Correlation Between Initial Potentials on a Signal-Averaged P-Wave and Indices of Electrophysiologic Measurements in the Right Atrium

Ryotaro Sasaki, MD^{*,**}; Kazuhiko Sugisawa, MD^{*}; Hiroshi Tani, MD^{*};
Takanori Inazumi, MD^{*}; Yukihisa Kitagaki, MD^{*}; Katsuhiko Nishian, MD^{*};
Jun Tateishi, MD^{*}; Tadaaki Iwasaki, MD^{*}

The aim of this study was to determine whether initial potentials of the P-wave on a signal-averaged electrocardiogram (SAE) during sinus rhythm reflect indices of electrophysiologic measurements in the high lateral right atrium. A total of 67 patients underwent P-wave signal averaging during electrophysiologic testing. The correlation between root mean square voltages for the initial 10 and 20 msec of the P-wave on the SAE and indices of electrophysiologic measurements, sinus node recovery time (SRT) and sinoatrial conduction time (SACT), obtained from programmed stimuli, was evaluated. It was found that the initial potentials of the P-wave on the SAE correlated negatively with SRT and SACT ($-0.37 \leq r \leq -0.30$). It was concluded that the initial potentials correlated with indices of electrophysiologic measurements, although the statistical significance was weak. (*Jpn Circ J* 1998; 62: 279–283)

Key Words: Signal-averaged electrocardiogram; P-wave; Electrophysiologic testing; Atrial fibrillation; Sick sinus syndrome

Previous studies have analyzed P-waves on signal-averaged electrocardiograms (SAEs) in patients with atrial dysrhythmia as a marker of the risk for the development of paroxysmal atrial fibrillation or flutter.^{1–3} These studies have shown that a decrease in the root mean square (RMS) voltage of the terminal portion of the P-wave on a SAE and the prolonged filtered P-wave duration indicate the presence of atrial late potentials. The decreased terminal potential was speculated to reflect fragmented activity within the left atrium.² In addition, the decreased initial potential of the P-wave on the SAE may reflect impaired conductivity in the sinoatrial perinodal region^{4,5} existing in the high lateral right atrium. If this hypothesis is confirmed, impaired conductivity in the sinoatrial perinodal region may be assessed by a decrease in the initial potential of the P-wave on the SAE. Thus, the aim of this study was to determine whether the initial potential of the P-wave on the SAE during sinus rhythm reflects indices of electrophysiologic measurements obtained from high lateral right atrial programmed stimulation.

Methods

Patients and Experimental Design

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*First Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan, and **Matsushita Science Center of Industrial Hygiene, Matsushita Health Insurance Organization, Kadoma, Osaka, Japan

Mailing address: Ryotaro Sasaki, MD, First Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, 663 Japan

A total of 112 consecutive patients referred to the electrophysiologic laboratory of Hyogo College of Medicine Hospital between 1992 and 1995 were studied. All patients underwent simultaneous P-wave signal averaging and electrophysiologic testing in a postabsorptive state. Informed consent was obtained from all patients. A physical examination and transthoracic echocardiography were performed for all patients. M-mode echocardiography was performed in the parasternal position under 2-dimensional guidance and left atrial diameters were measured. The patients' age (years), left atrial diameter (mm), and heart rate (beats/min) were recorded. The heart rate during P-wave SAE was used. Patients were excluded if they had ventricular pre-excitation, were not in sinus rhythm, or had valvular heart disease.

P-wave Signal Averaging

P-wave-triggered signal averaging was performed in the electrophysiologic laboratory equipped with an X-ray fluoroscopic system. The P-wave SAE was recorded from an orthogonal bipolar XYZ lead system using a Multicardiner VCM-3000 (Fukuda-Denshi, Tokyo, Japan). The signal from each lead was amplified, digitized, and passed through a low-pass filter of 300 Hz and a high-pass filter of 40 Hz. The signals of 200 beats were averaged before electrophysiologic evaluation. The filtered P-wave signals of the three bipolar leads were combined into a vector, $(X^2 + Y^2 + Z^2)^{1/2}$. The following P-wave SAE parameters were measured (Fig 1): RMS voltages [IP₁₀ and IP₂₀ (μ V), respectively] for the initial 10 and 20 msec of the filtered P-wave of the vector magnitude; RMS voltages [TP₁₀ and TP₂₀ (μ V), respectively] for the terminal 10 and 20 msec of the filtered P-wave of the vector magnitude; and filtered P duration (FPD, msec).

Fig 1. Measurements of the P-wave on a signal-averaged electrocardiogram (vector magnitude electrocardiogram). Root mean square (RMS) voltages for the initial *10 msec and **20 msec of the filtered P-wave of the vector magnitude. RMS voltages for the terminal #10 msec and ##20 msec of the filtered P-wave of the vector magnitude. FPD, filtered P-wave duration.

Electrophysiologic Testing

Three quadripolar electrode catheters were inserted into the right femoral vein and positioned in the high right atrium, across the tricuspid valve (to obtain a His-bundle electrogram), and in the right ventricle. Signals from leads I, II, V₁, and intracardiac electrocardiograms were displayed and recorded on a polyrecorder MCS-5000 system (Fukuda-Denshi). Pacing was performed with a programmable stimulator BC-03 (Fukuda-Denshi) at 2 msec pulse duration and an output twice the diastolic threshold.

We carried out the following electrophysiologic assessments in the high lateral right atrium. (1) Sinoatrial conduction time (SACT, msec): SACT was defined as half of the time obtained by subtracting the sinus cycle length from the return cycle, which was measured from the interval between the paced premature atrial electrogram and the spontaneous sinus atrial electrogram in the reset zone.^{6,7} (2) Sinus node recovery time (SRT, msec): the time required for resumption of the spontaneous sinus atrial electrogram following the termination of overdrive pacing for 1 min was measured and the maximum was taken as SRT.⁸ (3) Atrial effective refractory period (AERP, msec): the longest coupling interval during which a single premature extrastimulus fails to capture the atrium was measured. (4) Atrial vulnerability: single and double atrial extrastimuli and atrial rapid pacing were used to induce atrial fibrillation. We determined positive atrial vulnerability when atrial fibrillation or flutter was induced.

Correlation Analysis

Correlation matrix analysis was performed among the following variables; age (years), left atrial diameter (mm), heart rate (beats/min), IP₁₀ (μV), IP₂₀ (μV), TP₁₀ (μV), TP₂₀ (μV), FPD (msec), SACT (msec), SRT (msec), and AERP (msec). Before analysis, the normality of distribution was evaluated for all variables (Table 1). When variables demonstrated skewness >2.0, analysis was

Table 1 Range, Mean, Median and Skewness of Variables

	Range	Mean ± SD	Median	Skewness
Age (years)	16–80	56 ± 15	59	−0.99
LAD (mm)	21–45	33 ± 5	32	0.42
HR (beats/min)	30–92	63 ± 14	62	−0.09
IP ₁₀ (μV)	0.4–6.4	1.4 ± 0.9	1.2	3.6
IP ₂₀ (μV)	0.4–6.2	1.7 ± 1.0	1.5	2.6
TP ₁₀ (μV)	0.5–6.8	1.6 ± 1.0	1.3	3.1
TP ₂₀ (μV)	0.5–11.4	2.1 ± 1.5	1.6	4.1
FPD (msec)	111–210	141 ± 19	139	1.4
SACT (msec)	45–470	137 ± 65	135	2.1
SRT (msec)	860–9730	2130 ± 1870	1400	2.5
AERP (msec)	60–430	242 ± 47	245	1.1

LAD, left atrial diameter; HR, heart rate; IP₁₀ and IP₂₀, root mean square (RMS) voltages for the initial 10 and 20 msec of the filtered P-wave of the vector magnitude; TP₁₀ and TP₂₀, RMS voltages for the terminal 10 and 20 msec of the filtered P-wave of the vector magnitude; FPD, filtered P-wave duration; SACT, sinoatrial conduction time; SRT, sinus node recovery time; AERP, atrial effective refractory period.

performed following logarithmic transformation. A p value of <0.05 was regarded as significant.

Comparison Between Groups

The patient population consisted of 67 patients divided into 3 groups: the FFL group consisted of 18 patients who had paroxysmal atrial fibrillation or flutter; the SSS group consisted of 16 patients who had sick sinus syndrome without a history of paroxysmal atrial fibrillation and/or flutter; and the Others group consisted of 33 patients who had ventricular tachycardia (5 patients), supraventricular tachycardia (22 patients), atrioventricular conduction disturbance (1 patient), vasovagal reflex (3 patients), or unknown syncope (2 patients). The statistical significance of differences between the 3 groups was determined by the Kruskal–Wallis test, followed by multiple comparison analysis using Scheffé's procedure.

All 67 patients were also divided into 2 groups, depending on whether or not they exhibited positive atrial vulnerability. Thirty-three patients who exhibited positive atrial vulnerability were classified into the V(+) group; the others, 34 patients, were classified into the V(−) group. The V(−) group included 3 patients in whom a repetitive atrial response was induced during electrophysiologic testing. The statistical significance of differences between the 2 groups was determined by the Mann–Whitney U test. For all comparisons, a p value of <0.05 was regarded as significant.

Results

Correlation Analysis (Table 2)

IP₁₀ correlated negatively with SACT ($r = -0.36$) and SRT ($r = -0.33$). IP₂₀ correlated negatively with SACT ($r = -0.30$) and SRT ($r = -0.37$). The correlation between IP₁₀ and IP₂₀ was high ($r = 0.87$). IP₁₀ correlated positively with TP₁₀ ($r = 0.55$) and TP₂₀ ($r = 0.61$). IP₂₀ correlated positively with TP₁₀ ($r = 0.57$) and TP₂₀ ($r = 0.64$). Conversely, IP₁₀ and IP₂₀ correlated negatively with FPD ($r = -0.43$ and -0.55 , respectively). Figs 2 and 3 show the relationship between initial potentials and SACT and initial potentials and SRT respectively.

TP₁₀ correlated negatively with SACT ($r = -0.34$) and SRT ($r = -0.43$). TP₂₀ correlated negatively with SACT

Table 2 Correlation Matrix Analysis Among the Variables

	HR	LAD	Age	AERP	SRT#	SACT#	FPD	TP ₁₀ #	TP ₂₀ #	IP ₂₀ #
IP ₁₀ #	0.14	0.11	0.03	0.07	-0.33**	-0.36**	-0.43**	0.61***	0.55***	0.87***
IP ₂₀ #	0.19	0.09	0.04	-0.07	-0.37**	-0.30*	-0.55***	0.64***	0.57***	
TP ₁₀ #	0.10	0.09	0.02	-0.22	-0.43**	-0.34**	0.32**	0.94***		
TP ₂₀ #	0.19	0.08	0.02	-0.22	-0.48**	-0.43**	-0.38**			
FPD	-0.17	0.18	0.45**	-0.03	0.26	0.29*				
SACT#	-0.41**	-0.05	0.14	0.03	0.44**					
SRT#	-0.50***	-0.01	0.18	0.36**						
AERP	-0.28	0.22	0.23							
Age	-0.14	0.26								
LAD	-0.14									

Values are Pearson's coefficients; #indicates that the variable was log-transformed; LAD, left atrial diameter; HR, heart rate; IP₁₀ and IP₂₀, root mean square (RMS) voltages for the initial 10 and 20 msec of the filtered P-wave of the vector magnitude; TP₁₀ and TP₂₀, RMS voltages for the terminal 10 and 20 msec of the filtered P-wave of the vector magnitude; FPD, filtered P-wave duration; SACT, sinoatrial conduction time; SRT, sinus node recovery time; AERP, atrial effective refractory period.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Fig 2. Relationship between initial potentials of the P-wave on a signal-averaged electrocardiogram and sinoatrial conduction time. IP₁₀ and IP₂₀, root mean square voltages for the initial 10 and 20 msec of the P-wave on signal-averaged electrocardiogram, respectively. SACT, sinoatrial conduction time. (A) Relationship between IP₁₀ and SACT. (B) Relationship between IP₂₀ and SACT. ●, atrial fibrillation or flutter (FFL) group with positive atrial vulnerability; ○, FFL group with negative atrial vulnerability; ■, sick sinus syndrome (SSS) group with positive atrial vulnerability; □, SSS group with negative atrial vulnerability; ◆, others group with positive atrial vulnerability; ◇, others group with negative atrial vulnerability.

($r = -0.43$) and SRT ($r = -0.48$). The correlation between TP₁₀ and TP₂₀ was high ($r = 0.94$). TP₁₀ and TP₂₀ correlated negatively with FPD ($r = -0.32$ and -0.38 respectively). FPD correlated positively with SACT ($r = 0.29$) and age ($r = 0.45$). SACT and SRT correlated negatively with heart rate ($r = -0.41$ and -0.50 respectively). Positive correlations were observed between

Fig 3. Relationship between initial potentials of the P-wave on a signal-averaged electrocardiogram and sinus node recovery time. IP₁₀ and IP₂₀, root mean square voltages for the initial 10 and 20 msec of the P-wave on signal-averaged electrocardiogram, respectively; SRT, sinus node recovery time. (A) Relationship between IP₁₀ and SRT. (B) Relationship between IP₂₀ and SRT. ●, atrial fibrillation or flutter (FFL) group with positive atrial vulnerability; ○, FFL group with negative atrial vulnerability; ■, sick sinus syndrome (SSS) group with positive atrial vulnerability; □, SSS group with negative atrial vulnerability; ◆, others group with positive atrial vulnerability; ◇, others group with negative atrial vulnerability.

SACT and SRT ($r = 0.44$) and AERP and SRT ($r = 0.36$).

Comparison Between Groups (Tables 3 and 4)

Age in the SSS group was significantly higher than in the Others group ($p < 0.01$). FPD in the FFL group and the SSS group was significantly higher than in the Others group ($p < 0.05$). SACT in the SSS group was significantly

Table 3 Comparison Among the 3 Groups (FFL Group, SSS Group and Others Group)

<i>N</i> (male/female)	FFL 16 (10/6)	SSS 18 (5/13)	Others 33 (21/12)
Age (years)	58±14 (59)	64±9 (65)	51±16 (55)
LAD (mm)	32±4 (32)	33±5 (34)	32±4 (32)
HR (beats/min)	64±12 (64)	57±16 (56)	65±13 (66)
IP ₁₀ (μV)	1.2±0.6 (1.3)	1.1±0.3 (1.1)	1.6±1.1 (1.2)
IP ₂₀ (μV)	1.6±0.8 (1.5)	1.5±0.5 (1.4)	1.9±1.2 (1.6)
TP ₁₀ (μV)	1.6±0.7 (1.6)	1.3±0.5 (1.3)	1.8±1.3 (1.4)
TP ₂₀ (μV)	2.2±1.0 (1.5)	1.5±0.5 (1.5)	2.3±2.0 (1.6)
FPD (msec)	149±25 (140)	148±16 (144)	134±13 (132)
SACT (msec)	120±50 (110)	190±80 (170)	120±40 (120)
SRT (msec)	1320±250 (1300)	4030±270 (2800)	1440±570 (1310)
AERP (msec)	220±50 (220)	240±30 (250)	250±50 (250)

Values are means±SD (median); **p*<0.05; ***p*<0.01; ****p*<0.001; LAD, left atrial diameter; HR, heart rate; IP₁₀ and IP₂₀, root mean square (RMS) voltages for the initial 10 and 20 msec of the filtered P-wave of the vector magnitude; TP₁₀ and TP₂₀, RMS voltages for the terminal 10 and 20 msec of the filtered P-wave of the vector magnitude; FPD, filtered P-wave duration; SACT, sinoatrial conduction time; SRT, sinus node recovery time; AERP, atrial effective refractory period.

Table 4 Comparison Between the V(+) Group and V(-) Group

<i>N</i> (male/female)	V(+) 33 (19/14)	V(-) 34 (17/17)	Significance
Age (years)	58±15 (61)	55±15 (57)	0.30
LAD (mm)	33±5 (33)	33±5 (33)	0.57
HR (beats/min)	65±12 (65)	60±15 (60)	0.18
IP ₁₀ (μV)	1.3±0.7 (1.3)	1.4±1.0 (1.2)	0.75
IP ₂₀ (μV)	1.7±1.0 (1.6)	1.8±1.0 (1.5)	0.68
TP ₁₀ (μV)	1.7±1.0 (1.5)	1.5±1.1 (1.3)	0.07
TP ₂₀ (μV)	2.3±1.8 (2.0)	1.8±1.1 (1.5)	0.07
FPD (msec)	145±20 (142)	138±16 (135)	0.25
SACT (msec)	130±50 (130)	150±80 (150)	0.53
SRT (msec)	1540±610 (1370)	2700±2400 (1430)	0.22
AERP (msec)	230±40 (230)	260±50 (250)	0.02

Values are means±SD (median); LAD, left atrial diameter; HR, heart rate; IP₁₀ and IP₂₀, root mean square (RMS) voltages for the initial 10 and 20 msec of the filtered P-wave of the vector magnitude; TP₁₀ and TP₂₀, RMS voltages for the terminal 10 and 20 msec of the filtered P-wave of the vector magnitude; FPD, filtered P-wave duration; SACT, sinoatrial conduction time; SRT, sinus node recovery time; AERP, atrial effective refractory period.

higher than in the FFL group (*p*<0.01) and the Others group (*p*<0.001). SRT in the SSS group was significantly higher than in the FFL group (*p*<0.001) and the Others group (*p*<0.001). AERP in the V(+) group was significantly shorter than in the V(-) group (*p*=0.02). However, no significant difference was observed for any variable except for AERP between the V(+) group and the V(-) group, although the decrease in TP₁₀ and TP₂₀ in the V(+) group compared with that in the V(-) group was close to significant (*p*=0.07).

Discussion

Our results revealed that the correlation coefficients between the initial potentials of the P-wave on SAE, IP₁₀

and IP₂₀, and indices of electrophysiologic measurements in the high lateral right atrium, SACT and SRT, are significant ($-0.37 \leq r \leq -0.30$). When 33 patients without atrial dysrhythmia, the others group, were selected for study, we found that they were slightly higher ($-0.45 \leq r \leq -0.32$). Above-mentioned findings support our hypothesis that the initial potentials of the P-wave on SAE reflect indices of electrophysiologic measurements in the high lateral right atrium, although the statistical significance of these correlations was weak. This weakness may be explained by the following discrepancy: the increase in SACT and SRT is assumed to be affected by peri- and intranodal conductivity, and the increase in SRT relates to suppression of sinus automaticity^{9,10} whereas the decrease in the initial potentials is thought to be affected by perinodal conductivity, which should be independent of automatic control.

We also found a negative correlation between the terminal potentials, TP₁₀ and TP₂₀, and SACT and SRT and a positive correlation between FPD and SACT. In addition, positive correlations between the initial potentials and the terminal potentials and negative correlations between the initial potentials and FPD were observed. These findings suggest that the relationship between the initial potentials and indices of electrophysiologic measurements in the high lateral right atrium is non-specific. This non-specificity and the outcome of comparison analysis, in which no significant difference among the 3 groups (the FFL group, SSS group and Others group) was observed, suggest that patients with sick sinus syndrome (SSS) cannot be distinguished from patients with paroxysmal atrial fibrillation (AF) or flutter by assessing the P-wave on SAE. Yamada et al¹¹ however, reported that the initial potentials of the P-wave on SAE were a useful marker for identifying patients with SSS, and this is obviously contradictory to our results. We speculate that bias in patient selection may be the cause of this discrepancy. In this study, consecutive patients referred to our electrophysiologic laboratory were selected. However, in another study, patients with SSS and age-matched control subjects not exhibiting paroxysmal AF were selected.

In summary, the results of this study suggest that prolongation of SACT and SRT is reflected not only by decreased initial potentials but also by decreased terminal potentials, which may reflect fragmented activity within the left atrium, and prolonged FPD, which may reflect intra-atrial conduction delay. Do conduction disturbances occur simultaneously in both atria? This question may be answered by previous studies on patients with AF or flutter reported by Kumagai et al¹² Cosio et al¹³ Buxton et al¹⁴ and Shimizu et al¹⁵ which demonstrated that the intra-atrial conduction system may be widely involved in conduction disturbances. However, several histopathologic studies have shown that simultaneous involvement of both atria that include the sinoatrial region is rare. For instance, Sugiura et al¹⁶ have shown rare degeneration and/or fibrosis involving both atria even in patients with SSS complicated by paroxysmal AF. Similarly, Davies et al¹⁷ have reported no degeneration and/or fibrosis within the sinoatrial region in patients with paroxysmal AF except that which occurred frequently throughout the patients' history. These discrepant findings may indicate that electrophysiologic impairment of the intra-atrial conduction system precedes pathologic findings such as degeneration and/or fibrosis.

The causal relationship between AF and enlargement of the left atrium is still controversial!¹⁸⁻²⁰ Our results revealed that patients in the V(+) group did not exhibit enlargement of the left atrium, and neither did those in the V(-) group. Therefore, these findings suggest that enlargement of the left atrium should not precede the development of AF. Sanfilippo et al¹⁸ reported a similar outcome, which suggests that left atrial enlargement occurs as a consequence of maintained AF, although the study group included patients with valvular disease. In this study, patients in the V(+) group exhibited shorter AERP, which is thought to be essential for the maintenance of AF. Similar findings were reported by other researchers studying patients with AF!^{2,13,21}

We compared patients with positive atrial vulnerability and negative atrial vulnerability in each of the 3 groups using the Mann-Whitney U test. In the FFL group, SACT in patients with positive atrial vulnerability was significantly prolonged ($p < 0.05$). This result suggests that the more prolonged the SACT in patients with a history of AF, the more vulnerable to programmed stimuli are their right atria. When sinoatrial conduction delay is reflected by prolongation of SACT, the existence of sinoatrial conduction delay may not be unique to patients with SSS. Furthermore, in the SSS group, a shorter SRT ($p < 0.01$) and lower TP₁₀ ($p < 0.05$) and TP₂₀ ($p < 0.05$) in patients with positive atrial vulnerability were observed. A shorter SRT may be explained by the development of AF following suppression of sinus rhythm, which was indicated by overdrive pacing. Lower TP₁₀ and TP₂₀ could indicate the atrial late potential that is intrinsic to the development of paroxysmal AF, being frequently observed in patients with SSS as brady-tachy syndrome?²² In the Others group, however, there was no significant difference between patients with positive atrial vulnerability and negative atrial vulnerability.

Study Limitations

First, we did not demonstrate the reproducibility of this technique, which was reported previously by Yamada et al!¹ Second, the effect of aging on signal-averaged P-wave and indices of electrophysiologic measurements in the control group should have been evaluated because of the significantly higher age of patients with SSS in this study group and positive correlation between age and FPD. In addition, the control group was not adequately assessed so the detective value of atrial dysrhythmia, AF or SSS, was not evaluated in this study.

References

1. Engel TR, Vallone N, Windle J: Signal-averaged electrocardiograms in patients with atrial fibrillation or flutter. *Am Heart*

- J* 1988; **115**: 592-597
2. Fukunami M, Yamada T, Ohmori M, Kumagai K, Umemoto K, Sakai A, et al: Detection of patients at risk for atrial fibrillation during sinus rhythm by P-wave-triggered, signal-averaged electrocardiogram. *Circulation* 1991; **83**: 162-169
3. Guidera SA, Steinberg JS: The signal averaged P wave: a rapid and noninvasive marker of risk of atrial fibrillation. *J Am Coll Cardiol* 1993; **21**: 1645-1651
4. Boineau JP, Canavan TE, Schuessler RB, Cain ME, Corr PB, Cox JL, et al: Demonstration of a widely distributed atrial pacemaker complex in the human heart. *Circulation* 1988; **77**: 1221-1237
5. Chang BC, Schuessler RB, Stone CM, Branham BH, Canavan TE, Boineau JP, et al: Computerized activation sequence mapping of human atrial septum. *Ann Thorac Surg* 1990; **49**: 231-241
6. Mandel WJ, Hayakawa H, Allen HN, Danzig R, Kermaier AI: Assessment of sinus node function in patients with the sick sinus syndrome. *Circulation* 1972; **46**: 761-769
7. Strauss HC, Saroff AL, Bigger Jr JT, Giardina EGV: Premature atrial stimulation as a key to the understanding of sinoatrial conduction in man: presentation of data and critical review of the literature. *Circulation* 1973; **47**: 86-93
8. Nalura OS, Samet P, Javier RP: Significance of sinus-node recovery time. *Circulation* 1972; **45**: 140-158
9. Prinsze FJ, Bouman LN: The cellular basis of intrinsic sinus node recovery time. *Cardiovasc Res* 1991; **25**: 546-557
10. Kalman JM, Munawar M, Power J, Chen JM, Tonkin AM: A mathematical model of sinus node function: validation by recording of sinus node electrograms. *Am J Physiol* 1994; **266**: H681-692
11. Yamada T, Fukunami M, Kumagai K, Abe Y, Kim J, Sanada S, et al: Detection of patients with sick sinus syndrome by use of low amplitude potentials early in filtered P wave. *J Am Coll Cardiol* 1996; **28**: 738-744
12. Kumagai K, Akimitsu S, Kawahira K, Kawanami F, Yamanouchi Y, Hiroki T, et al: Electrophysiological properties in chronic lone atrial fibrillation. *Circulation* 1991; **84**: 1662-1668
13. Cosio FG, Palacios J, Vidal JM, Cocina EG, Gomez-Sanchez MA, Tamargo L: Electrophysiological studies in atrial fibrillation. Slow conduction of premature impulses: a possible manifestation of the background for reentry. *Am J Cardiol* 1983; **51**: 122-130
14. Buxton AE, Waxman HL, Marchlinski FE, Josephson ME: Atrial conduction: effects of extrastimuli with and without atrial dysrhythmias. *Am J Cardiol* 1984; **54**: 755-761
15. Shimizu A, Fukatani M, Tanigawa M, Mori M, Hashiba K: Intra-atrial conduction delay and fragmented atrial activity in patients with paroxysmal atrial fibrillation. *Jpn Circ J* 1989; **53**: 1023-1030
16. Sugiura M, Ohkawa A: A clinicopathologic study on sick sinus syndrome with histological approach to the sinoatrial node. *Jpn Circ J* 1980; **44**: 497-504
17. Davies MJ, Pomerance A: Pathology of atrial fibrillation in man. *Br Heart J* 1972; **34**: 520-525
18. Petersen P, Kastrup J, Brinch K, Godtfresen J, Boysen G: Relation between left atrial dimension and duration of atrial fibrillation. *Am J Cardiol* 1987; **60**: 382-384
19. Sanfilippo AJ, Abascal VM, Sheehan M, Oertel LB, Harrigan P, Hughes RA, et al: Atrial enlargement as a consequence of atrial fibrillation: a prospective echocardiographic study. *Circulation* 1990; **82**: 792-797
20. Andersen JS, Egeblad H, Abildgaard U, Aldershvile J, Godtfresen J: Atrial fibrillation and left atrial enlargement: cause or effect? *J Intern Med* 1991; **229**: 253-256
21. Luck JC, Engel TR: Dispersion of atrial refractoriness in patients with sinus node dysfunction. *Circulation* 1979; **60**: 404-412
22. Rubenstein JJ, Schulman CL, Yurchak PM, DeSanctis RW: Clinical spectrum of the sick sinus syndrome. *Circulation* 1972; **46**: 5-13