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INVASIVE ELECTROPHYSIOLOGY AND PACING (EK HEIST, SECTION EDITOR)

Programming Pacemakers to Reduce and Terminate Atrial Fibrillation

Margarida Pujol-López[1] · Rodolfo San Antonio[1] · José María Tolosana[1,2] · Lluís Mont[1,2,3]

Abstract

Purpose of Review The goal of this paper is to review present knowledge regarding preventive and antitachycardia pacing algorithms, aimed to reduce atrial fibrillation (AF) burden in patients when pacing is indicated.

Recent Findings Reactive antitachycardia pacing (ATP), the new generation of ATP, is significantly associated with a reduced risk of AF. In patients with indication for pacing and history of AF, pacemakers endowed with atrial preventive pacing and atrial ATP combined with managed ventricular pacing proved superior to standard dual-chamber pacing. Managed ventricular pacing is an algorithm that minimizes unnecessary right ventricular pacing. Progression to persistent AF is prevented by ventricular pacing minimization in patients with normal PR interval.

Summary The synergistic effect of pacemakers that combine atrial preventive pacing with reactive ATP and with algorithms that minimize ventricular pacing can reduce AF incidence and decrease the combined endpoint of permanent AF, hospital admissions, and mortality.

Keywords Atrial fibrillation · Atrial pacing therapies · Antitachycardia pacing · Pacing minimization algorithms

Abbreviations

AF	atrial fibrillation
AV	atrioventricular
AT	atrial tachycardia
ATP	antitachycardia pacing
DDDRP	dual-chamber pacemaker with atrial preventive pacing + atrial antitachycardia pacing
IRAF	immediate reinitiation of atrial fibrillation
MVP	managed ventricular pacing
PAC	premature atrial complex

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✉ Lluís Mont
lmont@clinic.cat

Margarida Pujol-López
mapujol@clinic.cat

Rodolfo San Antonio
rvsanan@clinic.cat

José María Tolosana
tolosana@clinic.cat

1 Institut Clínic Cardiovascular (ICCV), Hospital Clínic, Universitat de Barcelona, Barcelona, Catalonia, Spain

2 Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain

3 Institut Clínic Cardiovascular (ICCV), Hospital Clínic, Universitat de Barcelona, Catalonia, Spain. C/ Villarroel 170, 08036 Barcelona, Spain

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia [1]. In the USA, AF affects 3 to 6 million individuals and is expected to affect 12.1 million by 2030 [2]. In Europe, about 8.8 million people have AF, and this is expected to rise dramatically to 17.9 million by 2060 [3].

AF is independently associated with a 2-fold increase in all-cause mortality risk in women and a 1.5-fold increase in men [4]. AF is a well-known risk factor for ischemic stroke, which in some cases is the first manifestation of the arrhythmia. The huge contribution of AF to the incidence and outcome of ischemic stroke is shown by the 5-fold increased risk of stroke in patients with the arrhythmia [5] and the association of AF with 20–30% of all strokes. In addition, AF is associated with a higher risk of myocardial infarction, heart failure (20–30% of all AF patients have left ventricular

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dysfunction), and hospitalization (10–40% of AF patients are hospitalized every year) [6].

Both pharmacological and nonpharmacological options are available to treat AF. Nonpharmacological therapy includes cardiac pacing, whose usefulness in the prevention and treatment of AF has only been demonstrated in patients with conventional indication for pacing; the value of pacing as a primary therapy for prevention of recurrent AF has not been established [7].

In patients with implanted pacemakers, several studies have shown a higher incidence of AF, as compared to normal population of the same age; longer time elapsed since the implant and older age were associated with AF [8, 9]. For this reason, there is great interest in exploring the role of pacing in prevention and treatment of AF. Pacemakers may prevent AF by mechanisms such as correction of bradycardia-induced dispersion of atrial repolarization, suppression of AF triggers, change in atrial activation patterns, and prevention of electromechanically related atrial stretch [10].

On the other hand, in patients suffering from bradycardia, AF is a common comorbidity, being present in up to one third of patients [11, 12]. Antitachycardia pacing (ATP) algorithms can reverse this arrhythmia in some patients.

The goal of this paper is to review algorithms and techniques that aim to reduce and terminate AF in a population with implanted pacemakers.

Types of Programming to Prevent and/or Treat Atrial Fibrillation

Pacing Mode

Physiologic pacing has been shown to be superior to single-chamber ventricular pacing in the prevention of AF [9, 13]. Physiologic pacing modes maintain atrioventricular (AV) synchrony, which is associated with lower atrial pressure. This pacing is achieved by dual-chamber (DDD and DDDR) and atrium-based pacing (AAI and AAIR), in contrast to the ventricle-based mode of pacing (VVI and VVIR). However, the choice between AAI and DDD pacing in sinus node disease (SND) has been controversial. Atrial-based pacing modes (AAI and DDD) have been compared with ventricular-based pacing mode (VVI) in major randomized controlled trials [14–18] and reviewed in an expert consensus document [19]. According to the 2018 Guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay (American College of Cardiology/American Heart Association/Heart Rhythm Society) [20], atrial-based pacing modes appear to be associated with a lower incidence of AF, as an advantage over ventricular-based pacing modes. Regarding the efficacy of dual-chamber (DDD and DDDR) versus single-chamber atrial pacing (AAI and AAIR) in symptomatic patients with SND, the DANPACE trial showed that AAIR pacing is associated with a higher incidence of paroxysmal AF [18]. Nevertheless, after a mean register-based follow-up of 8.9 years, no difference was found in mortality or in any nonfatal clinical outcome (AF hospitalization, stroke, heart failure) among DANPACE trial participants [21].

In symptomatic patients with SND and intact AV conduction without evidence of conduction abnormalities, current guidelines [20] recommend dual-chamber or single-chamber atrial pacing. In patients with dual-chamber pacemakers and intact AV conduction, it is reasonable to program the dual-chamber pacemaker to minimize ventricular pacing. Unnecessary ventricular pacing could raise the rate of atrial arrhythmias [22].

Preventive Algorithms

Implantable devices have atrial pacing algorithms designed to prevent atrial arrhythmias. Vincenti et al. [23] described the onset mechanism of paroxysmal AF detected by ambulatory Holter monitoring as a triggering premature atrial complex (PAC), a bradyarrhythmic event or a post-extrasystolic pause. Most paroxysmal AF episodes are initiated by PAC, bradycardia, or immediate reinitiation of AF (IRAF) [24]. Coumel et al. [25] described how an AF crisis appeared predominantly in a vagal context in some patients. In athletes, AF episodes are predominantly vagal [26], and therefore, some algorithms have been designed for the post-exercise situation.

Preventive algorithms have been designed to increase the atrial baseline pacing rate by overdrive-pacing the atrium, suppressing PACs or preventing pauses [27]. Device algorithms attempt to counteract the onset of AF, on the one hand avoiding bradycardia and on the other hand responding to triggers. Algorithms can stimulate the atrium continuously beyond its intrinsic activity or respond to triggers (for example the detection of a PAC starts atrial pacing; post-exercise response or post-AF response) (Table 1).

Should Algorithms for the Prevention of Atrial Fibrillation Be Used?

The AF-preventive algorithms in pacemakers have not shown an unequivocal clinical efficacy, and no definitive conclusion on the merits of their use has been reached [28]. The *Atrial Dynamic Overdrive Pacing Trial* (ADOPT) [29] evaluated the efficacy and safety of the AF suppression algorithm (Abbott) in a randomized study of patients with sick sinus syndrome and AF. This algorithm increases the pacing rate when the native rhythm emerges and periodically reduces the rate in order to search for intrinsic atrial activity. Overdrive atrial pacing with the AF suppression algorithm decreased symptomatic AF burden significantly at 6 months in the ADOPT population. However, other studies have shown controversial

Table 1 The preventive algorithms offered by the various pacemaker companies are all very similar

Preventive algorithms	
Responding to triggers	Continuous overdrive atrial pacing
PAC suppression: Increases the heart rate upon detection of a PAC. Post-PAC response: Controls the atrial rate after a PAC by pacing.	Pace conditioning: Atrial pacing rate above the underlying intrinsic rhythm. Rate soothing: Overdrive pacing of the atrium at a rate just above the sinus rate. Similar to the pace-conditioning algorithm but without a large increase in heart rate.
Post-exercise response: Avoids a rapid drop in heart rate after exercise; the pacemaker maintains the post-exercise rate. Post-AF response: Attempts to prevent AF episodes by pacing at a high rate immediately after the end of the preceding arrhythmia.	

According to Mitchell et al. [27], the algorithms rely on the pacemaker's classification of atrial events, either in response to triggers or by continuous overdrive atrial pacing

PAC premature atrial complex

results. The *Atrial Septal Pacing Clinical Efficacy Trial* (ASPECT) researchers reported that the combination of three atrial prevention pacing algorithms did not decrease device-classified atrial tachyarrhythmia (AT) frequency or burden during a 3-month cross-over period in patients with bradycardia and either septal or nonseptal atrial pacing leads [30]. The *Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial* (ASSERT) results showed that continuous atrial overdrive pacing does not prevent AF [12] and the AFTherapy study did not find a significant benefit of conventional atrial overdrive pacing or preventive pacing therapies [31] (Fig. 1a).

In 2005, Knight et al. [36] published an advisory summarizing the evidence on pacing modalities and algorithms used to prevent and terminate AF: the evidence to support their use is limited, although these algorithms appear to be safe and usually add very little cost. In patients with a bradycardia indication for pacing, pacing algorithms play, at most, a modest adjunctive role in arrhythmia control.

Terminating Algorithms

Terminating algorithms correspond to ATP, a therapy based on atrium stimulation at high frequencies to cardiovert an atrial tachyarrhythmia to sinus rhythm. These algorithms treat the

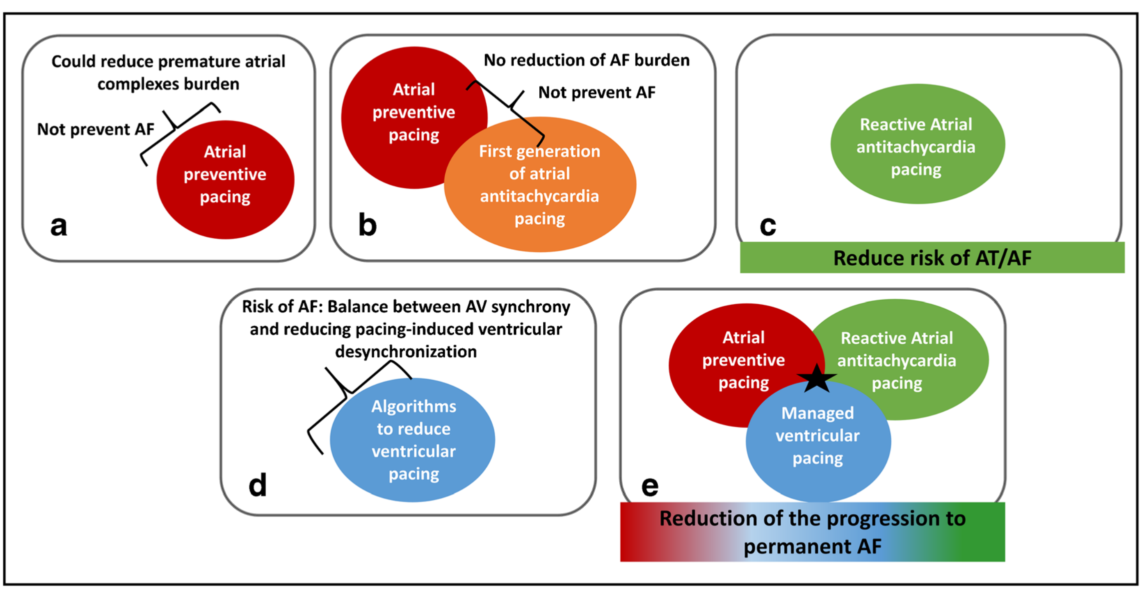

Fig. 1 Impact of atrial pacing therapies and algorithms to reduce ventricular pacing on the progression of atrial fibrillation [32–35]. *AF* atrial fibrillation, *AT* atrial tachycardia, *AV* atrioventricular

arrhythmia once established by delivering a series of atrial pacing stimuli at an atrial cycle length shorter than the detected arrhythmia. Many AF episodes are initiated as organized atrial arrhythmias (atrial tachycardia or flutter) susceptible to overstimulation [37]. There are three ATP types depending on the relationship with the tachycardia cycle [38]:

– Burst ATP: Impulse trains at constant coupling interval in a programmable number. The frequency corresponds to a percentage of the tachycardia cycle.

  *Burst +: Programmable number of pulses followed by 2 premature stimuli.

– Ramp ATP: Series of pacing stimuli delivered at decreasing intervals. Autodecremental coupling.
– Reactive ATP (Medtronic)**:** Multiple deliveries of programmed atrial ATP during an AT episode in response to either of the following events: (a) change in the atrial rhythm's cycle length or regularity (rhythm change); (b) programmed amount of time elapsed (time duration).

First generation of ATP therapy treated atrial arrhythmias as if they were ventricular arrhythmias, and all therapies were exhausted within 10 min. This type of ATP only allowed redelivery after an unsuccessful ATP therapy and expiration of a time interval, achieving 54% efficacy, as defined by the device, according to Atrial Therapy Efficacy and Safety Trial (ATTEST) results [39]. In a multivariate analysis, Boriani et al. [40] found that predictors of ATP efficacy include longer arrhythmia cycle lengths, shorter ATP delivery delays, NYHA class I, episode classification as nonimmediate recurrence of AT, absence of overlap in the atrial arrhythmia device detection windows, and flecainide treatment.

Reactive ATP (Medtronic), the new generation of ATP, allows multiple deliveries upon the detection of change in rhythm regularity or cycle length [32••, 33••]. This allows additional ATP therapy attempts during long AT or AF episodes. Standard ATP therapies fail to take advantage of rhythm changes and are unable to terminate long-lasting atrial tachyarrhythmia. Reactive ATP continues to monitor atrial rhythm, watches for any change in rate or regularity, and then applies ATP when the episode is most amenable to termination by pacing. When effective, reactive ATP prevents long episodes from being sustained for hours or days [34•]. Among real-world patients from a large device database, reactive ATP therapy was significantly associated with a reduced risk of atrial tachyarrhythmia and AF [35•] (Fig. 1c).

Combination of Atrial Prevention and Termination Therapies

The *Atrial Therapy Efficacy and Safety Trial* (ATTEST) was a randomized study to evaluate preventive pacing and ATP in patients with symptomatic AF or AT. The researchers implanted DDD pacemakers with three atrial preventive pacing algorithms and two ATP algorithms in 368 patients and concluded that the atrial prevention and termination therapies combined did not reduce AT/AF burden or frequency [39].

The *Prevention or Termination* (POT) trial [41] aimed to determine if ATP on top of preventive pacing algorithms decreased AF burden. In a crossover study, the authors randomized patients to two groups, preventive pacing algorithms or preventive pacing algorithms + ATP; the results showed that pacing with preventive pacing algorithms decreased AF burden in patients with pacing indication. However, the POT trial observed no further decrease in AF burden or in the number of episodes when adding ATP on top of preventive pacing algorithms.

A recently published systematic review and meta-analysis to evaluate the role of pacing algorithms in preventing AF progression showed that atrial pacing therapy algorithms could suppress premature atrial complex burden but did not prevent AF progression (Fig. 1a, b). Nevertheless, the use of these algorithms is considered safe and the decision about their utilization should be made on an individual basis [32].

Reducing Right Ventricular Pacing

The landmark *Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction* (SAVE PACe) trial associated right ventricular pacing minimization algorithms with reduced persistent AF, compared with conventional dual-chamber pacemakers, in patients with sinus node disease [22]. Both American and European guidelines recommend the use of pacing algorithms to reduce the burden of ventricular pacing [42, 43]. The *Mode Selection Trial* (MOST) found a linear increase in the risk of AF up to cumulative ventricular pacing rates even when AV synchrony is preserved [44]. On the other hand, the *Minimize Right Ventricular Pacing to Prevent Atrial Fibrillation and Heart Failure* (MINERVA) trial showed that a secondary endpoint of managed ventricular pacing (MVP, an algorithm designed to give priority to intrinsic ventricular activation, minimizing right ventricular pacing) did not significantly reduce incidence of AF compared with the control DDDR group. Similarly, a recent systematic review and meta-analysis of randomized clinical trials concluded that minimizing ventricular pacing using the current algorithms failed to significantly reduce risk of AF progression [32]. The explanation of this result could be related to the balance between AV synchrony and pacing-induced ventricular desynchronization (Fig. 1d). The benefit of preserving AV synchrony to avoid AF is well established from large randomized trials [14]. In the DANPACE trial, the reason for excess AF in the AAIR group may have been the prolonged AV conduction and AV decoupling that is often observed with atrial pacing [18, 33].

Different strategies and algorithms are offered by manufacturers to reduce unnecessary ventricular pacing to a minimum and to favor intrinsic AV conduction (Table 2) [45]. The concept of AV delay hysteresis refers to intermittent prolongation of the AV delay to promote intrinsic activation. In addition, devices have mode-switching algorithms: AAI/ADI ↔ DDD or AAI with VVI backup in order to minimize unnecessary ventricular pacing. In the first case (AAI/ADI ↔ DDD), the device switches to DDD mode when loss of AV conduction occurs, but can return to AAI/ADI when conduction is regained. In the second case (AAI with VVI backup), the device operates in AAI mode with asynchronous VVI backup pacing and mode switching relies on the detection of long R-R intervals.

One More Step: Combining the Preventing and Terminating Algorithms with Managed Ventricular Pacing

Advanced pacemakers have all three of the capabilities that we have analyzed separately in this review: atrial pacing algorithms to prevent atrial tachyarrhythmias, ATP, and algorithms to minimize right ventricular pacing. The MINERVA trial, a multicenter randomized study, evaluated the combination of atrial-preventing pacing + reactive ATP (Medtronic) + MVP (Medtronic) to reduce mortality, morbidity, or progression to permanent AF, compared with standard dual-chamber pacing (control DDDR) [33].

MVP (Medtronic) is an algorithm that aims to reduce right ventricular pacing (Table 2). It provides atrial-based pacing to promote intrinsic ventricular conduction and reduce unnecessary ventricular pacing. It also warrants ventricular backup pacing if loss of AV conduction is detected. This algorithm allows AAI pacing at long AV intervals to promote normal conduction and prompts switching to DDD mode when AV block is identified. MVP was recently updated to incorporate a limit to the maximal AV interval allowed (a difference with the first MVP version) [45].

The MINERVA study [33] randomized 1166 patients, after a 1-month run-in period, to 3 groups: (a) DDDR (control), (b) atrial preventive pacing+reactive ATP+MVP (DDDRP+MVP), and (c) DDDR+MVP. All participants had indication for permanent pacing and paroxysmal or persistent atrial tachyarrhythmias. The primary endpoint (2-year incidence of a combined outcome of death, cardiovascular hospitalization, or permanent AF) occurred at the following rates: 26.5%, DDDR (control group); 19.8%, DDDRP+MVP; and 21.4%, DDDR+MVP. The DDDRP+MVP approach proved to be superior to standard dual-chamber pacing. In additon, a post hoc analysis revealed that DDDRP+MVP was associated with a lower risk of permanent AF compared with MVP. Finally, the risk of AF lasting longer than 1 day and longer than 7 days was also significantly lower in the group with the combination of the 3 therapies (Fig. 1e).

Using data from the MINERVA trial, Padeletti et al. [34•] reported that DDDRP + MVP delays AF disease progression in patients with dual-chamber pacemakers, with reactive ATP efficacy being an independent predictor of permanent or persistent AF reduction. Permanent or persistent AF risk was significantly reduced in patients with high (> 44%) reactive ATP efficacy. The progression of atrial disease seems to be prevented or delayed through termination of atrial tachyarrhythmia episodes when they are slow and regular, thus becoming amenable to termination by pacing [34•].

In another substudy of the randomized MINERVA trial, Boriani et al. evaluated the atrial antitachycardia pacing impact on AT/AF-induced atrial remodeling. Compared to DDDR or MVP, DDDRP+MVP reduces early recurrence of AT/AF and favors reduction of left atrium diameter [46].

Effect of PR Interval and Pacing Mode on Persistent AF Incidence

Choosing between MVP and DDDR may be difficult due to the delicate balance between reestablishing a favorable AV synchrony by ventricular pacing with optimal transmitral left ventricle filling and inducing ventricular dyssynchrony and LV dysfunction by pacing. Based on the existence of a continuum from prolonged PR to third-degree AV block, Boriani

Table 2 Available algorithms to reduce to minimum ventricular pacing and to favor intrinsic atrioventricular conduction [45]

	Abbott	Biotronik	Medtronic	Boston	Sorin-LivaNova-Microport
AV conduction search interval	VIP mode	IRS^{plus}/I-Opt	SAV+	AV Search+	DDD CAM
Mode switching for enhancing AV conduction		Ventricular pace suppression (ADI↔DDD)	Managed ventricular pacing mode (MVP) (ADI↔DDD)	RYTHMIQ (AAI with VVI backup)	AAI-SafeR (ADI↔DDD)

ADI sensing in both chambers, but pacing only in the atrium, *AV* atrioventricular, *CAM* automatic mode switching, *IRS* intrinsic rhythm support, *SAV+* search AV+, *VIP* ventricular intrinsic preference

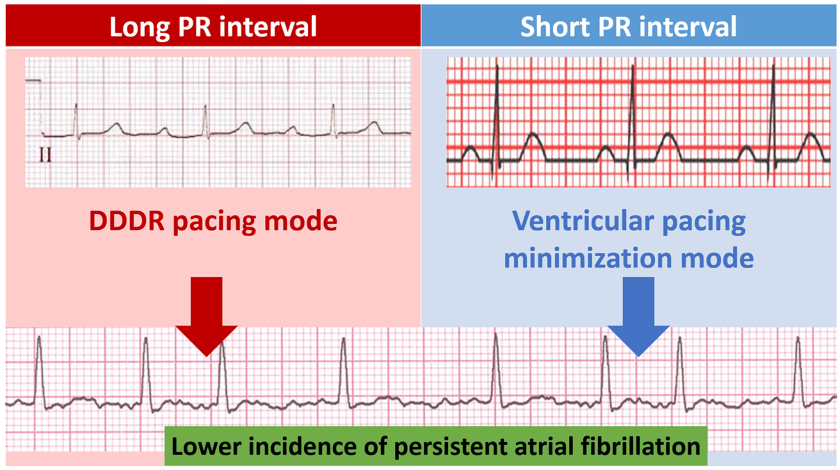

Fig. 2 PR interval may be used as a selection criterion to identify the optimal physiological pacing mode. Patients with prolonged PR interval (≥ 180 ms) receive physiological pacing when treated by DDDR pacing. Patients with normal AV conduction (short PR < 180 ms) benefit from algorithms which minimize right ventricular pacing [47•]

et al. hypothesized that PR interval may represent an important screening factor to select optimal pacing mode. In patients with a short PR interval, they found that ventricular pacing minimization is associated with lower incidence of persistent AF compared with DDDR pacing. On the other hand, in patients with a long PR interval, DDDR pacing is associated with a lower incidence of persistent AF, compared to MVP mode (Fig. 2). In summary, progression to persistent AF is prevented by right ventricular pacing minimization in normal PR patients and by standard dual-chamber pacing in long PR patients (≥ 180 ms) [47•].

Along the same line, the PREFER MVP trial showed a higher incidence of persistent AF in MVP vs. DDD pacing in patients with PR interval ≥ 230 ms. [48] The use of algorithms that minimize right ventricular pacing may benefit patients with normal spontaneous AV conduction but should be evaluated with caution in patients with long PR interval.

The findings by Boriani et al. [47•] reinforced the results of the SAVE PACe trial [22], in which the significant reduction of persistent AF risk in the right ventricular pacing minimization arm was attributable to prevention of ventricular pacing in patients with normal PR.

Reducing AF with Continuous Optimization of Resynchronization Therapy

Gasparini et al. [49] reported that about 10% of cardiac resynchronization therapy (CRT) patients with permanent AF revert spontaneously to sinus rhythm, mostly in the first year but late reversion even at 5 years is possible. They identified 4 predictors of reversion: smaller left ventricle end-diastolic diameter, shorter QRS duration after CRT, smaller left atrial diameter, and AV junctional ablation. Patients who had all four predictors had a 60% chance of resuming sinus rhythm. The authors suggested that implantation of an atrial lead should be considered at the time of CRT implantation [49].

In the same line, Badhwar et al. presented an abstract in *Heart Rhythm Scientific Sessions* (2019) reporting that spontaneous conversion of AF to sinus rhythm after CRT can occur within a relatively short time period. They attributed these results to a significant improvement in left ventricle hemodynamics and mitral regurgitation, while late cardioversion may be attributed to left atrium reverse remodeling [50].

Birnie et al. [51] and recent findings presented by Hsu et al. [52]—a real-world analysis of 37,450 patients—indicated that AdaptivCRT (Medtronic), an algorithm that automatically adjusts AV delays each minute to achieve ventricular fusion through left ventricle or biventricular pacing, was associated with a lower incidence of AF (54% lower 2-year risk of > 48 h of AF), compared to standard biventricular CRT (AdaptivCRT off).

Conclusions

Atrial preventive pacing therapies alone or in combination with first-generation ATP are safe but have scant beneficial effect. New-generation reactive ATP can reduce the risk of AF. The combination of atrial preventive pacing with new-generation reactive ATP and with algorithms that minimize ventricular pacing could offer a synergistic effect to reduce and terminate AF.

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Compliance with Ethical Standards

Conflict of Interest Margarida Pujol-López and Rodolfo San Antonio declare that they have no conflict of interest in relation to the content of this manuscript. Dr. JM Tolosana has received honoraria as a lecturer and consultant for Abbott, Boston Scientific and Medtronic. Dr. L. Mont has received unrestricted research grants, fellowship program support, and hononaria as a lecturer and consultant from Abbott, Biotronik, Boston Scientific, Livanova, and Medtronic.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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