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Atrial Septal Pacing to Resynchronize Atrial Contraction and Improve Atrial Transport Function

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Abstract

Objectives. Atrial septal pacing via a trans-septal breakthrough site within the right atrial septum can shorten global atrial activation time, resulting in significant reduction of recurrence of atrial fibrillation events. This study examined whether this pacing method will lead to resynchronization of atrial contraction and its benefit on hemodynamic function can be maintained for 24 months.

Methods. Thirty patients with atrial fibrillation and delayed atrial conduction were enrolled(17 males, 13 females, mean age 73±7 years). Trans-septal breakthrough site within the right atrial septum was identified through pacing from the dorsal left atrium. Continuous atrial septal pacing at the trans-septal breakthrough site was performed for 24 months. Time difference(TD)between right and left atrial contractions was measured during atrial septal pacing and sinus rhythm by pulse Doppler echocardiography of the trans-tricuspid(P-At)and mitral(P-Am)blood flows(TD＝P-Am－P-At).

Results. The atrial lead was screwed near the fossa ovalis in 29 of 30 patients. Atrial septal pacing yielded significantly shorter P wave duration(101.9±10.4 vs 139.6±14.7 msec, $p<0.001$), leading to significant reduction of TD in atrial contraction(－8.8±10.0 vs 29.8±13.6 msec, $p<0.001$)as compared to sinus rhythm. Both shorter P wave duration and reduced TD during atrial septal pacing remained statistically significant during the follow-up period as compared to sinus rhythm. Both left atrial diameter and A to E ratio of filling waves at mitral valve were significantly decreased at 12 months and remained decreased at 24 months.

Conclusions. Atrial septal pacing at the trans-septal breakthrough site can resynchronize atrial contrac-

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tion and results in improved hemodynamic effects during 24 months of follow-up.

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Key Words

■Pacing (atrial septal) ■Atrial fibrillation ■Hemodynamics
■Atrial function (atrial resynchronization, interatrial conduction delay)

INTRODUCTION

Atrial fibrillation is the most common cardiac arrhythmia; the prevalence increases markedly with age in older adults[1]. Atrial fibrillation is a major cause of morbidity and mortality, increasing the risk for death, congestive heart failure and embolic events[2,3]. The optimal treatment of atrial fibrillation should be to reduce the risk of thromboembolism as well as to prevent the worsening of cardiac function by maintaining sinus rhythm. Over the past decades, clinical trials using various antiarrhythmic drugs for the treatment of atrial fibrillation have met with variable success. In addition, the efficacies of those agents have been limited by the high incidence of atrial fibrillation recurrence, and poor tolerance because of the proarrhythmic and negative inotropic effects[4].

Data from recent studies have shown that specific atrial pacing methods can result in shorter global atrial activation time, leading to the reduced occurrence of atrial fibrillation events as compared to conventional right atrial appendage pacing. Some of these methods have included biatrial[5], dual-site[6] and single-site right atrial pacing[7,8]. We previously reported that atrial septal pacing via a trans-septal breakthrough site can shorten the global atrial activation time, resulting in a significant reduction in the frequency of atrial fibrillation episodes[9].

Few studies have investigated the influence of atrial septal pacing affecting atrial contraction. However, to our knowledge the relationship between continuous atrial septal pacing and hemodynamic effect has not been formally tested. The purpose of this study was to examine the hypothesis that atrial septal pacing via a trans-septal breakthrough site will lead to mechanical resynchronization of atrial contraction and whether its benefit on hemodynamic function can be maintained for at least 24 months.

SUBJECTS AND METHODS

Study population

Thirty consecutive patients (17 males, 13 females, mean age 73±7 years) enrolled in this study had brady-arrhythmia with indications for permanent pacing, and more than one episode of paroxysmal atrial fibrillation in the preceding 3 months before device implantation despite use of pharmacologic therapy. Informed consent was obtained from all patients before the procedure according to the protocol approved by the Human Research Committee of the Jikei University School of Medicine.

Twenty-four patients (80%) received a device for bradycardia-tachycardia syndrome and the remaining 6 patients (20%) for atrioventricular block with intraatrial conduction delay. The definition of delayed atrial conduction was both greater than 120 msec P wave duration in sinus rhythm and longer than 100 msec conduction time between the high right atrium and the pacing site in the esophagus during esophageal pacing. Fourteen patients (47%) had a history of hypertension, 16 patients (53%) valvular heart disease and one patient (3%) other structural heart disease. On average, 3±1 antiarrhythmic drugs previously prescribed were ineffective to control atrial fibrillation episodes in all patients. The classes of antiarrhythmic agents used were Class Ⅰ (26 patients), β adrenergic blocking agents (21 patients) and calcium channel antagonists (9 patients).

Study protocol

All patients visited the outpatient clinic in our hospitals at monthly intervals between 3 months before and 24 months after device implantation. Evaluation of the occurrence of atrial fibrillation was obtained by a questionnaire and direct reporting of symptoms by patients, 12-lead electrocardiogram (ECG) recording and 24-hour ambulatory ECG monitoring. In the patient interview, they were asked about symptoms associated with the occurrence of atrial fibrillation—*e.g.* irregularity of pulse, palpitation chest pressure and shortness of breath.

At the scheduled pacemaker clinic visits every 3 months, the performance of device system and the

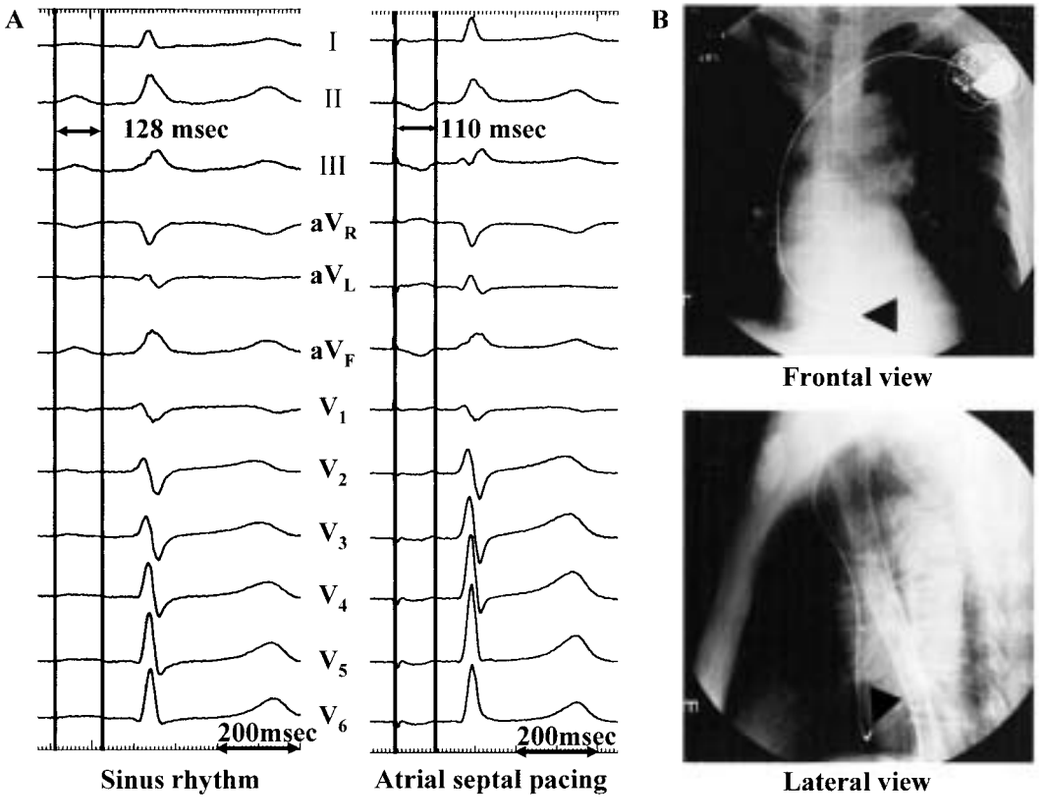

Fig. 1 Twelve-lead electrocardiograms and fluoroscopic views

A: Twelve-lead electrocardiograms during sinus rhythm and atrial septal pacing in Case 10. P wave duration during atrial septal pacing was obviously shorter as compared to sinus rhythm. The configuration of paced P wave is negative in the inferior leads, demonstrating biphasic(−/+)or negative in all patients.
B: Frontal and lateral fluoroscopic views in the same case with pacing via a trans-septal breakthrough site within right atrial septum. An atrial lead is screwed at the area surrounded by the fossa ovalis and the coronary sinus ostium.

occurrence of atrial fibrillation episodes were assessed by interrogating pacemaker data-logs[10]. The P wave duration was measured during sinus rhythm and also during atrial pacing(**Fig. 1−A**). This measurement was performed from the onset of P wave or the pacing spike to the end of P wave in all 12 leads. All ECG recordings were performed at a sweep speed of 50 mm/sec and a gain of 20 mm/mV. Each measurement was performed in duplicate, and the mean value was used.

Standard transthoracic echocardiographic measurements were periodically evaluated before and after operation. The interatrial contraction sequence was assessed during sinus rhythm and also during atrial pacing by the method as described below.

Prior to device implantation all antiarrhythmic drugs were discontinued for more than 5 half-lives and intravenous sedation was not used. After implantation all patients were hospitalized for 7 days with continuous 24-hour telemetry monitoring. Patients with atrial fibrillation events($n = 12$) during the in-hospital period were given the same antiarrhythmic treatment that they took before the procedure. Antiarrhythmic drugs could be discontinued or reduced at the physician's discretion, if sinus rhythm was maintained for at least 3 months. Warfarin was given to all patients to maintain an international normalized ratio range of 1.5 to 2.5.

Device implantation

The device implantation was performed as previously described[11]. Briefly, an active screw-in lead was fixed at the trans-septal breakthrough site within the right atrial septum(**Fig. 1−B**). The trans-septal breakthrough site was identified by pacing from the dorsal left atrial posterior wall. Thirteen patients(43%)were given an AAI generator(Model KSR701, Medtronic Inc.)and the remaining 17

patients(57%)a DDD generator(Model Pulsar Max II DR1280, Guidant Corp.). The lowest pacing rate was programmed at increments of 10−20 beats/min higher than the intrinsic heart rate at rest. The atrial pacing preference(Guidant Corp.)or the rate response function(Medtronic Inc.)was programmed to maintain overdrive pacing during exercise and the highest pacing limit was 120 beats/min.

Evaluation of interatrial contraction sequence

The interatrial contraction sequence was examined by pulse Doppler echocardiography of atrioventricular blood flow as previously described[11]. In summary, the contraction delay between right and left atrium was measured as the time difference (TD)between the atrial filling waves at the tricuspid and mitral valves(**Fig. 2**). Interatrial time delays were calculated separately for each atrioventricular valve. The measured intervals from the atrial pacing spike or the onset of P wave to the peak of the respective A wave(P-Am and P-At)was obtained. Each measurement was performed in triplicate, and the mean value was used for calculation of the interatrial contraction delay(TD = P-Am − P-At).

Statistical analysis

All data were presented as the mean ± SD. Means of various groups were compared using the paired or unpaired Student's *t*-test, as appropriate. Repeated measures were analyzed with analysis of variance(ANOVA)with Scheffe's method. Two-sided p values < 0.05 were considered statistically significant.

RESULTS

Before device implantation the P wave duration during sinus rhythm was prolonged in all patients and averaged 139.6 ± 14.7 msec(**Fig. 3**). The mean TD between the atrial filling waves at the tricuspid and mitral valves by the pulse Doppler echocardiography was 29.8 ± 13.6 msec(**Fig. 4**). These observations indicate that a severe conduction delay existed between the right and left atria. On echocardiogram, the left atrial diameter and the A to E ratio of the filling waves at the mitral valve were increased, whereas the left ventricular end-diastolic diameter and the left ventricular ejection fraction were within normal limits(**Table 1**). Episodes of atrial fibrillation occurred frequently in all 30 patients, 15 of whom had more than 2 episodes/week.

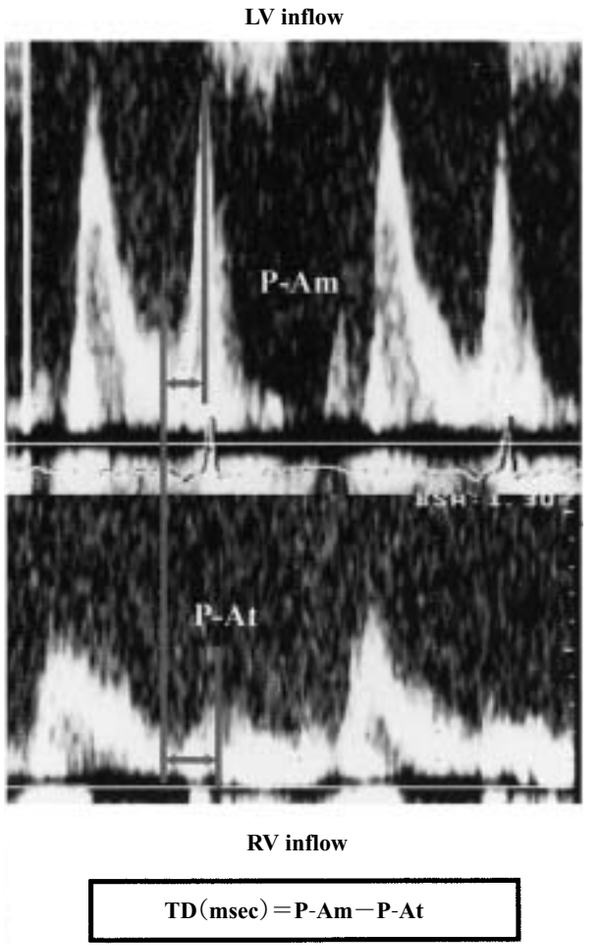

Fig. 2 Doppler echocardiogram recorded just below the mitral(*upper*)and tricuspid valves(*lower*)in Case 10
The interval between the atrial pacing spike and the peak of the atrial filling wave was measured at the left and right inflow, respectively considered as P-Am and P-At. The difference between P-Am and P-At was defined as the time difference(TD).
LV = left ventricular; RV = right ventricular.

Atrial septal pacing at trans-septal breakthrough site

In all cases an active screw-in lead was fixed at the trans-septal breakthrough site within the right atrial septum. This site was located at either the area between the fossa ovalis and the orifice of the coronary sinus in 29 patients or the right atrial site of Bachmann's bundle in 1 patient(**Fig. 1−B**). At implantation the measured atrial pacing threshold was 0.74 ± 0.25 V at a pacing pulse width of 0.5 msec, the sensed P wave amplitude was 3.4 ±

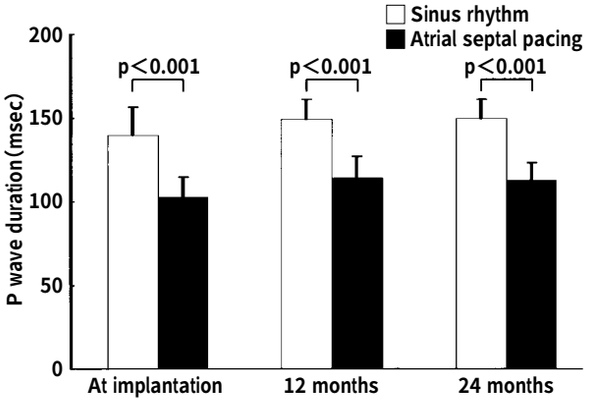

Fig. 3 Comparison of the P wave duration during sinus rhythm and atrial septal pacing
As compared to sinus rhythm, the P wave duration during atrial septal pacing was consistently shorter and this difference remained statistically significant during the follow-up period.

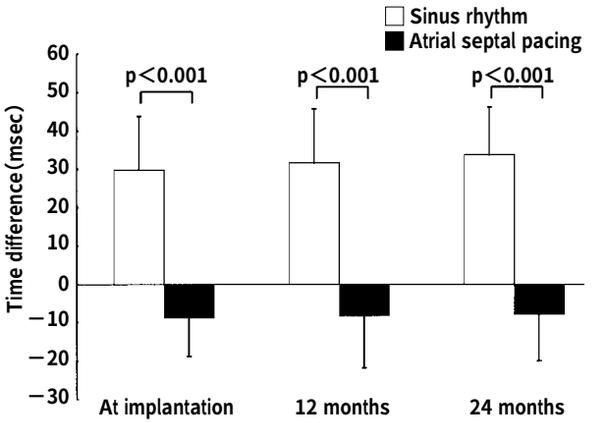

Fig. 4 Comparison of the time differences of atrial contraction during sinus rhythm and atrial septal pacing
As compared to sinus rhythm, time difference during atrial septal pacing was consistently smaller and this difference remained statistically significant during the follow-up period.

Table 1 Variation of echocardiographic parameters in right atrial septal pacing

	At implantation	12 months	24 months
Left atrial dimension (mm)	44.8±3.6	39.1±4.7*	37.5±4.4*
Left ventricular dimension (mm)	47.1±4.8	46.0±5.0	45.5±4.5
Left ventricular ejection fraction (%)	64.4±9.6	64.5±0.8	63.2±7.3
A/E ratio at mitral valve	1.19±0.08	0.84±0.16*	0.83±0.19*
P-Am (msec)	92.1±10.5	94.1±13.2	96.3±15.9
P-At (msec)	100.9±12.1	102.4±15.2	104.2±13.5
TD (msec)	−8.8±10.0	−8.3±13.4	−7.9±12.1

Values are mean±SD. *$p<0.05$ vs at implantation.
Abbreviations as in Fig. 2.

1.2 mV and the atrial lead impedance was 637 ± 129 Ω. These parameters were all within normal limits. There were no observed complications with this pacing method during 24 months of follow-up.

At the beginning of follow-up the atrial septal pacing yielded significantly shorter P wave duration as compared to sinus rhythm (101.9 ± 10.4 msec, $p < 0.001$; **Fig. 3**). The TD from right to left atrial contraction was also significantly less during atrial septal pacing as compared to sinus rhythm (− 8.8 ± 10.0 msec, $p < 0.001$; **Fig. 4**). These observations indicate that atrial septal pacing could be used as an effective pacing method to significantly decrease interatrial conduction delay, thereby minimizing asynchrony of atrial contraction.

Long-term efficacy of atrial septal pacing

The P wave duration was increased in both sinus rhythm and atrial septal pacing during the follow-up period (**Fig. 3**). However, as compared to atrial septal pacing, the P wave duration in sinus rhythm was consistently longer and this difference remained statistically significant during the follow-up period (12 months: 113.9 ± 13.2 vs 149.0 ± 12.1 msec, $p < 0.001$; 24 months: 112.8 ± 10.3 vs 149.4 ± 11.8 msec, $p < 0.001$). The TD between right and left atrial contraction did not change in either group during 24 months of follow-up (**Fig. 4**). There was a significant difference in the TD between right and left atrial contraction observed with the atrial septal pacing as compared to sinus rhythm (12 months: − 8.3 ± 13.4 vs 33.5 ± 14.2 msec, $p < 0.001$; 24 months: − 7.9 ± 12.1 vs

35.7 ± 12.4 msec, $p < 0.001$). These observations indicate that atrial septal pacing via the trans-septal breakthrough site could preserve the synchronization of atrial contraction over 24 months.

Following implantation, the atrial septal pacing completely suppressed the recurrence of atrial fibrillation episodes in 19 patients (63%), including 12 patients (40%) without antiarrhythmic drugs. Overall the frequency of atrial fibrillation events during either 12 or 24 month intervals after implantation was significantly fewer than before implantation (0.9 ± 2.0 or 1.7 ± 2.7 vs 10.3 ± 6.8 events/month, $p < 0.001$; **Fig. 5**). There were no patients with persistent atrial fibrillation during the follow-up period, whereas 3 patients (10%) had episodes of atrial fibrillation requiring electrical cardioversion prior to implantation. Both the left atrial diameter and the A to E ratio of the filling waves at the mitral valve were significantly decreased at 12 months and remained decreased at 24 months (**Table 1**). There was no significant difference in the left ventricular end-diastolic diameter and left ventricular ejection fraction during 24 months of follow-up. Furthermore, the degree of mitral regurgitation did not change during the follow-up period.

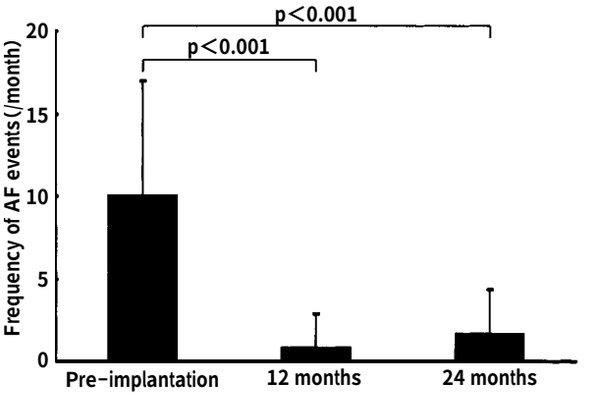

Fig. 5 Comparisons of frequencies of atrial fibrillation episodes before and after (12 and 24 months) pacemaker implantation
Continuous atrial septal pacing led to significant reduction in the frequencies of paroxysmal atrial fibrillation episodes.
AF = atrial fibrillation.

DISCUSSION

The main finding of this investigation is that atrial septal pacing at the trans-septal breakthrough site significantly improved the delayed interatrial conduction, leading to a minimization of time lag of the atrial contraction. As a result atrial fibrillation burden was significantly reduced during atrial septal pacing.

Atrial conduction delay and atrial fibrillation

Several reports have described that abnormalities of the P wave, especially increased P wave duration, are associated with an increased incidence of atrial fibrillation[12]. It has previously been shown that delayed intraatrial conduction can result in a disparity between atrial activation and recovery with a short effective refractory period in the atria[13–15]. This likely allows the formation of interatrial or intraatrial reentrant circuits, leading to the generation of atrial arrhythmias. Atrial septal pacing with shorter global activation time may decrease the atrial fibrillation burden by minimizing interatrial conduction delay. In the present study, we have shown that atrial septal pacing, resulting in a significantly shorter P wave duration, is associated with a decrease in the recurrence of atrial fibrillation events as compared to sinus rhythm. This benefit was maintained over 24 months after initiation of atrial septal pacing.

Atrial contraction sequence in atrial septal pacing

In the structurally normal heart, impulses generated in the sinus node are transmitted through Bachmann's bundle, resulting in a wave of depolarization across the entire left atrium. It has been hypothesized that during physiological atrial contraction this wave advances from the roof of left atrium toward the mitral annulus. Although various pacing methods with reduction in interatrial conduction delay have been used for the treatment of atrial fibrillation, there are few reports that have investigated the influence of atrial based pacing on atrial contraction sequence. Kindermann *et al.*[11] previously reported that atrial septal pacing at proximal coronary sinus shortens the time difference between right and left atrial contraction compared to conventional atrial pacing at the right atrial appendage. However, the activation sequence of both atria is reversed. In the present study, the time delay of interatrial contraction was significantly decreased in the atrial septal pacing as compared to sinus rhythm. The time from the beginning to the peak of contraction in the left atrium was significantly shorter in the atrial septal pacing than that

during sinus rhythm, whereas that in the right atrium did not show any significant difference between atrial septal pacing and sinus rhythm. The atrial septal pacing resynchronized the contraction of both atria by maintaining the delayed contraction of the left atrium with proper timing.

It is possible that atrial septal pacing at the low interatrial septum may worsen hemodynamic parameters. In this study, there was interval improvement of left atrial enlargement and reduction of the A to E ratio of the blood flow through the mitral valve during the 24 months follow-up in patients with atrial septal pacing. Atrial septal pacing may have been beneficial by reducing the mechanical load of the left atrium by resynchronizing atrial contraction. Fabritz *et al*.[16] recently reported that the progression of bradycardia leads to enlarged atrium in mice with heart-directed over-expression of adenosine receptors. Improvement of bradycardia may also reduce the mechanical load of the left atrium, leading to the decrease of its size. Further studies are needed to elucidate the mechanism of reduced atrial chamber by atrial pacing.

Efficacy of atrial septal pacing

We also evaluated the efficacy in continuous atrial septal pacing via the trans-septal breakthrough sites in this study. Although the P wave duration at baseline was prolonged in both groups, the P wave duration in atrial septal pacing of mean 112.8 msec at 24 months was significantly shorter compared to sinus rhythm. The time difference between right and left atrial contraction in atrial septal pacing did not change through the follow-up period. These observations suggest that right atrial pacing at the trans-septal breakthrough site could preserve the synchronized contraction of both atria over 24 months. Furthermore, the atrial fibrillation burden in patients with atrial septal pacing was significantly reduced as compared to before device implantation. The reduction of atrial conduction delay and the resynchronization of atrial contraction by right atrial pacing at the trans-septal breakthrough site could lead to a beneficial effect by decreasing the atrial fibrillation burden in patients with interatrial conduction delay.

Study limitation

As mentioned above, right atrial pacing at the trans-septal breakthrough, usually located at the area surrounded by the fossa ovalis and the coronary sinus ostium, can resynchronize the contraction of both atria and suppress the occurrence of atrial fibrillation over 24 months. Nevertheless, the present findings should be interpreted in the context of some limitations. First, the present study was not a prospective randomized study, thus the efficacy of this pacing method was not compared to previously reported methods. Second, only patients with interatrial conduction delay were enrolled in this study. Consequently, the efficacy of this pacing method for atrial fibrillation suppression remains unclear in patients with normal interatrial conduction.

CONCLUSIONS

Atrial septal pacing at the trans-septal breakthrough site can resynchronize atrial contraction and results in improved hemodynamic effects during 24 months of follow-up.

要　　約

心房中隔ペーシングは心房収縮を再同期させ心房機能を改善する

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目　的: 右房中隔内のtrans-septal breakthrough site（TBS）から行う心房中隔ペーシングは全心房興奮時間を有意に短縮させ，心房細動の再発予防効果に優れている．本研究ではTBSから心房中隔ペーシングを行うことで遅延伝導に伴い解離した心房収縮を再同期させることができるか検討を行った．また，持続的心房中隔ペーシングが血行動態に与える効果についても検討を行った．

方　法: 発作性心房細動と心房内伝導障害があり，心房中隔ペーシングを行った30例（男性17例，女性13例，平均年齢73±7歳）を対象とした．左房後壁ペーシング中に同定したTBSにペーシング

リードを固定し，24ヵ月間心房中隔ペーシングを行った．心室流入路で記録した僧帽弁(P-Am)および三尖弁(P-At)を通過する血流のパルスドップラー波形より心房収縮の時間差(TD)を計算した(TD＝P-Am－P-At)．

結　果: 30例中29例は卵円窩近傍に，残りの1例はBachmann束近傍に心房リードを固定した．ペースメーカー植え込み直後のペーシングP波は洞調律のP波より有意に短縮し(101.9±10.4 vs 139.6±14.7 msec，$p<0.001$)，ペーシング中のTDは洞調律時より有意に縮小した(－8.8±10.0 vs 29.8±13.6 msec，$p<0.001$)．心房中隔ペーシング中に認められたP波幅の短縮効果およびTDの縮小効果は24ヵ月間持続した．術前の心エコー図では左房の拡大および僧帽弁下で記録した流入速波形のA/E比の増大が認められたが，心房中隔ペーシング12ヵ月後には有意に縮小し，その効果は24ヵ月目まで持続した．

結　論: 右房中隔内のTBSから心房中隔ペーシングを行うことで，心房伝導障害を有する例の心房収縮を同期させることが可能であった．その効果は24ヵ月間安定し，心房収縮機能の改善に貢献した．

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