—Review—

Pacing Therapy for Atrial Fibrillation

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Introduction

Atrial fibrillation is the most common occurring clinical arrhythmia, often resulting in cerebral embolism and a deterioration of hemodynamics. According to the Framingham study, the incidence of atrial fibrillation is 0.5% in the fifties age group and rapidly increases to 8.8% in association with aging in people in their eighties[1].Many therapeutic methods have been proposed for atrial fibrillation, but unlike other atrial arrhythmias, no therapeutic method has been clearly established. It is certain that the guides for treatment of atrial fibrillation are to maintain the normal sinus rhythm, and to prevent cerebral embolism. Although there is no objection to the termination of paroxysmal atrial fibrillation with drug therapy, some debatable issues remain in its preventive effect. On the other hand, cardioversion is commonly used as a non-drug therapy, but the recurrence rate is very high even if it is successful. It is said that when patients after cardioversion are followed up without any treatment, about half of them show recurrence within 12 months[2]. Catheter ablation has not been abandoned in clinical research yet. Pacemaker therapy for atrial fibrillation has been preliminary performed for the purpose of improving bradycardia and improving the hemodynamics in patients with congestive heart failure. Although pacemaker therapy for the prevention of paroxysmal atrial fibrillation has not yet been established as a therapeutic method, its effectiveness is suggested and has been noticed in the results of the studies on several patients[3-5].This review summarizes current knowledge concerning the mechanism of prevention of atrial fibrillation by pacemaker therapy and the factors involved in the onset of atrial fibrillation.

Factors involved in the onset of atrial fibrillation

It is known that the presence of dispersion of atrial refractoriness beyond the physiological range and slow conduction is likely to induce and continue atrial fibrillation[6,7].The structural and functional changes of the atrium increase the dispersion of atrial refractoriness and reduce the conduction velocity. Where such as atrial substrate exists, episodes of atrial fibrillation are thought to be triggered by an abnormal timing cycle such as a short-long sequence and an atrial premature beat (**Fig. 1**). Also it is known that the autonomic nerve contributes greafly to the onset of atrial fibrillation and that atrial fibrillation occurs after stimulation of the parasympathetic nerve of the atrial wall and administration of acetylcholine. Bradycardia is involved in the onset of this type of atrial fibrillation, which is observed at night and at rest. This is considered to be caused by the shortening of the refractory period after stimulation of the parasympathetic nerve[8]. In sympathetic nerve-induced atrial fibrillation 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 type[9]. Additionally, in symptomatic nerve-induced atrial fibrillation, there are many patients with underlying cardiac disease. The triggering mechanism in-

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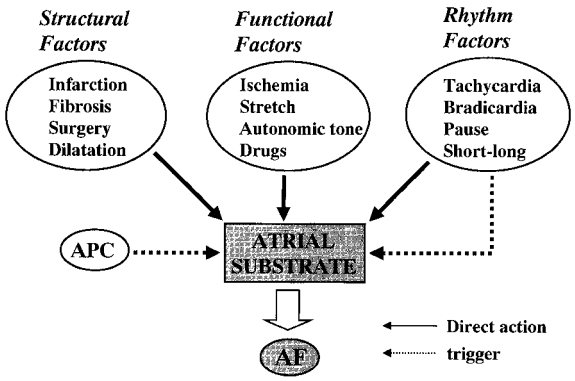

Fig. 1 Factor involved in the onset of atrial fibrillation. Atrial premature contraction and abnormal rhythm may trigger the onset of atrial fibrillation.

volved in sympathetic nerve-induced atrial fibrillation is unclear. However, basic studies have shown such etiologies as increased heart rate, the occurrence of atrial premature contraction due to the direct effect of adrenaline on the myocardium, increasing automaticity, and increased inappropriate contractility. Basically, the onset mechanism of atrial fibrillation has been well elucidated, but unfortunately clinical studies have not been conducted well. A multicenter collaborative study (AF Therapy) to examine the mechanism of the onset of atrial fibrillation is in progress in patients with drug-resistant paroxysmal atrial fibrillation. The preliminary results of this study were reported at the Cardiostim' 98 in 1998[10,11]. According to the results, among patients with arrhythmia immediately before the onset of atrial fibrillation, sinus bradycardia was most frequently observed (55%), followed by multiple atrial premature contraction (18%), and the onset of bradycardia derived from sinus rhythm secondary to atrial premature contraction (15%). 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 atrial fibrillation can be classified into four groups: the contribution of atrial premature contraction, pause after atrial premature contraction, that relating to exercise, and that in which identification is difficult.

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 atrial fibrillation decreases. The long pause, atrial premature contraction and sinus bradycardia may trigger atrial fibrillation. 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 with prevent a 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. With respect to the functional factor affecting the atrial substrate, there is a possibility that the hemodynamics, atrial ischemia and hyper-stretch of the atrial wall may be improved by selecting DDD pacing instead of VVI pacing because of coordinative pacing on the atrium and ventricle. Additionally, it is thought that pacing therapy prevents sympathetic nerve-or parasympathetic nerve-induced atrial fibrillation by keeping a balance between the sympathetic nerve and the parasympathetic nerve.

Pacing therapy for prevention of atrial fibrillation

Pacing therapy for paroxysmal atrial fibrillation is selected in the following three cases: First, in cases in when bradycardia contributes to the onset of atrial fibrillation, AAI or DDD pacing by which the atrium is regularly paced is indicated. Second, multi-site pacing such as bi-atrial pacing or dual-site pacing is indicated for patients with conduction disturbance in the atrium. Third, a DDDR pacemaker with an automatic mode switch is used when the organic mechanism in the atrium is not clear. Additionally, when the organic mechanism in the atrium is not clear and the symptoms of atrial fibrillation are severe or persistent, a DDDR pacemaker may be implanted after catheter ablation of the atrioventricular junction.

1. A-V synchronous pacing

One of the reasons why AAI or DDD pacing to maintain A-V synchronization is desirable compared to VVI pacing in pacemaker patients with a history of paroxysmal atrial premature contraction is to avoid inadequate atrial contraction during atrioventricular

Table 1. Onset of atrial fibrillation and pacing mode. The incidence of atrial fibrillation is clealy low in the patients selecting physiological pacing.

First Author	Patient(n)	Follow-up (month)	AF(%)	Death(%)	Difference in Survival(p=0.05)
Rosenqvist					
AAI	89	44	7	8	Yes
VVI	79	47	47	23	
Sutton					
AAI	410	33	4	NA	NA
VVI	651	39	22	NA	
Hesselson					
DDD	308	168	8	20	Yes
VVI	193	168	26	47	
Mizutani					
DDD	113	56	9	4	Yes
VVI	52	56	40	20	

NA: not available

valve closure. Inadequate atrial contraction leads to inappropriate mechanical stresses on the atrial muscle and induces atrial fibrillation. In the report by Sutton et al.[12], the incidence of chronic atrial fibrillation after implanting a pacemaker in patients with sinus dysfunction was as high as 22% with VVI pacing compared with 4% with AAI pacing. In the study of Hesselson et al.[13], it was 26% with VVI pacing compared with 8% with DDD pacing. In a study by the authors in 165 patients[14],it was 40% with VVI pacing compared with 9% with DDD pacing, indicating no racial difference (**Table 1**). Such results were confirmed in a prospective study in patients with sinus dysfunction[15]. Rosenqvist reported that the incidence of chronic atrial fibrillation was high in patients with a history of atrial fibrillation before implantation of a pacemaker compared with those without that history[16]. When subjects are limited to patients with bradycardia-tachycardia syndrome, it is said that the incidence of atrial fibrillation becomes higher[17]. In a study of 70 patients with a history of atrial fibrillation before implantation, the incidence of chronic atrial fibrillation was 78% in the patients undergoing VVI pacing compared with 45% with DDD pacing during the average period of observation of 8 years (**Fig. 2**)[18]. As seen from this result, the preventive effect is never satisfactory in patients with a history of atrial fibrillation, even if physiological pacing is selected.

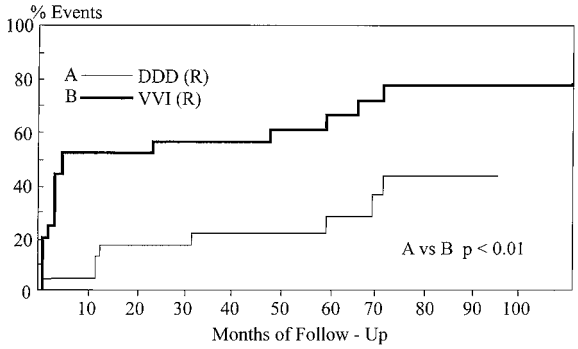

Fig. 2 Rate of conversion to chronic atrial fibrillation for each pacing mode. The incidence of chronic atrial fibrillation is not high in the DDD (R) group compared with the VVI (R) group. In the 96-month follow-up, 45% of the patients in the DDD (R) group had chronic atrial fibrillation.

2. Multi-site pacing

The most remarkable prevention of atrial fibrillation by pacing is achieued with multi-site pacing. This method includes either dual-site pacing in which the high and low positions in the atrium are simultaneously paced, or bi-atrial pacing in 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[19]. However, it is considered to be possible to reduce the P-wave duration by dual-site pacing[20] or by bi-atrial pacing[21]. Reduction of the P-wave duration results in an improvement of conduction disturbance in the atrium, and as a result, recurrence of paroxysmal atrial fibrillation is signifi-

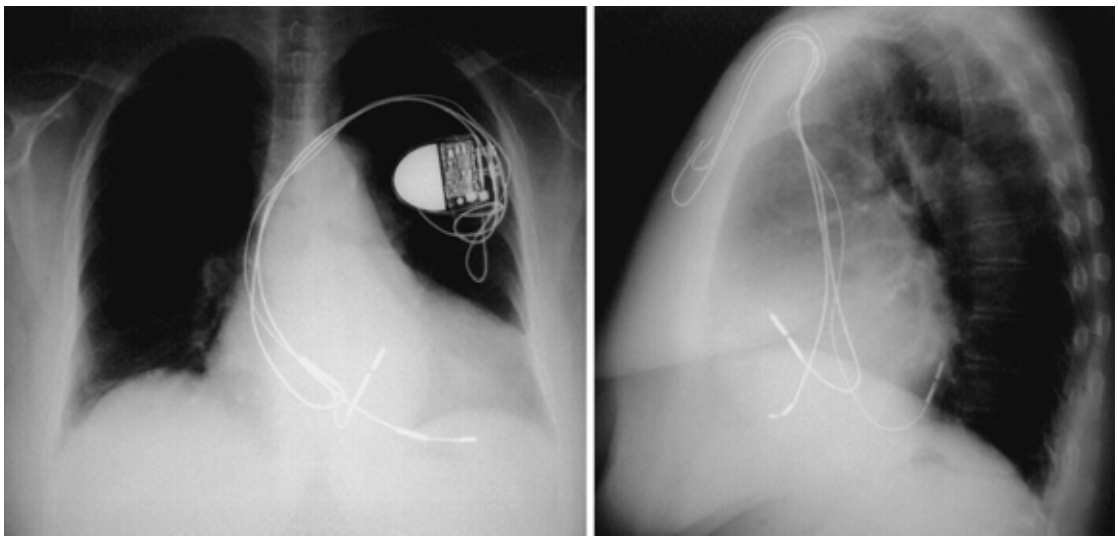

Fig. 3 An example of bi-atrial pacing. A coronary sinus lead was inserted into the great cardiac vein to pace the left atrium. The pacemaker used was a Talent DR of Ela, Inc.

cantly inhibited[3].

(1) Multi-site pacing (bi-atrial pacing)

It is known that atrial arrhythmia is observed in patients with intraatrial conduction delay accompanying retrograde conduction in the left atrium[22]. Daubert et al. reported that atrial arrhythmia could be inhibited by performing bi-atrial pacing on such patients[23]. It is considered that two factors, the dispersion of refractoriness and anisotropic conduction, are essential for atrial arrhythmia to pecict[24], and bi-atrial pacing improves these two factors. Additionally, improvement of slow conduction in the region of the right posterior interatrial septum is considered an important factor[25]. Judging from these findings, bi-atrial pacing is indicated for 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 remain procedural problems and the issue of 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, a model which offers a short AV delay is required, and if ventricular pacing is required, a Y-connector has to be used on the 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. The Authors have performed bi-atrial pacing using this pacemaker (**Fig. 3**). Because the patient was diagnosed as having sinus dysfunction and underwent implantation of a DDD pacemaker but frequently developed symptomatic paroxysmal atrial fibrillation and showed a resistance to drug therapy, a new pacemaker was implanted after acquiring the patient's consent. Fortunately, paroxysmal atrial fibrillation was completely inhibited by the bi-atrial pacing after changing the pacemaker.

(2) Multi-site pacing (dual-site pacing)

Saksena et al. consider that, although bi-atrial pacing is indicated for patients with paroxysmal atrial fibrillation, who have conduction disturbance of the right and left atria dual-site pacing is indicated for all patients with paroxysmal atrial fibrillation[26]. It is considered that patients with atrial fibrillation show abnormal dispersion of the atrial refractory period[27]. Josephson et al.[28] reported that the difference in the effective refractory period between the high right atrium and the ostium of the coronary sinus is 35 ms in patients with atrial fibrillation and 5 ms in those without atrial fibrillation. A dispersion of the refractory period is already present in the atrium of 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 stimulation of the ostium of the coronary sinus not only reduces the dispersion of

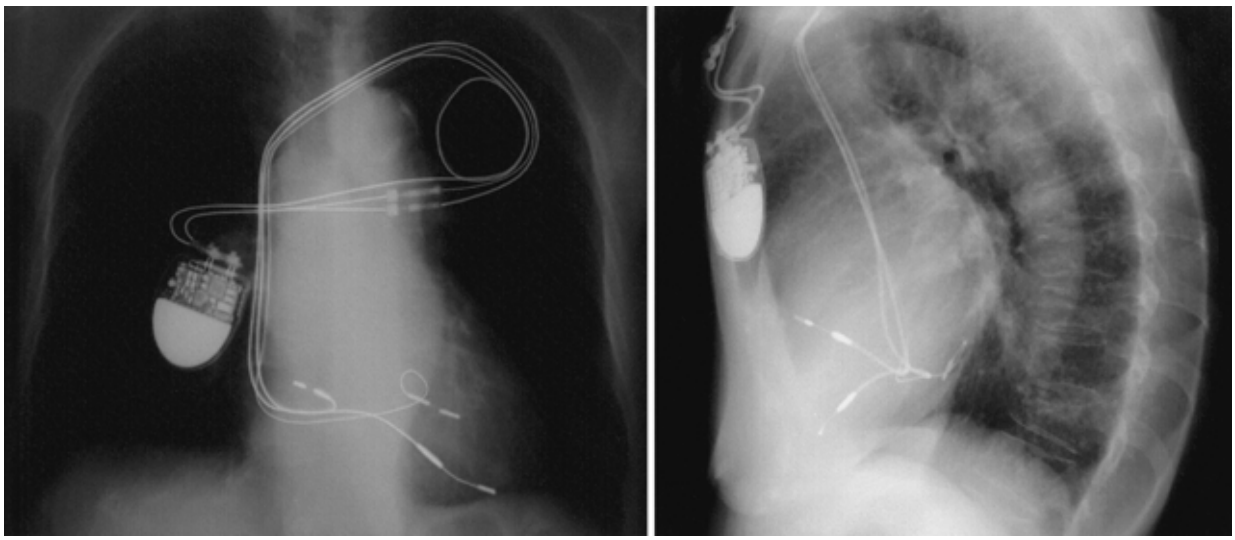

Fig. 4 An example of dual-site pacing. A coronary sinus lead was inserted into the mid cardiac vein to pace the are surrounding the ostium of the coronary sinus. The pacemaker used was a Talent DR of Ela, Inc.

the refractory period but also improves slow conduction and delayed conduction of the right and left atria[29]. 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, 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%[30]. **Fig. 4** shows a chest X-ray from a patient continuing dual-site pacing over 2 years. In this patient, although paroxysmal atrial fibrillation could not be inhibited completely, the number of attacks and the duration of atrial fibrillation wher markedly decreased, and finally the symptoms of arrhythmia disappeared through dual-site pacing.

3. Permanent 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. 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[31,32]. Recently, the 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 area surrounding the focus and the left superior pulmonary vein with relatively good results[33]. If it is important to inhibit atrial premature contraction occurring from the area surrounding of left superior pulmonary vein for the prevention the atrial fibrillation, it is theoretically possible that pacing of Bachmann's bundle is more effective than the stimulation of the left atrium by bi-atrial pacing. Until now, however, no clinical results showing that pacing of the Buchmann's bundle is superior to multi-site pacing have been reported.

4. Concepts for preventive therapy of atrial fibrillation using algorithms

At present, the algorithms considered for the prevention of atrial fibrillation include overdrive pacing, the specialized algorithm for the suppression of atrial premature complexes, the elimination of cycle length variation rate-smoothing algorithms, and post exercise rate control.

(1) Minimum increment atrial overdrive pacing

There should be no objection to the idea that constant overdrive pacing is a method of preventing atrial fibrillation, but there is a fear that maintenance of non-physiologically rapid heart rates may not only ignore the circadian variation of heart rate in the pa-

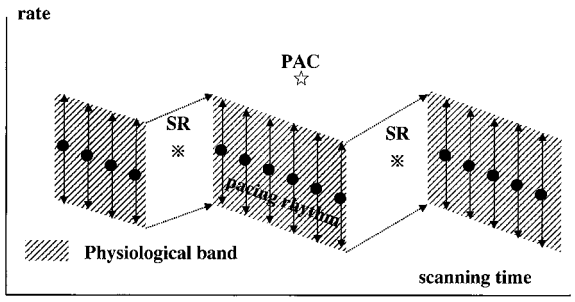

Fig. 5 A scheme of minimum incremental overdrive atrial pacing. The pacemaker conducts atrial pacing at a slightly faster than the sinus rhythm within the physiological band. PAC: premature atrial contraction, SR: sinus rhythm.

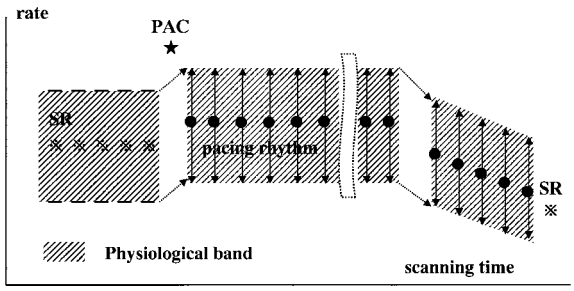

Fig. 6 A scheme of algorithm for the suppression of atrial premature complexes. When atrial premature contraction is recognized, this algorithm increases the pacing rate and suppresses atrial premature contraction. When atrial premature contraction ceases to be recognized, it gradually reduces the pacing rate to normal sinus rhythm.
PAC: premature atrial contraction, SR: sinus rhythm.

tient, but also induce angina pectoris due to an inappropriate increase in heart rates. Therefore, this algorithm has been proposed as a means to ensure constant pacing without a great increase in heart rate and always monitoring the intrinsic heart rate (**Fig. 5**).

(2) Specialized algorithm for the suppression of atrial premature complexes

The role of this algorithm is to reduce atrial premature contraction. It is believed that atrial premature contraction can be reduced by increasing the heart rate. Mugatroyd et al.[34] 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 in patients frequently showing paroxysmal atrial fibrillation before the study was a significant decrease in the number of attacks observed, suggesting the usefulness of this algorithm. **Fig. 6** shows the mechanism of the increase in the heart rate by the algorithm at detection of atrial premature contraction.

(3) Elimination of cycle length variation rate-smoothing algorithms

The purpose of this algorithm is to dissolve a long-short sequence after atrial premature contraction and to allow a smooth restoration of sinus rhythm. The atrial rate stabilization required to gradually slow the pacing rate, considering the coupling interval as the first cycle at appearance of atrial premature contraction and to return it to the sinus cycle before the occurrence of atrial premature contraction has been examined.

(4) Post exercise rate control

This algorithm is proposed to prevent ischemia by preventing a rapid rate drop after exercise and keeping the balance between the myocardial oxgen 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.

Fig. 7 shows the rate profile diagram immediately before the onset of atrial fibrillation, which was obtained from the telemetry data. In this case, atrial fibrillation occurred after only one atrial premature contraction. When an algorithm for suppression of atrial premature contraction and a program for prevention of long-short sequences after atrial premature contraction was applied, marked reduction of paroxysmal atrial fibrillation was observed. As shown in this patient, it is desirable to investigate the mechanism of the onset of atrial fibrillation in detail to select an appropriate algorithm.

5. Atrioventricular junctional ablation and permanent pacing

In the case of drug resistance atrial fibrillation and

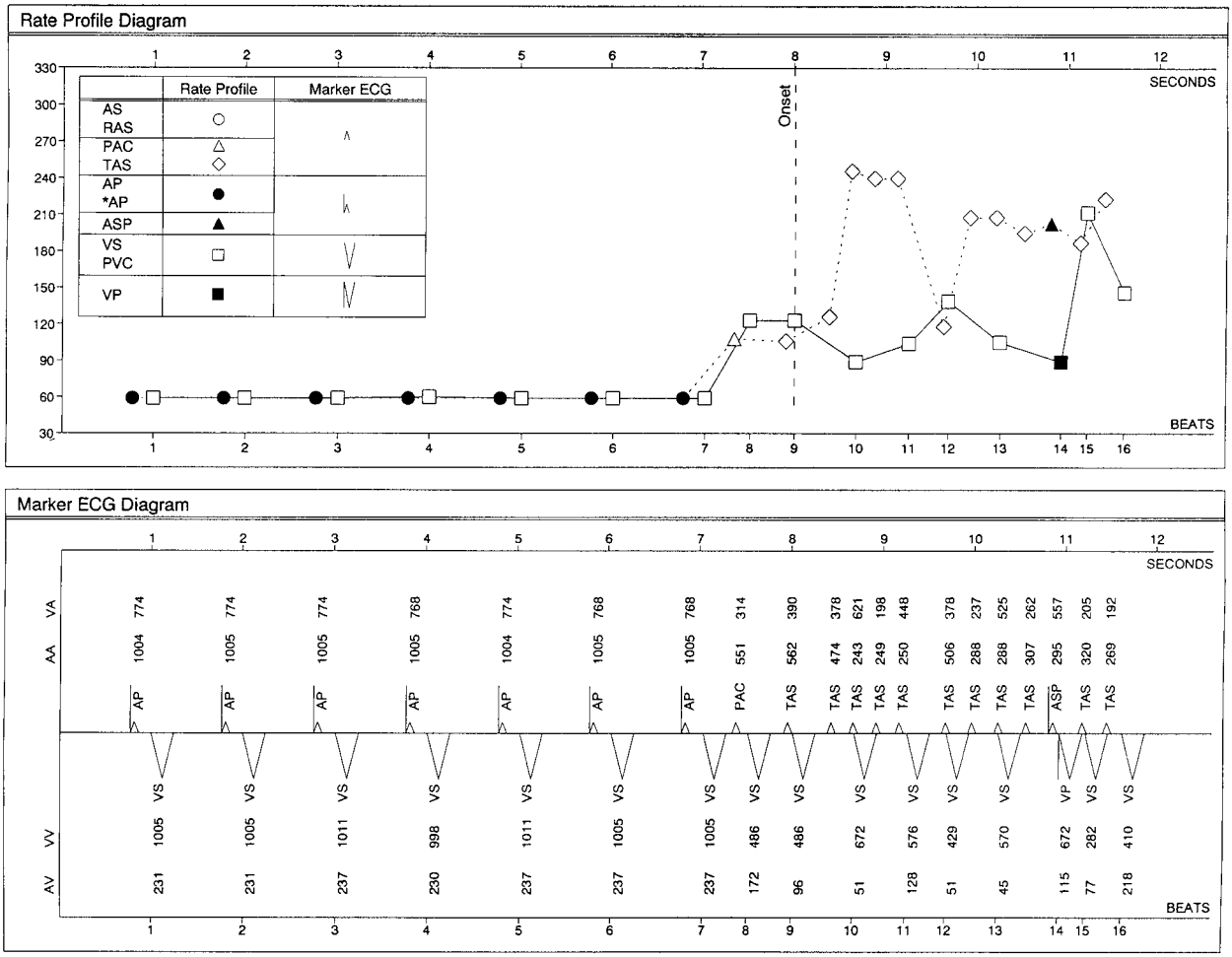

Fig. 7 Telemetry data obtained from patients with a history of paroxysmal atrial fibrillation. The pacemaker used was a Selection AF 1.0 of Vitatron, Inc. Change in rhythm from sinus rhythm to atrial fibrillation was recorded with rate profile diagram (upper tracing) and marker ECG diagram (bottom tracing). AP; atrial pacing. VS; ventricular sense, VP; ventricular pace, PAC; premature atrial contraction, TAS; tachycardic atrial sense, ASP; atrial synchronization pace.

poorly controlled ventricular rate, one of the effective therapeutic methods is to conduct catheter ablation of the atrioventricular junction and implant of a DDDR pacemaker with a mode switching function. Although it has already been demonstrated in a large-scale study[35] that this method is clinically effective, its indication for paroxysmal atrial fibrillation is still controversial. Additionally, there is no answer to the report that sudden death is observed in patients undergoing implantation of pacemakers after catheter ablation of AV node[36]. The authors have experienced marked improvement of symptoms in patients with hypertrophic obstructive cardiomyopathy after catheter ablation of the atrioventricular junction and implantation of a DDDR pacemaker with an auto mode switch function. As described above, although this method is useful, it is desirable to select the patients to use a rigid selection of patients for this procedure.

Conclusion

The goal of non-drug therapy for atrial fibrillation may be achieved by catheter ablation, but it takes some time to accomplish it. A new pacing therapy for atrial fibrillation is expected, but, pacing therapy for the prevention of atrial fibrillation is quite different from pacing therapy accompanying the conventional treatment of bradycardia. Additionally, it is not fully effective 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 cases of atrial fibrillation. In the pre-

sent state of affairs, it is also important to consider highbred therapy in which pacing therapy is combined with drug therapy or catheter ablation. Furthermore, regarding the technical aspects 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 necessary conditions. Finally, it is essential before expanding clinical application to demonstrate the utility of a new pacing therapy for atrial fibrillation through a large-scale prospective study.

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