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Case Report

Prompt and Long-term Prophylactic Effect of Closed Loop Stimulation against Paroxysmal Atrial Fibrillation in a Patient with Sick Sinus Syndrome

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A 72-year-old woman with sick sinus syndrome (SSS), who had frequent paroxysmal atrial fibrillations (PAfs) and normal cardiac function, was admitted to our hospital due to syncope. PAfs frequently occurred during the first week after DDD pacemaker implantation (PMI), with closed loop stimulation (CLS) rate-adaptive mode off, but were completely suppressed during the second week, with CLS on, and had been well-controlled over three years thereafter. However, PAfs occasionally occurred under intense sympathetic activity during 6 months after PMI as well, and were effectively terminated by disopyramide which had anticholinergic effect. Thus, the development and maintenance of PAf were thought to be associated with destabilized cardiac autonomic activities, that is, sympathetic and parasympathetic dominance, respectively. Additionally, heart rate variability analyses after implementation of CLS revealed the restoration of sympathetic and parasympathetic components. Accordingly, CLS mode was considered to play a critical role in preventing PAf by reflecting autonomic activity in heart rhythm in this SSS patient.
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Key words: Closed loop stimulation (CLS), Paroxysmal atrial fibrillation (PAf), Sick sinus syndrome (SSS), Autonomic activity, Normal cardiac function

Various physiological and rate-responsive pacing modes for sick sinus syndrome (SSS) patients have been developed. Either AAI or DDD pacing mode is generally thought to be more physiological and appropriate than VVI. Recent studies reported that these physiological pacing modes prevented atrial fibrillation (Af) in bradycardia patients.[1,2] More recently, the effect of minimal ventricular pacing (MVP) to reduce the development to chronic atrial fibrillation (CAf) has been reported.[3] On the other

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hand, various rate-responsive modes have been studied to search for the most physiological and Af-preventive mode.[4)]

The cardiac autonomic nerve controls cardiac output by inotropic and chronotropic action. The inotropic action is thought to be reflected in the electrical impedance of cardiac muscle during the systolic phase. Actually, the impedance gauged between the tip of ventricular pacemaker lead and the generator during the systolic phase in every single cardiac cycle was reported to be intimately related to the cardiac autonomic activity.[5)] Pacemakers adopting impedance as a marker of the autonomic activity which is applied to the rate-responsive mode have appeared in clinical settings. The rate-responsive mode is refered to as closed loop stimulation (CLS).

The CLS system monitors the beat-by-beat impedance changes during the systolic phase, calculates the chronotropic signals corresponding to the impedance, and then almost instantly utilizes the signals for subsequent pacing intervals. The regulation of heart rate and rhythm by the cardiac autonomic nerve have deteriorated in SSS patients. The reconstruction by means of a CLS system of the deteriorated feedback loop of chronotropic action in SSS seems to lead to physiological and adequate heart rate modulation. Recently, this rate-adaptive mode was shown to be possibly effective in suppressing paroxysmal atrial tachycardia burden.[6)] However, as far as we are aware, there are few case reports which showed that CLS mode had obvious benefit in preventing paroxysmal atrial fibrillation (PAf) in SSS patients, even with antiarrhythmic agents. We observed distinct immediate and long-term effectiveness of CLS mode along with drug administration in preventing frequently repetitive development of PAfs in an SSS case.

Case report

A 72-year-old woman with hypertension began to feel palpitations in September 2003 and her general practitioner diagnosed PAf. She was prescribed disopyramide (100 mg) as needed in the event of a PAf attack. PAfs occurred as frequently as 10 to 20 times per month and continued for several hours, but were usually terminated with disopyramide within the same day. By mid-November, PAfs started to occur every 2 days and lasted longer. She was then prescribed 300 mg of disopyramide daily. On December 4, palpitations started and continued until the afternoon on the following day, when syncope occurred immediately after a few occurrences of near syncope subsequent to delivering a speech at a meeting in her office. By the time an ambulance arrived 10 minutes later, she had recovered from the syncope. She was subsequently admitted to our hospital for further examination and therapy.

Upon admission, her pulse was regular bradycardia and blood pressure was 119/40 mmHg. Blood chemistry profiles, electrolytes, thyroid function and catecholamines were normal except for slight liver dysfunction. Electrocardiography (ECG) showed sinus bradycardia of 55 bpm. Chest X-ray and echocardiographic findings were essentially normal. Holter monitoring revealed 65,972 total heart beats per 24 hours, which confirmed extreme sinus bradycardia, and pauses of about 2 seconds in blocked atrial premature beats. Electrocardiographic monitoring in the ward showed repeated PAf attacks and a maximal pause of 8.7 seconds on conversion to sinus rhythm. The PAfs always spontaneously converted to sinus rhythm; however, the temporary use of flecainide, pilsicainide, aprindine or disopyramide had no effect immediately after admission. The patient was given 8 mg per day of candesartan, an angiotensin II receptor antagonist with some evidence of suppressing Af, to replace ormesaltan (20 mg) which had been prescribed for hypertension before admission. Aprindine (60 mg) daily was added after admission (**Figure 1A**).

On December 21, the patient was implanted with a rate-adaptive pacemaker with a CLS mode (Protos DR/CLS; BIOTRONIK; Germany). The pacemaker parameters were as follows: On implantation, pacemaker was programmed for DDD mode, 60 bpm basic pacing rate and 150 msec AV delay. Then, one week after PMI, CLS rate-responsive mode was added and at the same time the 150 msec AV delay was changed to the dynamic AV delay, ranging as follows according to heart rate: AV delay 160 msec: HR $<$ 70 bpm, 150 msec: 70–90 bpm, 140 msec: 91–110 bpm, 120 msec: 111–130 bpm, 100 msec: $>$ 130 bpm. As this patient worried about recurrence of PAfs, she had stayed in a sedentary or supine position in her bed throughout hospitalization. Thus, the pacemaker continued DDD pacing at a basic rate of 60 bpm during the first week after PMI. Even if the dynamic AV delay had been applied from the first week, the AV delay corresponding to a basic rate would have been 160 msec, which would have differed only by 10 msec from the 150 msec AV delay actually applied during the first week. The 10 msec difference would not have influenced the suppressive effect on PAf or heart rate variability much.

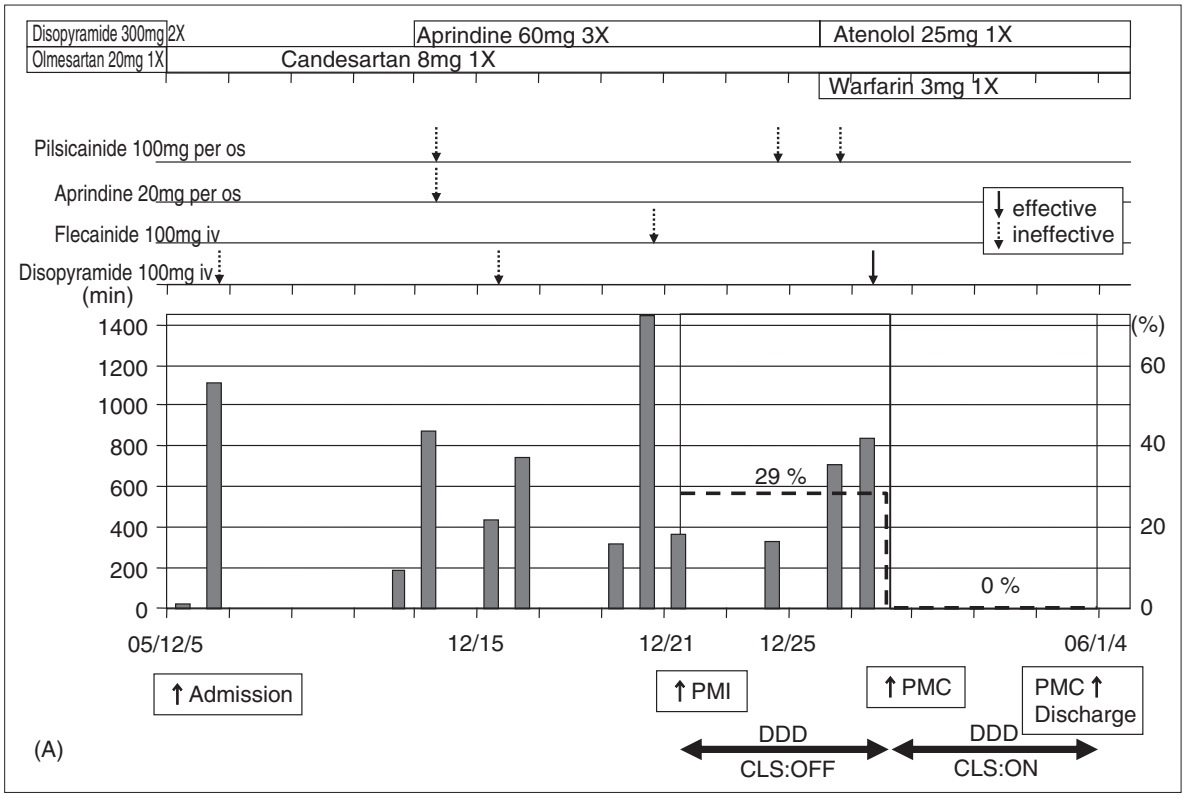

Figure 1 Duration and frequency of PAfs during hospitalization and after discharge
(**A**) ECG monitoring during hospitalization: PAf frequently occurred before implementation of CLS rate-adaptive mode even after PMI. Administration of several kinds of antiarrhythmogenic agents as needed did not work as indicated by the middle arrow. However, PAf was completely suppressed after the implementation of CLS. During hospitalization, PAf attacks documented by ECG monitoring coincided well with her symptom of palpitation.

On the day after PMI, atenolol (25 mg), β blocker, which was reduced to 12.5 mg on discharge because of disappearance of PAfs as well as bradycardia due to SSS, and warfarin (3 mg) daily were added for the rate control and anticoagulant therapy in case of PAf attack, respectively. Although PAfs occurred during the first week after PMI without CLS function as frequently as before PMI or admission, those were completely suppressed during the 2nd week after PMI with the CLS function on (**Figure 1A,2**). During hospitalization, PAf attacks documented by ECG monitoring coincided well with her symptom of palpitation. After the application of CLS, a 100 mg bolus of disopyramide or a 200 mg per os of it as needed became remarkably effective against the PAf, the frequency and length of which gradually decreased (**Figure 1B,2**). In 6 months after discharge. The patient remained almost free of PAf subjectively as well as objectively over more than three years to date (**Figure 2**), even after aprindine was withdrawn on October 12, 2006, although the data from pacemaker clinic between May 25 and September 15, 2006 were missing.

The PAf in this patient seemed to develop in association with increased sympathetic or mental activity, such as immediately after delivering the speech at her office or PMI in our hospital, on the day of discharge or the first day back to work after discharge and when driving for a long time or attending ceremonies. In addition, the anticholinergic drug, disopyramide, terminated the PAf extremely effectively after PMI.

Holter monitoring was conducted on December 4, 2007, 2 years after PMI, and revealed almost all heart beats were derived from atrial pacing with intermittent atrio-ventricular sequential pacing modulated by the CLS system throughout the day (cf. **Figure 2**). Heart rate variability was calculated using MemCalc®, the software prepared by NIHON KOHDEN Corp. Every single successive R wave was manually labeled and all the RR intervals were processed in chronological order for heart rate

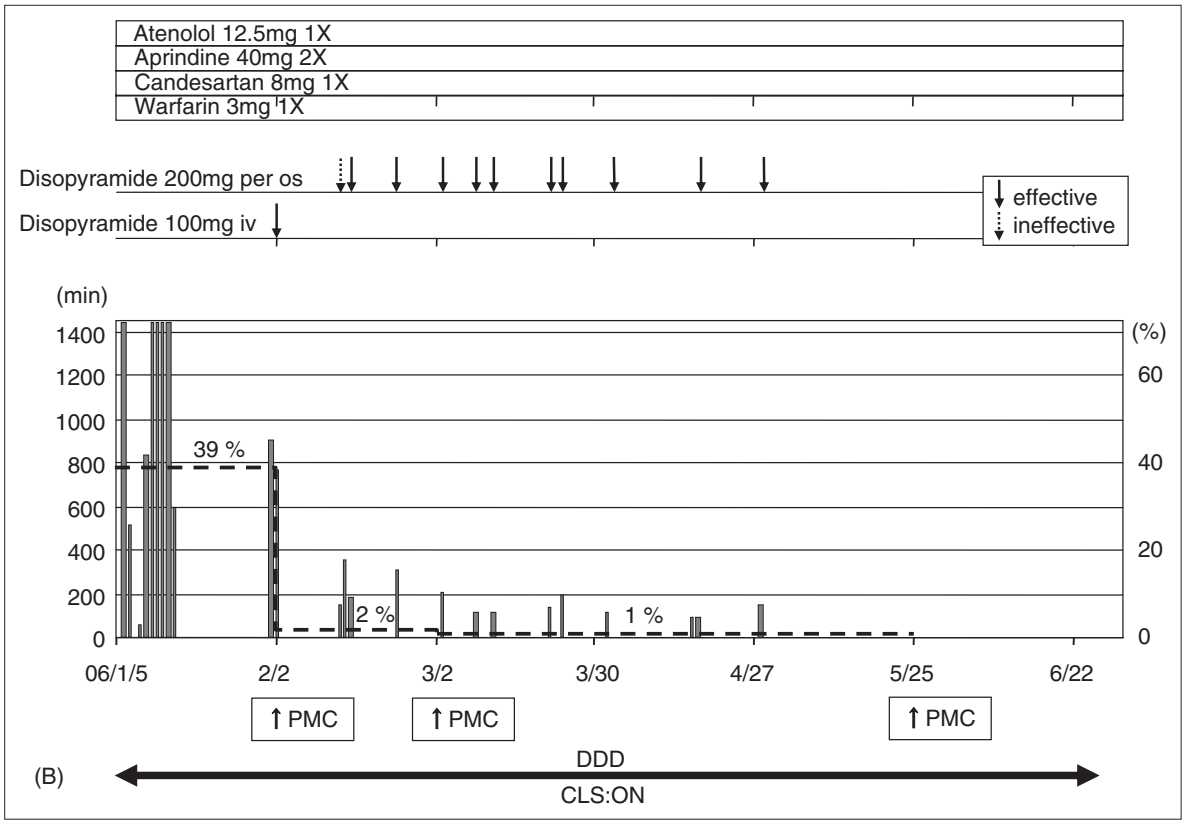

Figure 1

(**B**) Symptom and pacemaker memory after discharge: Although PAf attacks transiently increased shortly after discharge, probably due to increased physical and mental activity, disopyramide, as needed, effectively and obviously terminated PAf as indicated with arrows in the middle. The duration and frequency gradually decreased during a period of 6 months immediately after discharge.

The shaded bars indicate the duration as well as frequency of PAfs according to ECG monitoring (**A**) and symptom (**B**) on the left Y axis. The broken lines indicate the ratio of the total atrial sensing over 150 bpm to the total atrial sensing during the periods between each successive pacemaker clinic visits on the right Y axis.

PMI: pacemaker implantation, PMC: pacemaker clinic, CLS: closed loop stimulation

variability analysis. Premature beats were eliminated from the monitoring periods. Ultimately, 93,543 beats, 99.2% of total heart beats, were processed for analysis. Power spectral analyses revealed that heart rate variability derived from almost 100% of CLS restored the high frequency (HF) [0.15–0.40 Hz] and low frequency (LF) [0.04–0.15 Hz] components, both of which meant autonomic activity, along with very low frequency (VLF) [0.003–0.04 Hz] and ultra low frequency (ULF) [0.0001–0.003 Hz] components, and that each had distinct circadian rhythms (**Figure 3**).

The question how heart rate variability was analyzed at night when heart rate would decrease to a basic heart rate of the pacemaker might be raised. Fortunately, even at night or in the early morning, mean heart rate maintained at 62 to 67 bpm, and heart rate fluctuated around the mean heart rate and only transiently, if ever, decreased down to the basic heart rate. Actually, HF component, the parameter of parasympathetic activity calculated from Holter monitoring, showed prominent increase at nighttime and clear circadian rhythm. In addition, even if not so, because PAfs tended to develop exclusively in the daytime, heart rate variability in the daytime seemed crucial to the suppressive effect on PAf, but not as much in the nighttime.

Discussion

We described a patient who had SSS, group III, but normal cardiac function with repeated drug-resistant PAfs, which was finally suppressed by a pacemaker with the CLS rate-adaptive mode.

Although PAfs occurred during the first week after PMI without the CLS function as frequently as before PMI, PAf attacks did not develop during the

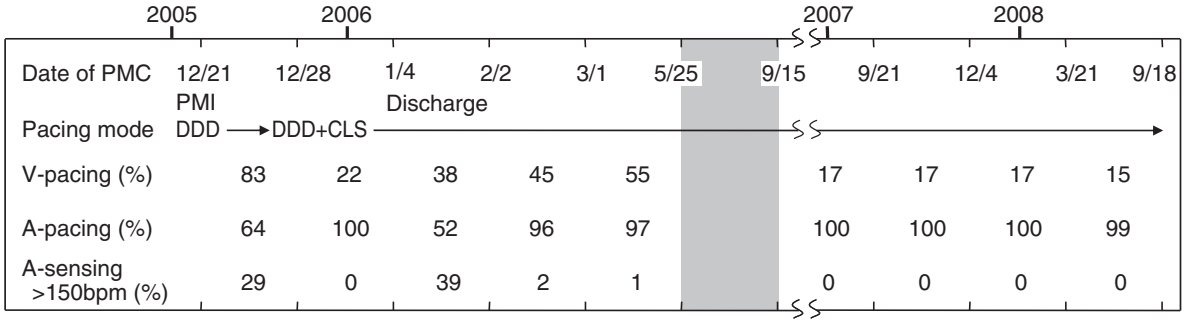

Figure 2 Memory data obtained from pacemaker

Based on memory data obtained from pacemaker clinic, the rates of ventricular and atrial pacing and atrial sensing more rapid than 150 bpm as surrogate marker of atrial fibrillation are shown. The on-and-off prophylactic effect of CLS against PAf attacks was obvious during hospitalization after PMI. The tachycardia episodes in atrium gradually decreased until May 25, 2006, after abrupt recurrence subsequent to discharge. Ventricular pacing rate was not necessarily proportionate to atrial tachycardia burden in this patient. The shaded area indicates the period when the data were missing. PMI, PMC and CLS as were described in **Figure 1**.

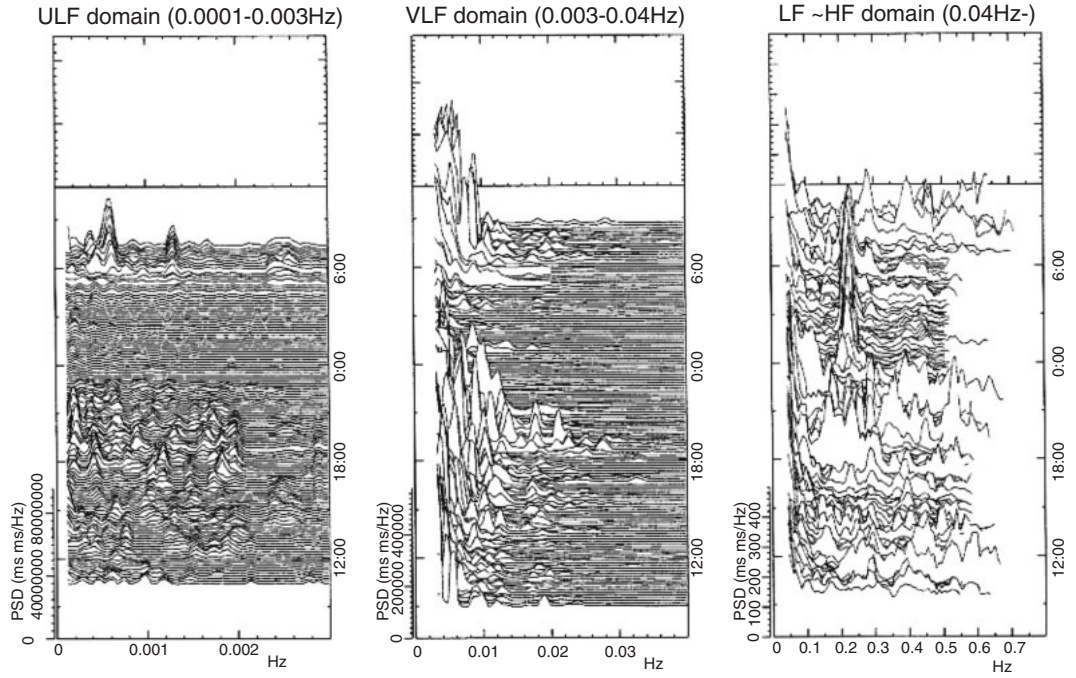

Figure 3 Heart rate variability modulated by CLS rate-adaptive mode

After almost 100% of atrial pacing modulated by CLS mode was verified by Holter monitoring, power spectral analyses of heart rate variability were conducted. The result revealed that the components of HF, LF, VLF and ULF appeared in heart rate variability. HF components increased in nighttime, whereas LF increased in daytime, which seemed to reflect circadian rhythms as well as beat-by-beat modulation of cardiac autonomic activity.

HF: high frequency, LF: low frequency, VLF: very low frequency, ULF: ultra low frequency, PSD: power spectral density

second week after PMI with the CLS on (**Figure 1A**). Thus CLS seemed to suppress PAf attacks in the short term. We have seldom experienced such distinct on-and-off and immediate prophylactic effects of a rate-responsive mode of pacemaker against PAfs in patients with SSS.

Lombardi F et al. showed that the LF/HF obtained from heart rate variability analyses 4 to 5 hours after electrical cardioversion was useful to predict the short-term recurrence of PAf, and insisted that autonomic activity was closely related to PAf recurrence around 2 weeks after cardioversion.[7] Puglisi A et al. evaluated the suppressive effect of three kinds of pacemaker rate-responsive algorithms on PAf, including conventional response, overdrive pacing and CLS modes, and found that the CLS mode effectively suppressed PAf for 4 and 7 months after PMI.[6] They inferred that turbulent autonomic

activity occurred immediately before PAf development, and that the CLS algorithm played a critical role in the time frame and thus reduced the PAf burden.

In our patient, PAfs developed in the setting of increased sympathetic activity, and, after PMI, were easily terminated by disopyramide which had an anticholinergic effect. These phenomena implied that the development and maintenance of atrial fibrillation in this patient were associated with destabilized autonomic activity, probably with sympathetic and parasympathetic dominance, respectively. Moreover, Holter monitoring 2 years after PMI showed that heart rhythm consisted of almost 100% of atrial pacing rhythms controlled by the CLS system throughout the day. Power spectral analyses of heart rate variability revealed HF component (vagal activity), LF component (sympathetic and vagal activity), the LF/HF ratio (sympathovagal balance or sympathetic activity), and their clear circadian rhythms (**Figure 3**). These findings suggested that the CLS system captured the dynamics of beat-by-beat and daily cardiac autonomic activity through electrical impedance of cardiac muscle and indeed realized the natural and physiological heart rate and rhythm modulation.

The prompt prophylactic effect immediately after implementation of CLS during the second week after PMI was attributable to the heart rate modulation based on the real-time cardiac autonomic activities by controlling heart rate variability beat by beat as well as improving bradycardia itself. It was also possible that β blocker administration would modify the abrupt excessive sympathetic activity in this patient. The reason PAf almost completely disappeared in the end could be that the PAf duration was shortened due to the immediate effect of disopyramide after PMI. In addition, the use of angiotensin II antagonist might have led to reverse electrical remodeling in the atrial muscle in the long term.

On the other hand, the randomized comparison of VVI and AAI pacing by Connolly SJ et al. found that the annual rate of Afs was significantly lower among patients with physiological AAI pacing than among those with VVI.[8] However, they also noted that the benefit of the physiological pacing did not become apparent until 3 years of follow-up. Sweeney MO et al. implanted DDD pacemakers in patients with bradycardia, 38% of whom had a histories of PAf. Their prospective comparative study (dual-chamber MVP vs. conventional dual-chamber pacing; ventricular pacing rate: 9.1% vs. 99.0%) demonstrated that the conversion rate into CAf was lower by 40% in the patients with MVP than with conventional pacing.[3] They concluded that dual-chamber MVP suppressed the development of CAf. However, CAf still developed in the rest (60%) of the patients who received the dual-chamber MVP. The CLS algorithm might have prevented CAf developing in some of them.

We first implanted a pacemaker with DDD mode in our patient, and then changed the pacing mode to DDD-CLS rate-adaptive mode one week later (**Figure 1A**). In reality, DDD-dominant pacing and AAI-dominant pacing were conducted during the first week and the second week after PMI, respectively (**Figure 2**). PAf was clearly suppressed during the 2nd week, and not the 1st week. However, over more than three years after PMI, ventricular pacing rate had fluctuated between 15% and 83%, whereas the total amount of atrial sensing more rapid than 150 bpm, which was regarded as the surrogate marker of PAf, was disproportionate to the ventricular pacing rate (**Figure 2**). Thus, with respect to this case, we supposed that the immediate and on-and-off suppressive effect against PAf attack might be attributed to the implementation of CLS, not to the reduction in ventricular pacing rate.

The limitations of this case report are given as follows: Since the suppressive effects of physiological pacing appear at various times after PMI depending on individuals,[9] the clinical course of this case might be peculiar to this individual, not to the CLS rate-responsive mode. Additionally, the natural course might have happened to coincide with the date of PMI. There are also several reports that DDD pacing even without rate-responsive mode suppressed PAfs. Accordingly, if possible, we need to confirm the reproducibility of the suppressive effect of the CLS mode on PAf in this patient by suspending CLS mode, or by conducting PMI with CLS rate-responsive mode in similar patients. However, this patient is doing well under the current condition of the pacemaker parameters, has been essentially free from PAf over more than three years, and is now in the process of withdrawing anticoagulant therapy. Therefore, it was difficult from an ethical point of view to verify the reproducibility. It was also true that this kind of case is quite rare.

In conclusion, we implanted a pacemaker into a patient with SSS, group III, whose cardiac function was normal yet who had recurrent PAfs under intense sympathetic activity. The CLS rate-responsive mode along with a daily β blocker elicited the obvious on-and-off prophylactic phenomenon of PAf shortly after PMI. The occasional administration of disopyramide was extremely effectively in terminating PAf attacks and then reduce the duration and

frequency in 6 months after PMI and thereafter the patient remains essentially free of PAf without disopyramide for more than three years. In addition, heart rate variability analyses after PMI showed the restoration of sympathetic and parasympathetic components manipulated by CLS mode. Accordingly, CLS rate-adaptive mode along with β-blocker was thought to play a critical role in prophylaxis of PAf attack by reflecting autonomic activity in heart rhythm in this patient with SSS, group III, and normal cardiac function.

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