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Review

# Current status of atrial pacing algorithms for the prevention of atrial fibrillation: Should algorithms be used?

Toshiko Nakai, MD*, Ichiro Watanabe, MD, Atsushi Hirayama, MD

*Division of Cardiology, Department of Medicine, Nihon University School of Medicine, 30-1 Oyaguchi kami-cho, Itabashi-ku, Tokyo 173-8610, Japan*

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ABSTRACT

Since the development of an atrial pacing algorithm for preventing atrial fibrillation (AF), approximately 20 years ago, many clinical trials have demonstrated the effectiveness of atrial pacing with respect to AF prevention. Nevertheless, the actual effectiveness of AF suppression via atrial pacing remains under debate, and no definitive conclusion has been reached. The AF suppression algorithms embedded in pacemakers have not demonstrated an unequivocal clinical efficacy that would support changing of the guidelines to recommend such algorithms. In this review of studies conducted since 2006, we discuss the efficacies of these AF suppression algorithms and their usefulness in patients requiring pacemaker implantation.



**Contents**



## 1. Introduction

Atrial fibrillation (AF) is a highly prevalent atrial arrhythmia that affects approximately 10% of individuals older than 75 years of age and tends to increase in prevalence with advancing age [1–3]. Although AF itself is not life threatening, it is a risk factor for stroke, and the AF-associated stroke mortality rate is high [4–6]. Antiarrhythmic agents are usually effective for treating AF; however, some cases are refractory to pharmacological agents. Although various treatments for AF such as catheter ablation have been used, perfect rhythm control is not easily achieved.

An atrial overdrive pacing algorithm for the prevention of AF was initially reported by Murgatroyd et al. in 1994 [7], and other alternative pacing algorithms have since been developed, including post-premature atrial contraction (PAC) and post-exercise response algorithms and atrial overdrive pacing [8–10,33]. Although many clinical trials have been conducted, the usefulness of AF control algorithms has remained a matter of debate during the past 20 years [8–16]. Additionally, none of the pacemaker guidelines includes an AF suppression algorithm as a standard programming feature for AF prevention in pacemaker patients. The stated reason is that pacemaker-embedded AF suppression algorithms have not demonstrated unequivocal clinical efficacy. In this review, we summarize the previous clinical trials, characterize the efficacy of atrial pacing for AF prevention, and discuss the practical clinical applications of this algorithm.

* Corresponding author. Tel.: +81 33972 8111x2412; fax: +81 33972 1098.
*E-mail address:* nakai.toshiko@nihon-u.ac.jp (T. Nakai).

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## 2. Prevalence and impact of AF in clinical practice

AF is the most common arrhythmia worldwide, and its prevalence increases with age; AF occurs in approximately 10% of the general population older than 75 years of age [1–3]. The prevalence of sick sinus syndrome or atrioventricular block, which requires pacemaker implantation, also increases with age [17,18]. Asymptomatic AF episodes are detected in approximately 10% of pacemaker recipients, an higher incidence than that observed in the general population [19–21]. AF poses a significant risk of stroke and systemic thromboembolism. Stroke resulting from a large cerebral infarction consequent to a left atrial appendage thrombus is the most severe complication of AF and is associated with a high mortality rate [22,23]. Annually, AF is responsible for 20% of all strokes. Strong evidence suggests that anticoagulant therapy could reduce the annual incidence of stroke in patients with AF; therefore, AF patients should certainly be treated with anticoagulation agents to prevent stroke [24]. However, anticoagulation therapy is underused in clinical practice because of the difficulty associated with drug administration and the risk of bleeding complications [25]. Nevertheless, AF prevention should be given the utmost priority.

## 3. Benefit of dual-chamber pacing for AF prevention

Several studies have demonstrated that dual-chamber pacing, through which ventricular pacing can be minimized, is superior to single-chamber ventricular pacing in terms of reducing the incidence of AF [26–31]. Atrial (atrial–atrial interval; AAI) and physiologic pacing (dual-chamber pacing, dual-chamber sensing, dual response, and rate-adaptive; DDDR) avoid atrioventricular dyssynchrony, which is associated with increased atrial pressure. The Mode Selection Trial (MOST) study [32] demonstrated a linear increase in the risk of AF up to cumulative ventricular pacing rates of approximately 80–85% in the DDDR and ventricular pacing, ventricular sensing, inhibition response and rate-adaptive (VVIR) modes (Fig. 1). Nielsen et al. [33] compared the AAI and DDDR modes by observing changes in the left atrial (LA) diameter and left ventricular fractional shortening (LVFS). In the DDDR mode, the LA diameter increased significantly ($p<0.05$) and the LVFS decreased significantly ($p<0.01$) [33]. Additionally, AF occurred significantly less often in the AAI mode. Therefore, by increasing the atrial stress associated with ventricular dyssynchrony, ventricular pacing might increase the risk of AF even when AV synchrony has been preserved. A large, randomized trial conducted by Connolly et al. [29] reported a significantly lower annual incidence of AF in the physiologic pacing group (5.3%) than in the ventricular pacing group (6.6%).

## 4. AF suppression algorithm and prevention mechanism

The atrial overdrive pacing algorithm is the most commonly used algorithm for AF prevention. Other pacing strategies have also been developed, including atrial pacing in response to atrial premature beats (post-PAC response), pacing in response to exercise (post-exercise rate control), and post-mode-switch pacing (Fig. 2) [34]. The suppression of potential AF triggers mechanisms, including long pauses after premature beats and atrial refractory period dispersion, through the elimination of pauses consequent to bradycardia or the reduction of premature beats is considered the mechanism responsible for overdrive pacing-mediated AF prevention. Atrial pacing has also been suggested to prevent AF by improving the synchronization of atrial depolarization. Therefore, alternative-site pacing such as Bachmann's bundle pacing, atrial septum pacing, and multisite pacing have been used to prevent AF in several pacing trials [16,35–39]. Several of these studies have demonstrated the efficacy of alternative site pacing versus conventional right atrial appendage pacing for reducing the incidence of AF; however, other studies have not demonstrated similar efficacies. Therefore, alternative-site pacing currently remains controversial in clinical settings.

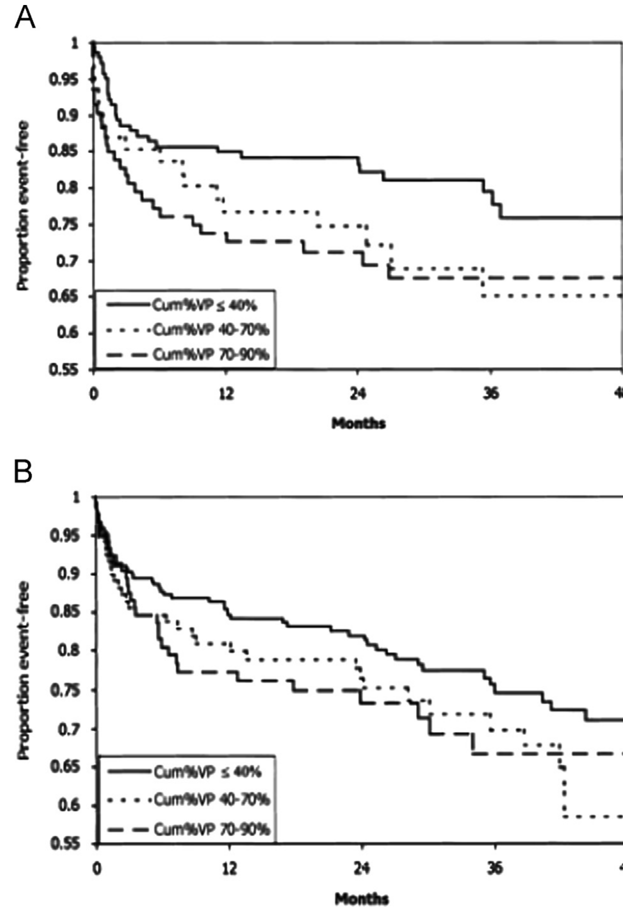


**Fig. 1.** Kaplan–Meier curves of freedom from documented incidences of atrial fibrillation (AF) as shown by the cumulative percentages of ventricular pacing (cum %VP) during the first 30 days. (A) DDDR mode; (B) VVIR mode (reproduced with permission: reference [31]).

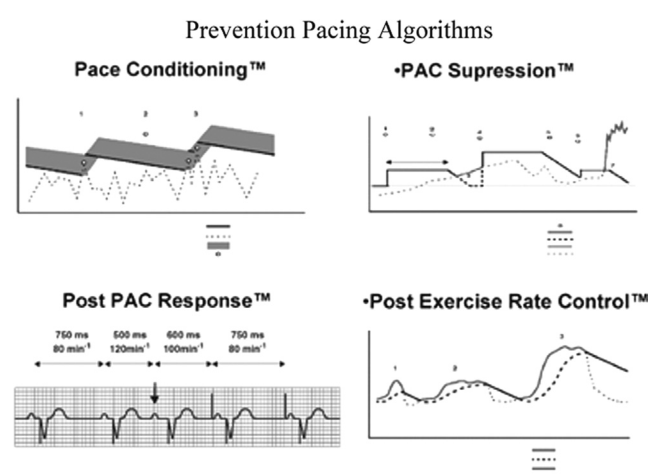


**Fig. 2.** Schematic view of 4 atrial fibrillation prevention pacing algorithms (reproduced with permission: reference [33]).

## 5. Clinical trials of AF suppression algorithms

Many randomized clinical trials of AF suppression algorithms were conducted during the previous decade. Most of these trials demonstrated the efficacy of atrial pacing for AF prevention; however, several studies yielded contrasting results. As a result, a consensus has not been reached regarding the utility of these algorithms. The study conditions, including the study populations, patients' ages, concomitant medications, pacing strategies, and study endpoints, varied among the trials. In addition, the study groups were fairly small. In 2005, Knight et al. summarized data obtained from the clinical trials of various AF prevention algorithms and published the findings as an American Heart Association science advisory [40]. Furthermore, Mizutani summarized the various pacing techniques used for AF prevention, including the pacing modes and pacing site or sites [41]. Therefore, we decided to review the clinical trials that were published in 2006 and thereafter. These trials are summarized in Table 1. The study patients ranged in age from 50 to 73 years. A majority of the trials compared atrial pacing in the AF suppression algorithm ON condition vs. the OFF condition.

Shuchert et al. [13] used 4 different atrial pacing algorithms for AF prevention: pace conditioning (continuous dynamic overdrive pacing) and 3 triggered pacing algorithms (PAC suppression, post-PAC response, and post-exercise response). The patients were randomly selected to undergo triggered atrial overdrive pacing alone (3 pacing functions; "triggered group") or a combination of continuous and triggered atrial overdrive pacing (4 pacing functions; "combined group"). Several patients in the combined group could not tolerate the high-rate pacing and were consequently excluded from the evaluation. The percentage of patients undergoing atrial pacing in the combined group was 97%, and the AF burden in this group was 2.1%. The percentage of atrial pacing in the triggered group was significantly lower at 85%; however, the AF burden was also significantly lower at 0.1%, thus demonstrating the pacing algorithm to be effective for AF prevention. In contrast, Camm et al. [10] had previously used the same device (Selection 9000, Vitatron, Maastricht, Netherlands) and had been unable to confirm the effectiveness of preventative atrial pacing in a very similar population. The discrepant results between these 2 trials highlight the difficulty in establishing convincing evidence for the efficacy of preventative atrial pacing. Most trials have selected 90 beats per minute (bpm) as the upper limit for continuous overdrive pacing because pacing above 90 bpm cannot be tolerated for a long period. Only 1 relatively early study, conducted by Pürefellner et al. [9], used a relatively high pacing rate of 90 bpm or 120 bpm for 10 min of post-mode-switch overdrive pacing (PMOP), and the percentage of atrial pacing in that study was high in comparison to that of other trials. Given the results of that trial, the authors recommended programming the device at a PMOP rate of 90 bpm and concluded that PMOP could effectively prevent the early occurrence of AF and that the pacing rate was well tolerated. In contrast, Sulke et al. used atrial pacing at an upper limit of 80 bpm and did not observe that atrial pacing could effectively reduce the AF burden. The results of these studies suggest that the atrial pacing rate for AF prevention should be sufficiently high to inhibit the AF triggers.

In a study of the atrial pacing preference (APP) algorithm, Ogawa et al. [12] randomly programmed pacemakers as APP OFF and APP ON at 3 different settings (8, 16, and 33 cycles). The authors found that the most effective setting differed according to the patient and thus concluded that this therapy necessitated the determination of the "optimal" setting for each patient. The efficacy of any atrial pacing algorithm depends on background factors such as hypertension, diabetes, and any other condition that could promote tissue fibrosis. Furthermore, the effect of the

**Table 1**
Summary of the clinical trials of AF prevention algorithms conducted between 2006 and 2013.

| Study/authors | Sample size (*n*) | Mean age (years) | Study patients (inclusion criteria) | Algorithm | Follow-up period | Device used | Primary endpoints | RA pacing (%) | RV pacing (%) | Study conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| **PMOP**/Pürefellner et al. [9] | 122 | 70 | Bradycardia with AF history | Post-mode-switch overdrive pacing | 8 months | AT 5000 (Medtronic) | Frequency of AT/AF, AF burden | No data available | No data available | Algorithm effective |
| **AFTherapy study**/Camm et al. [10] | 372 | 65 | Bradycardia with drug-refractory AF | Pace conditioning, PAC suppression, post-PAC response, post-exercise response | 4 months | Selection 9000 (Vitatron) | AF burden | 89 | 79 | Controversial |
| **PAFS study**/Sulke et al. [11] | 182 | 72 | Bradycardia with AF history | Post-AF pacing of the atrium at 80 bpm up to 600 beats | 4 months | Selection 9000 (Vitatron) | AF burden | 82 | 62 | Algorithm ineffective |
| **APP study**/Ogawa et al. [12] | 51 | 70 | Bradycardia with AF history | Pacing interval reduction by 8 ms when a *P–P* wave is detected | 6 months | Model 1280 (Guidant) | AF burden | 86 | 94 | Algorithm effective |
| **APP study**/Schuchert et al. [13] | 171 | 72 | Bradycardia with AF history | Dynamic overdrive pacing, PAC suppression, post-PAC response, post-exercise response | 6 months | Selection 9000 (Vitatron) | AF burden | 81 | 93 | Algorithm effective |
| **SAFARI trial**/Gold et al. [14] | 555 | 72 | Bradycardia with AF history | Six different prevention pacing therapies | 6 months | Selection 9000 (Vitatron) | Permanent AF, AF burden | 96 | 46 | Algorithm effective |
| **ASSERT**/Hohnloser et al. [15] | 2343 | 76 | Bradycardia without AF history | Continuous atrial overdrive pacing | 30 months | IDENTITY (SJM) | Symptomatic/asymptomatic AT/AF lasting > 6 min | No data available | No data available | Algorithm ineffective |
| **SAFE study**/Lau et al. [16] | 385 | 70 | Sick sinus syndrome | Overdrive pacing by 5–10 bpm up to 130 bpm | 36 months | IDENTITY (SJM) | Occurrence of AF | 92 | 26 | Algorithm ineffective |

PMOP, post-mode-switch overdrive pacing; AFTherapy, Atrial Fibrillation Therapy; PAFS, Pacemaker Atrial Fibrillation Suppression; APP, Atrial Pacing Preference; SAFARI, Study of Atrial Fibrillation Reduction; ASSERT, ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial; SAFE, Septal Pacing for Atrial Fibrillation Suppression Evaluation; Asymptomatic Atrial Fibrillation and Stroke Evaluation; PAC, post-premature atrial contraction; bpm, beats per minute; SJM, St. Jude Medical; AT, atrial tachycardia; AF, atrial fibrillation.

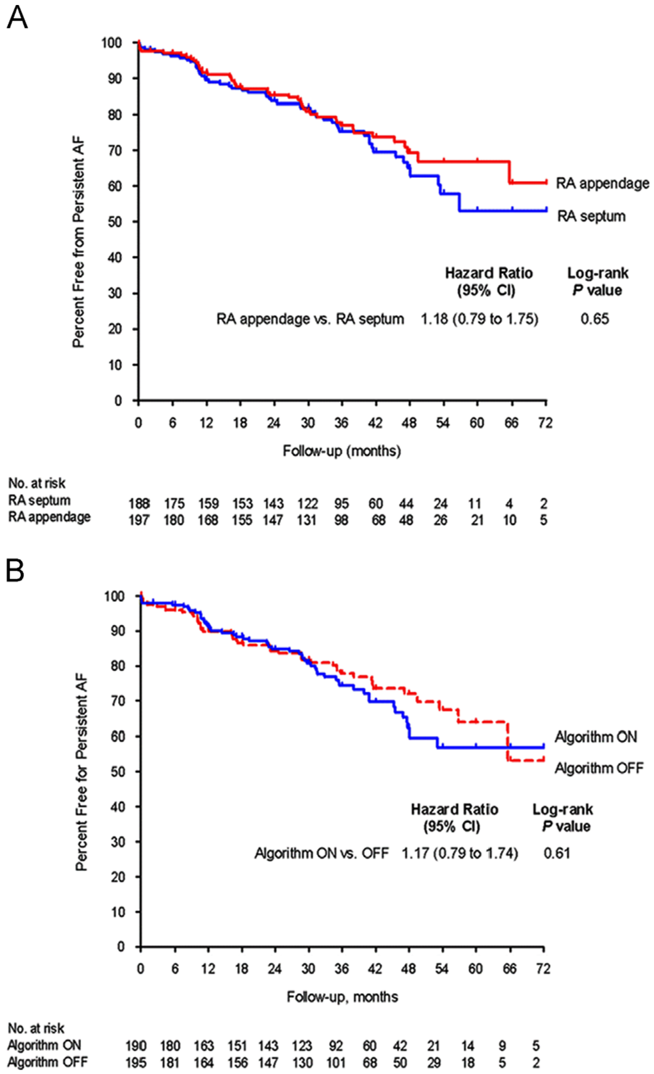


**Fig. 3.** Freedom from persistent atrial fibrillation (AF). (A) Comparison of the times to persistent atrial fibrillation between right atrial (RA) septal and RA appendage pacing. (B) Comparison of the times to persistent atrial fibrillation between the ON and OFF settings of the continuous atrial overdrive pacing algorithm. CI, confidence interval (reproduced with permission: reference [16]).

algorithm is influenced by programming options such as the atrioventricular delay, the pacing rate, and the number of pacing cycles. Garrigue et al. [42] used programmed increases in the lower rate from 55 ppm to 72 ppm, along with increases in the atrial pacing rate from 32% to 67%, to achieve significant reductions in the number and duration of paroxysmal AF episodes. That trial demonstrated that a relatively high atrial pacing rate might be necessary to inhibit the AF triggers and that it would also be necessary to set the pacemaker rate according to the tolerance of each patient.

The ventricular pacing rates differed greatly among the trials (from 11% to 93%). Interestingly, the ventricular pacing rate was not associated with the effectiveness of AF suppression. In a randomized trial, Gold et al. [14] demonstrated a reduction in the AF burden with a right ventricular pacing rate of 96%. However, these ventricular pacing data do not agree with other reported evidence suggesting that ventricular pacing is inferior to atrial pacing for reducing the incidence of AF. Overall, atrial pacing appears to play a more important role than ventricular pacing in this setting. Most trials had a relatively short follow-up period and did not produce consistent results.

An interesting finding of the Study for Atrial Fibrillation Reduction (SAFARI) trial was that the AF reduction benefit was greater among patients with a high baseline AF burden than among those with a relatively low baseline AF burden [14]. This finding might possibly explain why a subsequent large trial [15] failed to confirm the efficacy of an AF suppression algorithm in patients with no history of AF. That very large randomized study of 2343 patients without a history of AF reported that continuous atrial overdrive pacing did not prevent new-onset AF, was poorly tolerated, and accelerated pulse generator battery depletion. Data from the trial with the longest follow-up period [16] revealed that AF prevention pacing was effective for at least 66 months in more than 50% of the study patients (Fig. 3). An overall assessment of the long-term effects of AF prevention pacing is difficult to conduct because the general conditions of the patients and their surrounding circumstances vary on a case-by-case basis because of aging, blood pressure, and many other factors. AF mechanisms such as the PAC trigger might also influence the responses to pacing-based AF suppression therapies.

Most trials have demonstrated the short-term effectiveness of the AF prevention pacing algorithm. We believe that all cardiologists should endeavor to adopt AF prevention pacing algorithms in their clinical practices, given that the algorithm can be easily programmed to the ON or OFF mode as needed. Currently, there is no consensus regarding the prevention of AF with atrial pacing via AF suppression algorithms. However, most trials have demonstrated the safety of this treatment modality, and the characteristics of patients who respond to these atrial pacing algorithms can be evaluated.

## 6. Summary

A lack of confirmatory data from an adequate number of large randomized trials is among the reasons for the lack of a gold standard AF suppression therapy in pacemaker recipients. However, the safety of atrial pacing algorithms for AF prevention has been demonstrated, and these algorithms have been shown to be truly effective in certain cases. Symptomatic AF greatly affects the patient's quality of life, and asymptomatic AF is an important cause of thromboembolism. Given the risk of AF complications, it might be beneficial to use an AF suppression algorithm in patients with a history of AF and indications for permanent pacemaker implantation. However, each pacemaker should be programmed carefully to ensure the most effective or so-called “optimal” setting. A full understanding of all cases in which this therapy might be effective is advised to ensure the appropriate clinical application of this therapy.

## Conflict of interest

The authors have no conflicts of interest to declare.

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