Pacing Therapy for Prevention of Atrial Fibrillation

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Nonpharmacological therapy is being evaluated for the prevention of atrial fibrillation (AF). Pacing has been proposed as one of the option to prevent AF. In patients with bradycardia and requiring pacemaker, physiological pacing such as dual chamber pacing or atrial pacing has an advantage against ventricular pacing in prevention AF. Pacing from novel site like the dual-site atrium, biatrial, Bachman, and low septal pacing may reduce AF burden and new anti-AF pacemakers with atrial prevention algorithm may decrease AF further. However, selecting the appropriate patients and adopting tailored-therapy for individual patient is likely to remain one of the difficulties in achieving an advantage. This review discusses the current status of pacing therapy for the prevention of AF. It also discusses the some of merits and limitations of pacing therapy for the treatment of AF.


Key words: Atrial fibrillation, Bi-atrial pacing, Dual-site atrial pacing, Pacemaker algorithms, Preventive pacing

Introduction

Atrial fibrillation (AF) is the most common atrial arrhythmia, often resulting in cerebral embolism and a deterioration of hemodynamics. According to the Framingham study,1) AF patients had a nearly two-fold increase in all-cause mortality and a five-fold risk for a stroke. The incidence of AF is 0.5% in the fifties age group and rapidly increases to 8.8% associated with aging in the eighties.3) The management of AF has been started with antiarrhythmic drugs in combination with anticoagulant drugs as the first-line therapy but it is still unsatisfactory. Strategies to treat AF include rate control or rhythm control such as maintaining of sinus rhythm obtained from pharmacologic therapy, pacing therapy and catheter ablation intervention. AF has been considered as a benign arrhythmia for many years. If it is true, the rate control is an acceptable therapy for management of patients with recurrent AF2–5) and anticoagulant therapy should not be discontinued in high-risk patients, even though sinus rhythm has been restored and maintained. Besides, the components of heart rate such as resting rate, activity rate, night-time rate and chronotropic competence need to be further investigated. On the other hand, recent studies have shown that AF increased the risk for cardiovascular morbidity and mortality.2,4,6,7) Therefore attempts aiming to maintain sinus rhythm have been performed in recent years. In the last two decades the number of nonpharmacologic therapy for AF has markedly increased. With advances in medical engineering, a variety of devices have been
applied to arrhythmia therapy. Radiofrequency catheter ablation is highly effective for the treatment of many forms of supraventricular tachycardia and implantable cardioverter for the life-threatening ventricular tachycardia. However, there is no consensus and recommendable devices regarding optimal management of AF. The pacemaker therapy for AF has been preliminary performed for the purpose of improving bradycardia and improving the hemodynamics in patients with congestive heart failure. Although pacemaker therapy for prevention of paroxysmal AF now has not been the established therapeutic method yet, its effectiveness is suggested and noticed in the results of the study on several patients.8–10 This paper reviews recent and on-going developments in pacing management of AF.

Factors involved in the onset of atrial fibrillation

A variety of abnormalities of atrial electrophysiology have been found in patients susceptible to AF, including a spatially heterogeneous shortening of atrial refractoriness, conduction delay,11–13 abnormal adaptation of refractoriness to rate,14 and a dispersion of atrial refractoriness. It is known that the presence of dispersion of atrial refractoriness beyond the physiological range and slow conduction is likely to induce and continue AF.15,16 The structural and functional changes of the atrium increase the dispersion of atrial refractoriness and reduce the conduction velocity. Where atrial substrate exists, episodes of AF are thought to be triggered by abnormal timing cycle such as the short-long sequence and the atrial premature beat (Figure 1). Also it is known that the autonomic nerve is deeply concerned with the onset of AF and that AF occurs after stimulation of the parasympathetic nerve of atrial wall and administration of acetylcholine. Bradycardia is involved in the onset of this type of AF, which is observed at night and at rest. This is considered to be caused by shortening of the refractory period after stimulation of the parasympathetic nerve.17 In the sympathetic nerve-induced AF, it is induced by marked exercise or stress, on the other hand, the attack occurs during the daytime, which is obviously different from the parasympathetic nerve-induced one.18 Additionally, in case of symptomatic nerve-induced AF, there are many patients with underlying cardiac disease. The triggering mechanism involved with the sympathetic nerve-induced AF is unclear. However, basic studies have shown the etiologies such as the increased heart rate, the occurrence of atrial premature contraction due to the direct effect of adrenaline on the myocardium, the increasing automaticity, and the increased inappropriate contractility. Basically, the onset mechanism of AF has been elucidated well, but unfortunately the clinical study has not been conducted well.

Analysis the onset mechanisms of atrial fibrillation stored in the pacemakers

It is believed that the memory function in dual chamber pacemaker offer distinct diagnostic advantages in the long term follow up of patients.19 The data obtained from 24-h Holter ECG might be reliable to evaluate the prevalence of paroxysmal AF, but the storage period is too short. The only reliable way to diagnose paroxysmal AF is to continuously monitor the patient’s intrinsic cardiac

![Figure 1](image.png)
rhythm. Recently, a multicenter collaborative study (AF Therapy) to examine the mechanism of the onset of AF is in progress in the patients with drug-resistant paroxysmal AF.20–22) According to the results, among patients with arrhythmia immediately before the onset of atrial fibrillation, sinus bradycardia was most frequently observed (55%), then multiple atrial premature contraction (18%), and the onset of bradycardia derived from sinus rhythm secondary to atrial premature contraction (15%), and the remaining patients showed a sudden drop in heart rate due to sequence abnormality and hypersensitive carotid sinus syndrome. From these results, the onset of AF is classified into four group; the contribution of atrial premature contraction (Figure 2), the pause after atrial premature contraction, the one relating to exercise, and the one on which identification is difficult.

Mechanism of prevention of atrial fibrillation by pacing

It is well known that when the atrium is regularly paced in patients with sinus dysfunction, the incidence of AF may decrease. The long pause, atrial premature contraction and sinus bradycardia may trigger AF. It is therefore important to keep regular pacing on the atrium. If there is a structural dispersion of refractoriness in the atrium, it is expected that pacing prevent unidirectional conduction block of ectopic excitation by the synchronization of depolarization and the preliminary activation of the site of slow conduction. If a conduction disturbance is already present in the atrium, the site of pacing may be important, and multi-site pacing may be useful.23) With respect to the functional factor affecting the atrial substrate, there is a possibility that the hemodynamics, atrial ischemia and hyper-stretch of atrial wall may be improved by selecting DDD pacing instead of the VVI pacing because of coordinative pacing on the atrium and ventricle. Additionally, it is considered that the pacing therapy prevents sympathetic nerve- or parasympathetic nerve-induced AF by keeping the balance between the sympathetic nerve and the parasympathetic nerve.24)

Preventing pacing for atrial fibrillation

1) Pacing mode selection

Retrospective study have suggest that physiological pacing has been offered substantial benefit in reducing the incidence of persistent AF and the prevalence of paroxysmal AF, as compared with ventricular pacing.25–27) In our series, the long-term evaluation of the development of persistent AF and recurrence of paroxysmal AF were studied in 70 patients with a history of AF before pacemaker implantation. In a mean follow-up of 8 years, the incidence of chronic AF was 78% in the patients undergoing VVI pacing compared with 45% in DDD pacing and recurrence of paroxysmal AF was 93% in VVI pacing and 58% in DDD pacing.28) Despite all the studies suggesting a disadvantage of VVI mode, a few randomized, controlled study has been performed.27–29) Although the Canadian Trial of Physiologic Pacing (CTOPP)30) did not show benefit of physiologic pacing on overall mortality, CTOPP reported an 18% reduction (6.6% annual rate with ventricular pacing vs 5.3% with physiological pac-
ing) in the risk of all AF episodes in patients with physiologic pacing compared with those in the ventricular pacing. This beneficial AF reducing effect have been appeared at approximately six months and continue over 4 years after pacemaker implantation.31) In spite of lacking the reduction of mortality in physiological pacing, subgroup analysis showed beneficial effect on combined end point of stroke or cardiovascular death, as well as cardiovascular-death and total mortality in pacemaker dependent group but not in non-pacemaker dependent group.32) In addition, this study reported that unpaced heart rate at first follow-up has an important influence on cardiovascular death and total mortality. Ongoing pacing trial like as the Danish Multicenter Randomized Study (DANPACE)33) and the United Kingdom Pacing and Clinical Event Trial (UK-Pace)34) may provide prospective data on the relation between underlying heart rate and pacing mode selection in view point of mortality. However, the issue on indication for AF patients without brady-cardia is still remained. One study, the Atrial Pacing Periablation of Paroxysmal Atrial Fibrillation (PA3) reported that atrial rate-adaptive pacing (DDIR) dose not prevent paroxysmal atrial fibrillation (PAF) in patients with drug-resistant PAF without symptomatic bradycardia. Several limitations of the PA3 studies need to be addressed. There was no total AF burden were used to verify AF recurrence, time to first recurrence of PAF is not a random event, and pacing percentage in the DDIR group was only 67%.35,36)

One of the main disadvantages of conventional DDD pacing is its ability to track atrial events. For the appropriate DDD pacing, high sensitivity programming is needed to detect all intrinsic P waves and sustained programming upper rate pacing were easily induced by these condition during the atrial arrhythmia. Automatic mode switching is one of the mechanisms in some DDDR pacemakers to prevent the inappropriate high rate pacing. When the arrhythmia are detect as nonphysiologic by the pacemaker, the pacing mode automatically switches from the DDDR to DDIR or VVIR pacing mode. This algorithm might be released rapid irregular response to ventricular stimulation37,38) but dose not prevent paroxysmal atrial fibrillation.

2) Effect of atrial pacing site

There is much current interest in alternative-site and dual-site atrial pacing for the prevention of atrial fibrillation. The prevention of AF was usually attempted with single site atrial pacing,39–49) originally from right atrial appendage, recently from other site like the coronary sinus or high and low interatrial septum.41) More recently, multisite atrial pacing has been proposed. This method includes either dual-site pacing with which the high and low positions in the atrium simultaneously paced or bi-atrial pacing with which the right and left atria are simultaneously paced. If there is a conduction disturbance in the atrium, the prolonged P-wave duration is easily recognized on surface electrocardiograms. It is impossible to reduce the P-wave duration sufficiently by single-site pacing from the right atrium or the coronary sinus.45) However, it is considered to be possible to reduce the P-wave duration by dual-site pacing45) or by bi-atrial pacing.46) Reduction of the P-wave duration results in an improvement of conduction disturbance in the atrium.

Figure 3  An example of bi-atrial pacing.
A coronary sinus lead was inserted into the great cardiac vein to pace the left atrium. The pacemaker used was Talent DR of Ela, Inc.
atrium, and as a result, recurrence of paroxysmal atrial fibrillation is significantly inhibited. \(^{45}\)

3) Multi-site pacing (bi-atrial pacing) (Figure 3)

It is known that atrial arrhythmia is observed in patients with intraatrial conduction delay accompanying retrograde conduction in the left atrium. \(^{46}\) Daubert et al. reported that atrial arrhythmia could be inhibited by performing the bi-atrial pacing on such patients. \(^{47}\) It is considered that two factors such as the dispersion of refractoriness and anisotropic conduction are essential for persistence of atrial arrhythmia, \(^{48}\) and bi-atrial pacing improves these two factors. Additionally, in recent time, improvement of slow conduction in the region of right posterior interatrial septum is considered an important factor. \(^{49}\) Judging from these findings, bi-atrial pacing is indicated for the patients with a wide P-wave showing delayed intraatrial conduction or positive and negative bidirectionality. In order to perform bi-atrial pacing, it is necessary to pace the left atrium with a lead inserted into the coronary sinus. However, there remains the procedural problem and an issue whether stable implantation can be achieved chronically. Although various leads for the coronary sinus have been developed, we are not fully satisfied with them. If a DDD pacemaker is selected for pacing, the model which offers a short AV delay is required and if ventricular pacing is required, a Y-connector has to be used on atrial port. Recently, a DDTA pacemaker to detect the intrinsic P-wave and to pace the right and left atria simultaneously was developed and noticed. Authors also have an experience with bi-atrial pacing using this pacemaker (Figure 3). Because this patient was diagnosed as sinus dysfunction and underwent implantation of a DDD pacemaker but frequently developed symptomatic paroxysmal atrial fibrillation and showed a resistant to drug therapy, a new pacemaker was implanted after obtaining the patient’s consent. Fortunately, paroxysmal atrial fibrillation is completely inhibited over 5 years by the bi-atrial pacing after changing the pacemaker.

4) Multi-site pacing (dual-site pacing) (Figure 4)

Saksena et al. consider that, although bi-atrial pacing is indicated for patients with conduction disturbance of the right and left atria among patients with paroxysmal atrial fibrillation, the dual-site pacing is indicated for all patients with paroxysmal atrial fibrillation. \(^{50}\) It is considered that the patients with atrial fibrillation show abnormal dispersion of the atrial refractory period. \(^{51}\) Josephson et al. \(^{52}\) reported that the difference in the effective refractory period between the high right atrium and the ostium of coronary sinus is 35 ms in patients with atrial fibrillation and 5 ms in those without atrial fibrillation. A dispersion of refractory period is already present in the atrium of the patients with atrial fibrillation. Additionally, it is said that the isthmus between the tricuspid valve and Koch’s triangle is a key zone for occurrence of arrhythmia in patients with atrial fibrillation and that the stimulation of the ostium of coronary sinus not only reduces the dispersion of refractory period but also improves slow conduction and delayed conduction of the right and left atria. \(^{53}\) According to the results of a multicenter cooperative study, DAPPAP (dual atrial site pacing for prevention of atrial fibrillation), performed on 120 patients with drug-resistant atrial fibrillation.
fibrillation, it has been reported that paroxysmal atrial fibrillation was completely inhibited in 55% of the patients and that the clinical effect in combination with drugs reached 80% to 90%.54) Figure 4 shows a chest X-ray from the patient continuing the dual-site pacing over 2 years. In this patient, although paroxysmal atrial fibrillation could not be inhibited completely, the number of attacks of atrial fibrillation and the duration of atrial fibrillation was markedly decreased, and finally symptoms of arrhythmia disappeared by dual-site pacing.

5) Atrial septal pacing
When the right atrial appendage is paced electrophysiologically, the conduction time to the left atrium is prolonged compared with the time of sinus rhythm, but when the high atrial septum is paced, the same conduction time to the left atrium as that at sinus rhythm is achieved. In addition, high degree interatrial conduction delay between right and left atria is associated with atrial reentrant tachyarrhythmias.55,56) Bailin et al. therefore considered that the pacing of the right atrial Bachmann’s bundle could reduce the conduction time to the left atrium and prevent atrial fibrillation.57,58) Recently, a great involvement of lone atrial premature contraction in the onset of atrial fibrillation has been noticed and catheter ablation has been performed aggressively on the surrounding of the focus and left superior pulmonary vein, and relatively good results have been reported.59) If it is important to inhibit atrial premature contraction occurring from the surrounding of left superior pulmonary vein for prevention of atrial fibrillation, it is theoretically considered that pacing of Bachmann’s bundle is more effective than the stimulation of left atrium by the bi-atrial pacing. Until now, however, no clinical result showing that pacing of Bachmann’s bundle is superior to multi-site pacing has been reported. More recently, there are some reports that lower septal pacing was more effective than conventional atrial pacing for AF prevention.

6) Termination of AF
Pacing therapy for termination of AF has been receiving increasing attention as a result of the limited clinical efficacy with antiarrhythmic drugs. Also, nonpharmacological techniques for preventing PAF have not been reported to be associated with a complete elimination of PAF. Experimental studies have shown that AF consist of microreentrant wavelets propagating within the atrial tissue.60,61) Similarly, patients with a history of AF have been shown to exhibit altered characteristics of atrial refractoriness.62) It is therefore vital to termination soon after initiation of PAF. Allessie et al.63) demonstrated that local atrial capture by pacing was possible during AF. However, preliminary results with single site atrial pacing have failed to terminate chronic AF.64,65) Apparent success was only reported in some cases of acutely induced paroxysmal AF, but not in clinical cases.65) Therefore, persistent AF cannot be terminated by rapid single site atrial pacing at present time. Recently, a relative large clinical trial, the AT 500 Verification Study, the AT 500 pacemaker associated with rapid pacing program to terminate AF was compared to conventional DDD pacemaker. The success rate using by atrial tachycardia pacing (Burst pacing; 12% and Ramp pacing 43%) was 54.7% and showed the same efficacy as conventional DDD pacemaker.66) We can reasonably assume that in the near future atrial Burst and Ramp pacing will have an important role in the prevention of highly recurrent and drug-resistant atrial fibrillation. However, it is unlikely that atrial Burst and Ramp pacing will ensure complete and permanent protection. Therefore, further technical improvements are necessary to achieve the clinical efficacy of atrial Burst and Ramp pacing for AF.

7) Ventricular pacing intervention
Numerous reports have shown that AF are more likely to occur with ventricular pacing than with dual-chamber pacing. It has been suggested that AF can be prevent by controlling the atrial rate. However, DVI pacing may be associated with a high incidence of AF because of lacking AV synchrony and competition with the spontaneous atrial rhythm.67) Also, Benditt reported that DDD pacing may not control the development of AF in patients with frequent atrial tachyarhythmia.68) One of the reason why DDD pacing could not be prevented AF totally is that DDD pacing results in right ventricular pacing. A number of studies have shown that right ventricular pacing is detrimental to hemodynamics, atrioventricular valve regurgitation and a higher prevalence of AF. Sweeney reported that a significant increasing risk of AF has been documented corresponding with right ventricular pacing up to 40% in DDDR mode.69) Patients implanted with DDD pacemaker may therefore have a higher AF burden if they are programmed to the short AV delay than spontaneous AV conduction time. On the other hand, ventricular rate instability could affect the recurrence of AF in some patients. If this is an acceptable theory, stabilization of ventricular rate during paroxysmal AF may prevent recurrence of AF.
and some studies have been developed. In these studies ventricular rate stabilization (VRS) reduced ventricular rate irregularity and improved Quality of Life and exercise tolerance.\(^{70}\) However, there is no evidence that VRS could be prevented the early restarts of AF.

**Preventative pacing algorithms**

1) **Overdrive pacing algorithms**

Pacing algorithms for preventing AF have been proposed for the suppression of atrial extrasystoles by overdriving pacing. The role of this algorithm is to reduce atrial premature contraction. It is believed that atrial premature contraction will be reduced following by increasing the heart rate. Mugatroyd et al.\(^{71}\) reported that when an algorithm is used to increase the heart rate to 12.5% higher than the previous sinus rhythm at detection of atrial premature contraction by dissolving the resting phase after premature contraction was obtained, atrial premature contraction and the short run of atrial premature contraction were reduced by 69% and 75%, respectively. Unfortunately, no significant reduction of paroxysmal atrial fibrillation could be achieved. Only the patients frequently showing paroxysmal atrial fibrillation before the study, a significant decrease in the number of attacks was observed,
suggesting the usefulness of this algorithm. In manual overdrive rate setting, the atrial rate is constantly set to 10 or 15 beats faster than the intrinsic heart rate at some detecting point. This allows having a good percentage of pacing at rest but not reacting during sympathetic over activity state such an atrial arrhythmia or high emotional episodes. The increase of atrial basic rate until 100 ppm is acceptable and feasible for young patients without distinct cardiac diseases, but majority of older patients with or without cardiac disease do not tolerate such high atrial rates. Therefore, pacing algorithms have been developed to increase the pacing rate after a sensed premature atrial contraction (PAC) and to reduce the pacing rate during no atrial sensing (Figure 4). Despite high percentages of atrial pacing because of automatic overdrive algorithms, these algorithms do not increase the mean heart rate significantly and thus are well tolerated by patients.\textsuperscript{72} One study showed a proportion of atrial pacing with an automatic overdrive pacing algorithms of 84\% with a concomitant reduction of the number and duration of mode switching episodes.\textsuperscript{73} However, these overdriving algorithms achieved a high atrial pacing rate and significant reduction of PACs but no significant reduction in the AF burden have been reported.\textsuperscript{74}

2) Elimination of short-long cycle

The purpose of this algorithm is to dissolve a short-long sequence after premature atrial contraction (PAC) and to allow smooth restoration of sinus rhythm. The atrial rate stabilization to gradually make the pacing rate slow considering the coupling interval as the first cycle at appearance of atrial premature contraction and to return it to the sinus cycle before occurrence of atrial premature contraction has been examined. Several pacemaker companies have developed these algorithms to prevent AF. In Vitatron BV, Post PAC Response, this have been designed that a single pulse with a coupling interval equal to the mean of the preceding beats (Figure 5) and Ela Medical, Acceleration on PAC, also designed that a pacing rate accelerate for a programmable time.

3) Prevention of early reinitiation of AF

The AF therapy study evaluated the phenomenon of early reinitiation of AF (ERAF) and ERAF has been attributed to the concept of atrial remodeling. In Medtronic, Post Mode Switching Overdrive Pacing, which increase the lower pacing rate for a programmable time if the pacemaker cessation of exercise...
automatic mode switching, has been evaluated to protect the ERAF (Figure 6). In addition with the atrial rate stabilization algorithm, this preventive pacing mode reduced the mean number of AT episodes.75)

4) Post exercise rate control
It has been reported that AF can be easily induced by sudden decrease of atrial rate in susceptible patients.76) To prevent this AF triggering mechanisms, Post-Exercise Response™ has been designed to maintain a higher pacing rate as soon as the rate drop was detected by pacemaker after termination of exercise (Figure 7). Also, this algorithm is proposed to prevent the ischemia by preventing a rapid rate drop after exercise and keeping the balance between the myocardial oxygen supply and demand. It is because ischemia acts on the atrial muscle to affect the atrial substrate and contributes to the onset of atrial fibrillation.

Patient selection for preventive AF pacing

What type of patients will be indicated for pacing therapy in the future? It is believed that almost AF patients are indicated for catheter ablation. Indeed, AF is often initiated by triggering with PAC from the pulmonary veins and pulmonary veins isolation can effectively cure. However, these patients have some specific characteristics such as: younger people, less association with cardiac disease, drug-refractory, and no bradycardia. Especially, in younger patients, about 45% of paroxysmal AF and 25% of persistent cases occur as lone AF.77) Recently, it was recognized that there are differences in patients characteristics between pacemaker and catheter ablation patients. The characteristics in patients who will be indicated preventing AF pacing are older people, associated with bradycardia and cardiac disease, and more co morbidities. In AF patients older than 70 years and who received coronary artery bypass surgery, prevention by atrial pacing is particularly useful,78,79) whereas beta-blocker therapy was found to be of little benefit in all patients with paroxysmal atrial fibrillation. It is therefore necessary to decide the indication after examining the mechanism and trigger of the onset of individual atrial fibrillation. Furthermore, regarding technical aspect of multi-site pacing, improving the procedure for lead insertion into the coronary sinus and the method of tip fixation, and developing a new lead as well as the shape of the lead for coronary sinus are a necessary condition. Finally, it is essential to expand clinical application to demonstrate the utility of a new pacing therapy for atrial fibrillation by a large-scale prospective study.

Conclusion

Novel Preventive Pacing offer a new therapeutic method for the prevention of atrial fibrillation. These therapeutic methods are safe and well tolerated and reduces AF burden. Also, the preventive pacing may eliminate the need for multiple drugs in many patients or frequent cardioversion shock. However, the success rate of preventing AF by pacing technique is still low and it might need Hybrid therapy such as pacing with ablation. Therefore, in contrast to bradyarrhythmia, preventive pacing of AF is still a new therapeutic method that needs further improvement before it may be considered as a first-line therapy. A new pacing therapy for atrial fibrillation is expected, however, the pacing therapy for prevention of atrial fibrillation is quite different from the pacing therapy accompanying the conventional treatment of bradycardia. In addition, it is not fully effective in all patients with paroxysmal atrial fibrillation. It is therefore necessary to examine the mechanism and trigger of the onset of individual atrial fibrillation. Furthermore, regarding technical aspect of multi-site pacing, improving the procedure for lead insertion into the coronary sinus and the method of tip fixation, and developing a new lead as well as the shape of the lead for coronary sinus are a necessary condition. Finally, it is essential to expand clinical application to demonstrate the utility of a new pacing therapy for atrial fibrillation by a large-scale prospective study.

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