Level B)[48] and the North American clinical practice guidelines recommends CRT when LVEF is ≤35% but state that it should also be considered for patients with less severe dysfunction.[2]

## HF Patients with Concomitant Permanent AF Receiving CRT

Almost all randomized controlled trials that have established the clear clinical benefits of CRT in patients with symptomatic HF, prolonged QRS duration and reduced LVEF included only patients in sinus rhythm.[48] However, a large proportion of HF patients present AF and despite the limited evidence the available results suggests that CRT is also useful in these patients,[46,49] for which reason it shares the same indications as for patients in SR (when in NYHA class III-IV).[48,50] Nonetheless AF in itself is linked to a poorer prognosis in HF patients,[51] and there is substantial data that CRT is associated with a higher risk of non-responders in patients with AF undergoing CRT.[52] This is most likely due to the absence of atrioventricular optimization benefit and a high intrinsic ventricular rate with irregular RR intervals, which leads to reduction in fully captured biventricular pacing beats through fusion and pseudo-fusion beats. Indeed, the greatest magnitude of reduction in mortality is observed when biventricular pacing is >98%.[6] Furthermore, it is important to note that device counters have been found to overestimate the degree of effective biventricular pacing in patients with AF due to fusion and pseudo-fusion beats, in which instances a 12-lead Holter monitor is helpful to assess the presence of effective pacing.[7] Therefore, in order to optimize the CRT derived benefits in patients with AF, rate regulation is paramount, either pharmacologically or by AVJ ablation (after pharmacological and/or direct catheter ablation rhythm control has been deemed unsuitable).[48,50]

### Medical Rate Control vs. AVJ Ablation

Although there is no randomized controlled trial data available, most observational studies indicate that AVJ ablation is associated with significant clinical benefits when compared with medical rate control in patients with AF who undergo CRT implantation (Table 3). A metaanalysis published in 2012 that included 768 CRT patients with AF, from 4 retrospective and 2 prospective cohort studies, reported that AVJ ablation in CRT-AF patients was associated with significant risk reduction in all-cause mortality (risk ratio 0.42; 95% confidence interval [CI]: 0.26 to 0.68; P<0.001), cardiovascular mortality (risk ratio 0.44; 95% CI: 0.24 to 0.81; P=0.008), and

**Table 2: Randomized controlled trials comparing RVA pacing versus CRT after AVJ ablation in symptomatic AF**

| Study (year) | Patients (n) | Follow-up (months) | Baseline LVEF (%) | Study endpoints | CRT benefits |
|---|---|---|---|---|---|
| MUSTIC AF[46] 2002 | 59 | 3 (cross-over) | 25 ± 10 | 6 min walk distance* Peak oxygen uptake, hospitalization for HF, QoL, and mortality | Improved 6 min walk distance, peak oxygen uptake and QoL.** Non-significant reduction in hospitalization for HF. No difference in mortality. |
| OPSITE[45] 2005 | 56 | 3 (cross-over) | 38 ± 14 | 6 min walk distance*, NYHA* and QoL* LVEF, LVESD and LVEDD | Improved NYHA, LVEF and LVESD. No differences in other endpoints. |
| PAVE[43] 2005 | 184 | 6 | 46 ± 16 | 6 min walk distance* QoL and LVEF No difference in QoL | Improved 6 min walk distance and LVEF. No difference in QoL. |
| AVAIL[47] 2010 | 127 | 6 | 56 ± 9 | 6 min walk distance*, NYHA* and QoL* LVEF, LVESV, LVEDV and LA volume | Improved NYHA, LVEF, and LV and LA volumes. No differences in 6 min walk distance or QoL. |
| APAF[44] 2011 | 186 | 20 | 38 ± 14 | Composite of death due to HF, hospitalization for HF or worsened HF* Total mortality, hospitalization for HF, worsened HF, LVEF, LVESD, or LVEDD | Reduction in composite endpoint. No difference in mortality. Non-significant improvement in LVEF and LVEDD. |

*Primary endpoint; **Significant improvement was only observed in the 37 patients where therapy was delivered and not in the intention-to-treat analysis; AF = atrial fibrillation; AV = atrioventricular; CRT = cardiac resynchronization therapy; HF = heart failure; NYHA = New York Heart Association functional class; LA = left atium; LVEF = left ventricular ejection fraction; LVEDD/V = left ventricular end diastolic diameter/volume; LVESD/V = left ventricular end systolic diameter/volume; QoL = quality of life; RCT = randomized controlled trial; RVA = right ventricular apex. (Adapted from Akerström F et al.[36] with permission.)

improvement NYHA class (mean difference -0.34; 95% CI: -0.56 to -0.13; P=0.002) (Figure 4).[8] Of the studies included, 3 consisted solely of permanent AF patients, 1 of persistent AF lasting >3 months and 1 did not report data on AF subtype. One year later the results from the prospective, multicenter, international, observational Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry (CERTIFY) study were published.[53] The study reported the clinical outcome of CRT patients with permanent AF undergoing CRT implantation followed by AVJ ablation (n=443) or pharmacological rate control (n=895) compared with patients in SR (n=6046). After a median follow-up of 37 months total mortality (6.8 vs. 6.1 per 100 patient-years) and cardiac mortality (4.2 vs. 4.0) were similar for those with AF+AVJ ablation. On the contrary, the AF+drug group had a significantly higher total and cardiac mortality than the sinus rhythm (SR) group (11.3 and 8.1 respectively; P<0.001). The biventricular pacing capture (by means of device counters) in the AF + AVJ ablation group was significantly higher than the AF+drug group (96±6% vs. 87±14%; P<0.001), reinforcing the importance of achieving a high percentage of biventricular capture, particularly in AF patients (the SR group presented 92±13% biventricular pacing). Interestingly, in the same year a single-center prospective observational study,[54] including 155 patients with permanent AF treated with CRT, found that AVJ block (either spontaneous or ablation induced) did not improve survival at a mean follow-up of 30 months. The contradictory results could be explained insufficient statistical power with a study population of only 155 patients and a lower baseline LVEF.[55] Future randomized controlled trials, comparing the 2 rate-control strategies, are in great need and if such trials would prove AVJ ablation superior to medical rate-control we might see an ablate and CRT pace strategy becoming increasingly prevalent for HF patients with concomitant AF and CRT indication. Finally, it should also be noted that rhythm control through direct catheter ablation might be an option in selected HF patients with paroxysmal/persistent AF receiving CRT, although there is currently no data available to supports this strategy.

### Clinical Guidelines

Both the North American and European clinical practice guidelines underline the importance of ensuring a near 100% biventricular pacing in patients with AF undergoing CRT implantation.[48,50] The European guidelines further states that, since most studies favor AVJ ablation over pharmacological rate control in most AF patients, this should be considered in most patients always taking into account the risks associated with creating pacing dependency.

## Conclusions

AVJ ablation with subsequent permanent pacemaker implantation represents an effective and safe therapeutic option in patients with fast AF refractory to pharmacotherapy when rhythm and rate control are not achievable. It provides symptom relief through lowering of ventricular rates and regularization of RR intervals, and reversal of tachycardia-induced cardiomyopathy when present. Due to the deleterious effects caused by RVA pacing induced electro-mechanical dyssynchrony in patients with reduced LVEF, CRT is the preferred pacing strategy and should always be considered in this patient group. Nonetheless, data on predictors of poor response to RVA pacing and potential benefit of CRT is scarce and warranted. HF patients with concomitant AF receiving CRT is another patient group that may benefit from AVJ ablation since this guarantees a near 100% of biventricular pacing. So far, multiple cohort studies indicate that in this patient group AVJ ablation is associated with improved LV function, functional class, cardiac and total mortality when compared

**Table 3: Clinical cohort studies comparing pharmacological rate control vs. AVJ ablation (AVJA) in HF patients with concomitant permanent AF receiving CRT (NYHA II-IV, LVEF ≤35% and QRSd ≥120ms)**

| Study (year) | Intervention groups (n) | Follow-up (months) | AVJA criteria | %BVP | Results |
|---|---|---|---|---|---|
| Gasparini[56] 2006 | CRT-SR (511)<br>CRT-AF-AVJA (114)<br>CRT-AF-drug (48) | Prospective 25.2±18 months | BVP <85% at 2 months follow-up | CRT-SR: 98.5±1.8%<br>CRT-AF-AVJA: 98.4±2.1%<br>CRT-AF-Meds: 88.2±3.1% | -CRT significantly improved LVEF, LVESV, NYHA class, functional capacity score in both CRT-SR and CRT-AF-AVJA/Meds groups<br>-CRT-AF-AVJA group, and not CRT-AF-drug group, showed significant improvements in LVEF, LVESV and functional capacity score<br>-Significantly higher rate of responders in CRT-AF-AVJA group (68%) than CRT-AF-drug group (18%) |
| Ferreira[57] 2008 | CRT-SR (78)<br>CRT-AF-AVJA (26)<br>CRT-AF-drug (27) | Retrospective 6 months | Not specified | CRT-SR: 95±13%<br>CRT-AF-AVJA: 98±6%<br>CRT-AF-Meds: 87±19% | -CRT significantly improved NYHA class in both CRT-SR and CRT-AF-AVJA/drug groups<br>-Significantly higher rate of responders in CRT-AF-AVJA group (85%) than in CRT-AF-drug group (85% vs. 52%; P<0.008)<br>-CRT-AF-drug was independently associated with higher mortality (HR 5.22; CI: 1.60-17.01; P=0.006) |
| Gasparini[58] 2008 | CRT-SR (1042)<br>CRT-AF-AVJA (118)<br>CRT-AF-drug (125) | Retrospective 34 (10-40) months | BVP <85% at 2 months follow-up | CRT-SR: not reported<br>CRT-AF-AVJA: 98.7±1.8%<br>CRT-AF-Meds: 89.4±2.4% | -CRT-AF-AVJA/drug and CRT-SR groups showed similar total mortality (8.4 vs. 8.9 per 100 person-year)<br>-CRT-AF-AVJA group showed significantly higher overall survival compared to CRT-AV-drug, primarily by reducing HF death (4.3 vs. 15.2 per 100 person-year; P<0.001) |
| Dong[59] 2010* | CRT-AF-AVJA (45)<br>CRT-AF-drug (109) | Retrospective 2.1 (1.4-3.0) years | Not specified | CRT-AF-AVJA: 99.0%<br>CRT-AF-Meds: 96.5% | -CRT improved LVEF (8.1% vs. 6.8%) and LVEDD (-0.7 vs. -0.4) in both CRT-AF-AVJA and CRT-AF-drug groups with no significant intergroup differences<br>-Improvement in NYHA class was significantly greater in CRT-AF-AVJA group than CRT-AV-drug group (-0.7 vs. -0.4; P=0.04)<br>-CRT-AF-AVJA was associated with increased survival (HR 0.13; CI 0.03-0.58; P=0.007) |
| Gasparini[53] 2013 | CRT-SR (6046)<br>CRT-AF-AVJA (443)<br>CRT-AF-drug (895) | Prospective 37 (14-58) months | BVP <85% and/or inadequate clinical response at 3 months follow-up | CRT-SR: not reported<br>CRT-AF-AVJA: 96±6%<br>CRT-AF-Meds: 87±14% | -CRT-AF-AVJA/drug and CRT-SR groups showed similar total mortality (6.8 vs. 6.1 per 100 person-year) and cardiac mortality (4.2 vs. 4.0)<br>-CRT-AF-drug was associated with significantly higher total mortality (HR 1.52; CI 1.26-1.82; P<0.001) and cardiac mortality (HR 1.57; CI 1.27-1.94; P<0.001) |
| Tolosana[54] 2013** | CRT-AF-AV Block*** (76)<br>CRT-AF-drug (79) | Prospective 30 (13-51) months | BVP <85% at 45 days follow-up | CRT-AF-AVJA: 97±4%<br>CRT-AF-Meds: 94±5% | AV Block did not improve overall and cardiovascular mortality in CRT-AF patients |

*88% permanent AF; **Only NYHA class III-IV; ***72% AVJA and 28% spontaneous AV block; BVP = biventricular pacing; CI = confidence interval; CRT = cardiac resynchronization therapy; HF = heart failure; HR = hazard ratio; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association functional class; QRSd = QRS complex duration; SR = sinus rhythm.

to pharmacological rate control. Future randomized controlled trials, comparing AVJ ablation vs. pharmacotherapy in CRT-AF patients are needed in order to establish the definite role of AVJ ablation in this patient group.

## References


1. European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010;12:1360-420.
2. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1-76.
3. Gupta S, Figueredo VM. Tachycardia mediated cardiomyopathy: pathophysiology, mechanisms, clinical features and management. Int J Cardiol 2014;172:40-6.
4. Patel D, Daoud EG. Atrioventricular junction ablation for atrial fibrillation. Cardiol Clin 2014;32:573-83.
5. Stavrakis S, Garabelli P, Reynolds DW. Cardiac resynchronization therapy after atrioventricular junction ablation for symptomatic atrial fibrillation: a meta-analysis. Europace 2012;14:1490-7.
6. Hayes DL, Boehmer JP, Day JD, et al. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. Heart Rhythm 2011;8:1469-75.
7. Kamath GS, Cotiga D, Koneru JN, et al. The utility of 12-lead Holter monitoring in patients with permanent atrial fibrillation for the identification of nonresponders after cardiac resynchronization therapy. J Am Coll Cardiol 2009;53:1050-5.
8. Ganesan AN, Brooks AG, Roberts-Thomson KC, Lau DH, Kalman JM, Sanders P. Role of AV nodal ablation in cardiac resynchronization in patients with coexistent atrial fibrillation and heart failure a systematic review. J Am Coll Cardiol 2012;59:719-26.
9. Scheinman MM, Morady F, Hess DS, Gonzalez R. Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias. JAMA 1982;248:851-5.
10. Huang SK, Bharati S, Graham AR, Lev M, Marcus FI, Odell RC. Closed chest catheter desiccation of the atrioventricular junction using radiofrequency energy--a new method of catheter ablation. J Am Coll Cardiol 1987;9:349-58.
11. Hoffmayer KS, Scheinman M. Current role of atrioventricular junction (AVJ) ablation. Pacing Clin Electrophysiol 2013;36:257-65.
12. Scheinman MM, Huang S. The 1998 NASPE prospective catheter ablation registry. Pacing Clin Electrophysiol 2000;23:1020-8.
13. Sousa J, el-Atassi R, Rosenheck S, Calkins H, Langberg J, Morady F. Radiofrequency catheter ablation of the atrioventricular junction from the left ventricle. Circulation 1991;84:567-71.
14. Proclemer A, Facchin D, Pagnutti C, Fioretti P, De Michele C. Safety of pacemaker implantation prior to radiofrequency ablation of atrioventricular junction in a single session procedure. Pacing Clin Electrophysiol 2000;23:998-1002.
15. Twidale N, Manda V, Holliday R, et al. Mitral regurgitation after atrioventricular node catheter ablation for atrial fibrillation and heart failure: acute hemodynamic features. Am Heart J 1999;138:1166-75.
16. Ozcan C, Jahangir A, Friedman PA, et al. Sudden death after radiofrequency ablation of the atrioventricular node in patients with atrial fibrillation. J Am Coll Cardiol 2002;40:105-10.
17. Nowinski K, Gadler F, Jensen-Urstad M, Bergfeldt L. Transient proarrhythmic state following atrioventricular junction radiofrequency ablation: pathophysiologic mechanisms and recommendations for management. Am J Med 2002;113:596-602.
18. Can I, Krueger K, Chandrashekar Y, Li JM, Dykoski R, Tholakanahalli VN. Images in cardiovascular medicine. Gerbode-type defect induced by catheter ablation of the atrioventricular node. Circulation 2009;119:e553-6.
19. Hindricks G. The Multicentre European Radiofrequency Survey (MERFS): complications of radiofrequency catheter ablation of arrhythmias. The Multicentre European Radiofrequency Survey (MERFS) investigators of the Working Group on Arrhythmias of the European Society of Cardiology. Eur Heart J 1993;14:1644-53.
20. Ozcan C, Jahangir A, Friedman PA, et al. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. N Engl J Med 2001;344:1043-51.
21. Spinale FG, Hendrick DA, Crawford FA, Smith AC, Hamada Y, Carabello BA. Chronic supraventricular tachycardia causes ventricular dysfunction and subendocardial injury in swine. Am J Physiol 1990;259:H218-29.
22. Balijepalli RC, Lokuta AJ, Maertz NA, et al. Depletion of T-tubules and specific subcellular changes in sarcolemmal proteins in tachycardia-induced heart failure. Cardiovasc Res 2003;59:67-77.
23. Selby DE, Palmer BM, LeWinter MM, Meyer M. Tachycardia-induced diastolic dysfunction and resting tone in myocardium from patients with a normal ejection fraction. J Am Coll Cardiol 2011;58:147-54.
24. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation : a meta-analysis. Circulation 2000;101:1138-44.
25. Kay GN, Ellenbogen KA, Giudici M, et al. The Ablate and Pace Trial: a prospective study of catheter ablation of the AV conduction system and permanent pacemaker implantation for treatment of atrial fibrillation. APT Investigators. J Interv Card Electrophysiol 1998;2:121-35.
26. Geelen P, Goethals M, de Bruyne B, Brugada P. A prospective hemodynamic evaluation of patients with chronic atrial fibrillation undergoing radiofrequency catheter ablation of the atrioventricular junction. Am J Cardiol 1997;80:1606-9.
27. Twidale N, Sutton K, Bartlett L, et al. Effects on cardiac performance of atrioventricular node catheter ablation using radiofrequency current for drug-refractory atrial arrhythmias. Pacing Clin Electrophysiol 1993;16:1275-84.
28. Daoud EG, Weiss R, Bahu M, et al. Effect of an irregular ventricular rhythm on cardiac output. Am J Cardiol 1996;78:1433-6.
29. Brignole M, Gianfranchi L, Menozzi C, et al. Assessment of atrioventricular junction ablation and DDDR mode-switching pacemaker versus pharmacological treatment in patients with severely symptomatic paroxysmal atrial fibrillation: a randomized controlled study. Circulation 1997;96:2617-24.
30. Marshall HJ, Harris ZI, Griffith MJ, Holder RL, Gammage MD. Prospective randomized study of ablation and pacing versus medical therapy for paroxysmal atrial fibrillation: effects of pacing mode and mode-switch algorithm. Circulation 1999;99:1587-92.
31. Brignole M, Menozzi C, Gianfranchi L, et al. Assessment of atrioventricular junction ablation and VVIR pacemaker versus pharmacological treatment in patients with heart failure and chronic atrial fibrillation: a randomized, controlled study. Circulation 1998;98:953-60.
32. Ueng KC, Tsai TP, Tsai CF, et al. Acute and long-term effects of atrioventricular junction ablation and VVIR pacemaker in symptomatic patients with chronic lone atrial fibrillation and normal ventricular response. J Cardiovasc Electrophysiol 2001;12:303-9.
33. Weerasooriya R, Davis M, Powell A, et al. The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). J Am Coll Cardiol 2003;41:1697-702.
34. Chatterjee NA, Upadhyay GA, Ellenbogen KA, McAlister FA, Choudhry NK, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis and systematic review. Circ Arrhythm Electrophysiol 2012;5:68-76.
35. Rodríguez-Mañero M, Pujol Salvador C, Martínez-Sande L, et al. Two-year follow-up In atrial fibrillation patients referred for catheter ablation of the

atrioventricular node. Journal of Atrial Fibrillation 2014;6:32-6.
36. Akerstrom F, Pachon M, Puchol A, et al. Chronic right ventricular apical pacing: adverse effects and current therapeutic strategies to minimize them. Int J Cardiol 2014;173:351-60.
37. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107:2932-7.
38. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002;288:3115-23.
39. Sharma AD, Rizo-Patron C, Hallstrom AP, et al. Percent right ventricular pacing predicts outcomes in the DAVID trial. Heart Rhythm 2005;2:830-4.
40. Steinberg JS, Fischer A, Wang P, et al. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. J Cardiovasc Electrophysiol 2005;16:359-65.
41. Tops LF, Schalij MJ, Holman ER, van Erven L, van der Wall EE, Bax JJ. Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. J Am Coll Cardiol 2006;48:1642-8.
42. Chen L, Hodge D, Jahangir A, et al. Preserved left ventricular ejection fraction following atrioventricular junction ablation and pacing for atrial fibrillation. J Cardiovasc Electrophysiol 2008;19:19-27.
43. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol 2005;16:1160-5.
44. Brignole M, Botto G, Mont L, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. Eur Heart J 2011;32:2420-9.
45. Brignole M, Gammage M, Puggioni E, et al. Comparative assessment of right, left, and biventricular pacing in patients with permanent atrial fibrillation. Eur Heart J 2005;26:712-22.
46. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J 2002;23:1780-7.
47. Orlov MV, Gardin JM, Slawsky M, et al. Biventricular pacing improves cardiac function and prevents further left atrial remodeling in patients with symptomatic atrial fibrillation after atrioventricular node ablation. Am Heart J 2010;159:264-70.
48. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281-329.
49. Healey JS, Hohnloser SH, Exner DV, et al. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail 2012;5:566-70.
50. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013;61:e6-75.
51. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107:2920-5.
52. European Heart Rhythm A, European Society of C, Heart Rhythm S, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Heart Rhythm 2012;9:1524-76.
53. Gasparini M, Leclercq C, Lunati M, et al. Cardiac resynchronization therapy in patients with atrial fibrillation: the CERTIFY study (Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry). JACC Heart Fail 2013;1:500-7.
54. Tolosana JM, Trucco E, Khatib M, et al. Complete atrioventricular block does not reduce long-term mortality in patients with permanent atrial fibrillation treated with cardiac resynchronization therapy. Eur J Heart Fail 2013;15:1412-8.
55. Gasparini M, Galimberti P, Leyva F. Complete atrioventricular block DOES reduce mortality in patients with atrial fibrillation treated with cardiac resynchronization therapy. Eur J Heart Fail 2014;16:114.
56. Gasparini M, Auricchio A, Regoli F, et al. Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. J Am Coll Cardiol 2006;48:734-43.
57. Ferreira AM, Adragao P, Cavaco DM, et al. Benefit of cardiac resynchronization therapy in atrial fibrillation patients vs. patients in sinus rhythm: the role of atrioventricular junction ablation. Europace 2008;10:809-15.
58. Gasparini M, Auricchio A, Metra M, et al. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. Eur Heart J 2008;29:1644-52.
59. Dong K, Shen WK, Powell BD, et al. Atrioventricular nodal ablation predicts survival benefit in patients with atrial fibrillation receiving cardiac resynchronization therapy. Heart Rhythm 2010;7:1240-5.