

Monophasic Action Potential Duration at the Crista Terminalis in Patients With Sinus Node Disease

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Background The repolarization properties of the crista terminalis (CT) cells have not been elucidated in patients with sinus node disease (SND). In the present study a new technique of recording the monophasic action potential (MAP) at the CT was used to examine the repolarization of the right atrium (RA) in SND patients.

Methods and Results Symptomatic SND (n=13) patients and age-, sex-matched control patients (n=13) were tested. The MAP duration (MAPD) at a basic cycle length of 600 ms was recorded at the CT in the superior vena cava–RA junction and at the middle–anterior RA with the effective refractory period (ERP) at the high RA. In 6 controls and 4 SND patients, the effect of adenosine triphosphate on the MAPD was examined. The MAPD at the CT exceeded that at the middle–anterior RA in both groups. The MAPD at the CT in the SND group was significantly prolonged compared with the control group (CT: 358 ± 39 ms vs 289 ± 43 ms). Between the SND and control groups, the MAPD at the middle–anterior RA (278 ± 36 ms vs 265 ± 39 ms) and ERP (294 ± 42 ms vs 266 ± 41 ms) did not differ. Both the corrected-sinus node recovery time and sinoatrial conduction time were better correlated with the MAPD at the CT than the MAPD at the middle–anterior RA and ERP. Adenosine triphosphate shortened the MAPD, which was augmented at the CT in the SND patients.

Conclusion A novel method of estimating the MAP at the CT revealed the characteristics of atrial repolarization in SND patients. (Circ J 2005; 69: 1361–1367)

Key Words: Adenosine triphosphate; Crista terminalis; Humans; Monophasic action potential; Sinus node disease

Sinus arrest and sinoatrial block (sinus node disease: SND) decrease cardiac output and elicit Adam-Stokes syndrome. To improve the activities of daily life of patients with SND, pacemaker therapy is used, but because the incidence of SND increases with age, the number of the patients and cost of pacemaker therapy are increasing in developed countries.

SND occurs because of either a decrease in the pacemaker potential to a level below the threshold of overshoot of the action potential or exit block of the pacemaker activity to the surrounding atrial muscle. Recently, an electro-anatomical mapping technique demonstrated that structural and electrical abnormalities of the atrium characterized SND! However, the properties of repolarization, based on structural differences of the right atrium (RA), have not been clarified in SND patients.

The monophasic action potential (MAP) of the human heart enables us to estimate the repolarization of the human ventricle² and atrium³ in the clinical setting. In this study, we developed a new technique of recording the MAP at the crista terminalis (CT) in the superior vena cava–RA junction. Using this method, we estimated the properties of the

MAP at the CT in the SND patients and compared it with the conventional indices of sinus node function. Also, we demonstrated the effect of adenosine triphosphate, known to enhance sinus arrest or sinoatrial block,⁴ on the MAP at the CT in the SND patients.

Methods

Patient Population

Thirteen consecutive SND patients and 13 age- and sex-matched control patients were enrolled. All subjects underwent diagnostic electrophysiological studies (EPS) while in a postabsorptive nonsedated state. SND patients were defined as those having a ventricular pause lasting for more than 3 s because of either sinus arrest or sinoatrial block with symptoms related to a pause (Rubinstein type II or III). Control patients were defined as having none of those findings. Patients with (1) sinus bradycardia less than 50 beats/min in mean heart rate (Rubinstein type I), (2) atrial fibrillation, atrial flutter or atrial tachycardia during the monitoring described later, (3) a past history of heart failure and (4) ongoing cardiac ischemia were excluded because we wanted to focus on the characteristic of the MAP related to the particular type of ventricular pause. All patients underwent electrocardiography and ambulatory 24 h-Holter electrocardiogram (ECG) at least twice in the outpatient clinic. In addition, ambulatory monitoring by ECG for 24–48 h after admission and before the EPS was performed. All antiarrhythmic or cardioactive medications were ceased for at least 5 times the biological half-life of the drugs.

Written informed consent from the patients and approval

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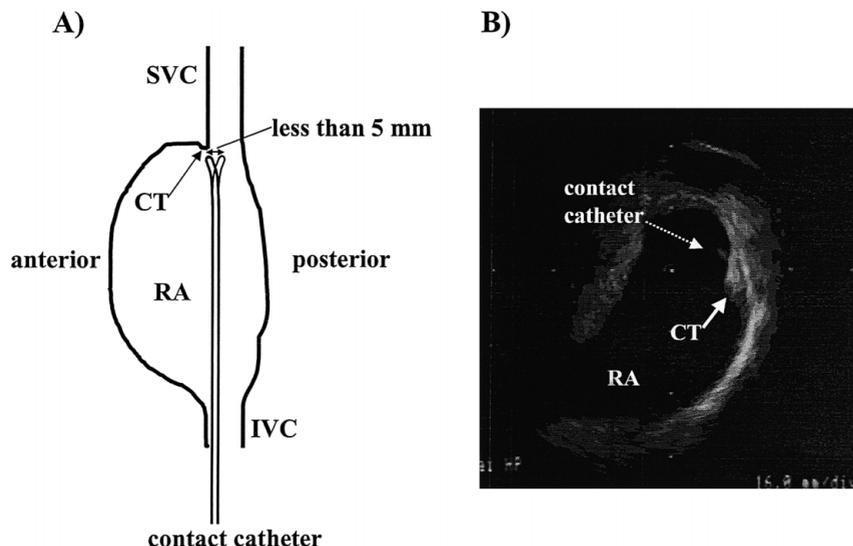


Fig 1. (A) Schema of the lateral view of the fluoroscopic image for identifying the crista terminalis (CT) using contact catheter electrodes. The width of the CT was 5–8 mm. The catheter was pulled or pushed while moving the tip anterior or posterior until the distance between the catheter tips that contacted and those that did not contact the right atrium (RA) roof was less than 5 mm in the lateral view. The former position was defined as the CT. See text for details. (B) Intra-atrial ultrasound image. The dotted arrow indicates the tip of the contact catheter electrode, which contacts the CT indicated by the solid arrow. SVC and IVC, superior and inferior vena cava.

by the Ethics Committee of Tohoku University Hospital were obtained before the study. Organic heart disease was diagnosed by chest X-ray, exercise ECG, B-mode and pulse Doppler echocardiography and, when necessary, cardiac catheterization. The RA area was calculated as an ellipsoid comprising the short and long axes of the RA in the 4-chamber view of a B-mode echocardiogram. The peak E wave, peak A wave and ratio of peak E wave to peak A wave in transtricuspid valve flow (E/A), left atrial diameter, left ventricular (LV) end-diastolic diameter, LV ejection fraction, and the diameter of the inferior vena cava were measured with a standard echocardiographic method. The SND group included 3 patients with second-degree atrioventricular (AV) block and the control group included 8 patients with second-degree AV block, 4 with AV nodal reentrant tachycardia and 1 with neuromediated syncope. The SND group contained 2 patients with organic heart disease (1 chronic pulmonary thromboembolism and 1 angina pectoris) and the control group contained 3 patients with organic heart disease (1 myocardial infarction, and 2 hypertensive LV hypertrophy).

Procedures

After the diagnostic EPS, two 7Fr contact catheter electrodes with tip diameters of 4 mm (combination catheter, EP Technologies) were introduced into the right femoral vein and advanced to the RA under bi-directional fluoroscopic guidance. To record the MAP at the CT, 1 contact catheter was positioned at the posterior edge of the RA roof in the superior vena cava–RA junction as follows. In the first 5 successive cases, a 20-MHz intracardiac ultrasound system (8Fr catheter, Ultrasound Imaging System, Boston Scientific Japan) demonstrated that the CT, 5–8 mm in the width, was positioned at the posterior edge of the RA roof. Next, the catheter was positioned straight into the center of the RA, slightly bent to the anterior, and moved upward. If the catheter touched the RA roof, it was pulled back and slightly bent to the posterior until it did not touch the RA when moved upward again. If the catheter did not touch the RA roof, it was pulled back and slightly bent further to the anterior until it touched the RA when moved upward again. These procedures were repeated until the distance between the catheter tips that contacted and those that did not contact the RA was less than 5 mm in the lateral view of the fluoro-

scopic image (Fig 1A). The former position was defined as the CT, which was confirmed by the intracardiac ultrasound system in 5 successive cases (Fig 1B). To record the MAP of the RA muscle, another contact catheter was positioned at the middle–anterior RA. In the preliminary study, we confirmed that once the MAP was stably recorded, the amplitude of the MAP decreased by approximately 80% of the control level during continuous recording of the MAP for 15 min but the duration until 90% repolarization of the MAP (MAPD) did not change. Therefore, the duration of all study protocols was restricted to 15 min or less, which prevented multiple recording of the MAP at more than 2 sites of the RA. A 6Fr quadri-polar catheter electrode with a 1-cm interelectrode distance (BARD electrophysiology) was positioned at the high RA to estimate the conventional effective refractory period (ERP).

Protocol and Data Analysis

The MAP at the CT and middle–anterior RA, the potential of the high RA and standard limb lead ECG were simultaneously recorded on a thermal recorder (Omnirecorder 8M, NEC) and digital data recorder (RD-130TE, TEAC) at a sampling frequency of 2 kHz. The MAP was recorded using a modification of Franz's method⁵ The bandwidth filter was set at a range of 0.05–1,000 Hz. Care was taken to record the MAP until the following criteria were satisfied: (1) the amplitude of the MAP was higher than 5 mV, (2) no beat-to-beat variation in the MAP could be observed, and (3) the time-dependent loss in the MAP amplitude was less than 20% during all protocols. As an index of the action potential duration, MAPD was simultaneously measured at the CT and the middle–anterior RA. The MAPD by electrical stimulation at a cycle length (CL) of 600 ms was averaged from the 5 beats following the 200th beat because in our preliminary study the MAPD at the RA reached a plateau level at the 200th beat. To compare the steady-state MAPD with the conventional ERP in high RA, the latter was determined by a conventional single extrastimulus method with 10 ms decrements at a basic CL of 600 ms with a 6Fr quadri-polar catheter electrode. Electrical stimulation to the high RA was performed with the distal pair of electrodes and the high RA potential was recorded with the proximal pair of electrodes. The ERP at the CT and the middle–anterior RA using the contact catheter were not mea-

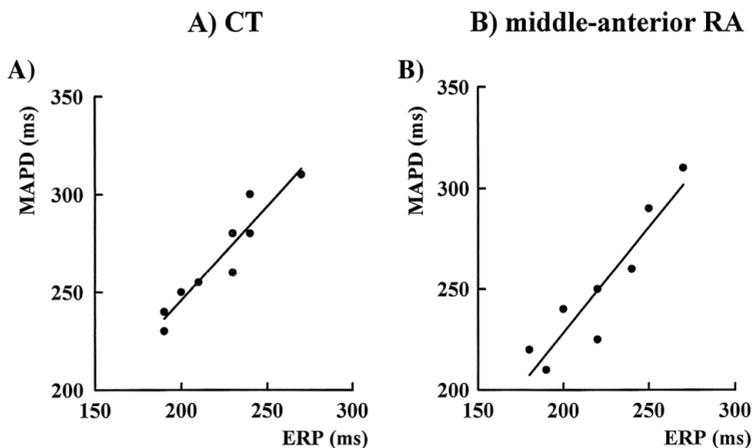


Fig 2. Relationship between the monophasic action potential duration (MAPD) and effective refractory period (ERP) at (A) the crista terminalis (CT) and at (B) the middle–anterior right atrium (RA) in the validation study. The MAPD closely correlated with the ERP at the CT ($r=0.95$, $p<0.001$) and at the middle–anterior RA ($r=0.93$, $p<0.001$).

sured in this protocol because differences in the electrode design and contact pressure of the contact catheter and quadripolar catheter may affect the ERP, and also because we wanted to minimize the time-dependent loss of the MAP amplitude and the possibility of dislodgement of the contact catheter during the 15 min used to measure MAP.

The effect of adenosine triphosphate on the MAPD was examined in 4 SND and 6 control patients. Adenosine is not available for clinical use in Japan, so we used adenosine triphosphate as a substitute for adenosine, which is generated by degradation of adenosine triphosphate.⁶ A 10 mg bolus was injected rapidly via a forearm vein followed by flushing with a 10 ml bolus of physiological saline⁴ during sequential pacing at either the high RA or the CT and right ventricle at a CL of 600 ms. This amount of adenosine triphosphate was enough to induce sinus pause, even though it was not the maximal effect, as a diagnostic tool for SND.⁴ The MAPD changing maximally after the injection of adenosine triphosphate was estimated.

To examine sinus node function, the corrected sinus node recovery time (CSNRT), sinoatrial conduction time (SACT) and sinus CL were measured. The sinus node recovery time was defined as the interval from the high RA potential in the last pacing to the first sinus potential after atrial overdrive pacing for 60 s at 80 beats/min to 200 beats/min with increments of 10 beats/min. CSNRT was the maximal difference between the sinus node recovery time and the atrial CL just prior to each pacing.⁷ SACT was measured with a single extra stimulus during the sinus rhythm according to the Strauss method.⁸

Validation Study

To test whether the MAPD measured by our method reflected the repolarization of the same site, both the MAPD and ERP using the contact electrode were simultaneously estimated at the CT and middle–anterior RA in another patient group (age 43 ± 18 , $n=9$) consisting of 3 patients with second-degree AV block, 1 with AV reentrant tachycardia, and 5 SND patients. In this protocol, the MAPD was measured in the 8th atrial excitation during the conventional single extrastimulus method to estimate ERP.

Statistics

The data are expressed as mean \pm SD. Statistical evaluation between the 2 groups was performed with paired and unpaired t-tests and the chi-square test. The statistically significant p-value was less than 0.05. Linear regression analy-

Table 1 Patients' Characteristics

	Control	SND
Age (years)	61 \pm 16	62 \pm 15
Male (%)	54	54
Organic heart disease (%)	23	15
Left atrial diameter (mm)	34 \pm 6	36 \pm 8
LV end-diastolic diameter (mm)	47 \pm 5	47 \pm 6
LV ejection fraction (%)	74 \pm 8	75 \pm 7
Diameter of inferior vena cava (mm)	12 \pm 1	13 \pm 3
RA area (cm ²)	13 \pm 4	14 \pm 5
E wave (m/s)	0.48 \pm 0.12	0.44 \pm 0.10
A wave (m/s)	0.43 \pm 0.17	0.37 \pm 0.14
E/A	1.29 \pm 0.55	1.33 \pm 0.59
CSNRT (ms)	446 \pm 174	2,560 \pm 2,243*
SACT (ms)	109 \pm 34	179 \pm 50*
Sinus cycle length (ms)	878 \pm 113	1,121 \pm 187*

SND, sinus node disease; LV, left ventricular; RA area, right atrial area in 4-chamber view divided by body surface; E and A waves, peak velocity of E and A waves in transtricuspid inflow; E/A, ratio of peak velocity of E wave to A wave; CSNRT, corrected sinus node recovery time; SACT, sinoatrial conduction time. * $p<0.001$ vs control.

sis was performed to show the relationships between sinus node function (CSNRT and SACT) and the repolarization of the RA (MAPD and ERP) and between the MAPD and ERP in the validation study.

Results

In the validation study, there were close correlations between the MAPD and ERP at the same site (Fig 2, $r=0.95$, $p<0.001$ at the CT and $r=0.93$, $p<0.001$ at the middle–anterior RA). The ratio of ERP to MAPD at the CT and middle–anterior RA was 0.83 ± 0.03 and 0.88 ± 0.05 , respectively.

Age, gender, percentage of organic heart disease and echocardiographic findings did not differ between the control and SND groups (Table 1). CSNRT, SACT and sinus CL in the SND group were significantly increased compared with the control group (Table 1).

Fig 3 shows representative recordings of the MAP. All recordings of the MAPs at both the CT and middle–anterior RA in the control patients and those at the middle–anterior RA in the SND patients had a triangular shape (Fig 3A). In contrast, the shape of the MAP at the CT in 6 of the 13 SND patients appeared to be rectangular (Fig 3B). In pooled data (Fig 4A), the MAPD at the CT was signifi-

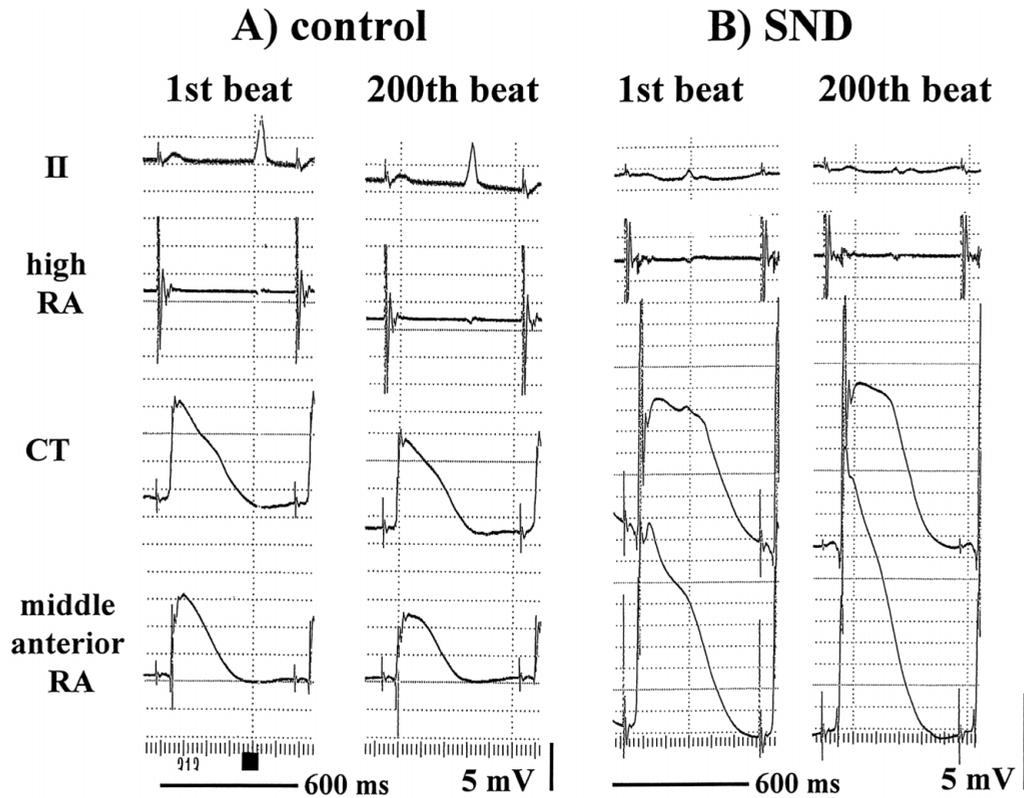


Fig 3. Representative recordings of the monophasic action potential at the crista terminalis (CT) and middle-anterior right atrium (RA) in (A) the control and (B) the sinus node disease (SND) patients. The 1st and 200th pacing beats at the basic cycle length of 600 ms are shown. II, lead II of the electrocardiogram; high RA, bipolar potential of high right atrium.

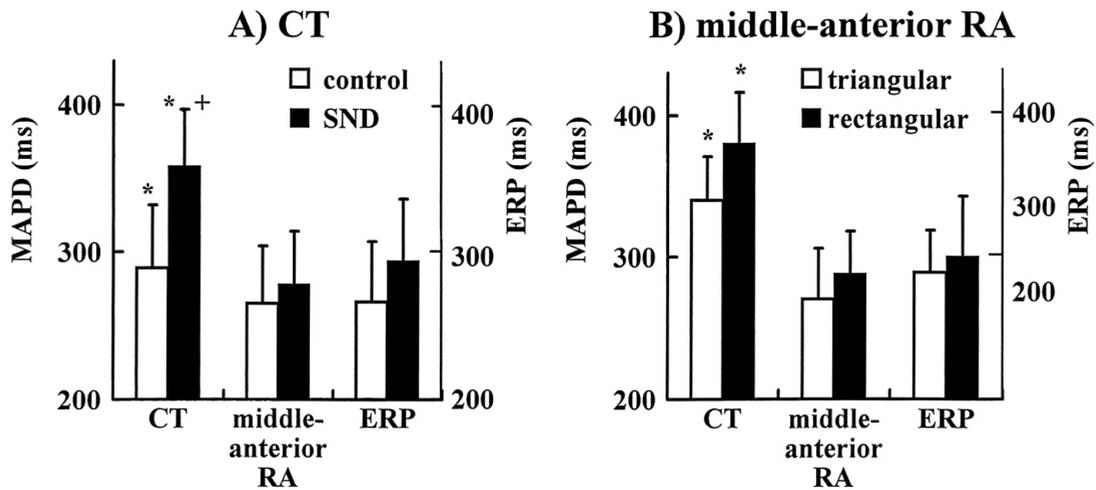


Fig 4. (A) Monophasic action potential duration (MAPD) at the crista terminalis (CT) and middle-anterior right atrium (RA) and effective refractory period (ERP) in the control (white bar) and sinus node disease (SND, black bar) patients. * $p < 0.001$ vs middle-anterior RA, + $p < 0.001$ vs control. Error bar=SD. (B) MAPD at the CT and middle-anterior RA and ERP in SND patients with triangular (white bar, $n=7$) and rectangular (black bar, $n=6$) MAP at the CT. * $p < 0.001$ vs middle-anterior RA. Error bar=SD.

cantly prolonged compared with that at the middle-anterior RA in both groups. The MAPD at the CT in the SND group (358 ± 39 ms) was significantly prolonged compared with the control group (289 ± 43 ms). Between the SND and control groups, there were no significant differences in the MAPD at the middle-anterior RA (278 ± 36 ms vs 265 ± 39 ms, respectively) and ERP in the high RA (294 ± 42 ms

vs 266 ± 41 ms, respectively).

In the SND patients with triangular or rectangular shaped MAP at the CT, there were no significant differences in background characteristics (Table 2) and in the MAPD at the CT and middle-anterior RA and ERP (Fig 4B).

The MAPD was compared in patients with and without second-degree AV block to examine its influence. There

were no significant differences in the MAPD at the CT in the SND group (323±15 ms and 369±38 ms, respectively) and in the control group (290±42 ms and 288±44 ms, respectively). Also, there were no significant differences in the MAPD at the middle–anterior RA in either the SND group (273±6 ms and 280±41 ms, respectively) or the control group (269±52 ms and 258±36 ms, respectively).

CSNRT was better correlated with the MAPD at the CT ($r=0.61$, $p<0.001$, Fig 5A) than either the MAPD at the middle–anterior RA ($r=0.41$, $p<0.05$, Fig 5C) or ERP ($r=0.38$, NS, Fig 5E). Also, SACT was better correlated with MAPD at the CT ($r=0.72$, $p<0.001$, Fig 5B) than the MAPD at the middle–anterior RA ($r=0.52$, $p<0.01$, Fig 5D) or ERP (and $r=0.44$, $p<0.05$, Fig 5F).

Bolus injection of adenosine triphosphate shortened the MAPD in both groups (Fig 6). In the SND patients, it changed the rectangular shape of the MAP at the CT to triangular and maximally shortened the MAPD at the CT (Fig 6B). In the pooled data (Fig 7), the percent change of the MAPD at the CT in the SND group ($-34±11%$) was

Table 2 Characteristics of the Patients With Sinus Node Disease

	Shape of MAPD	
	Triangular	Rectangular
<i>n</i>	7	6
Age (years)	62±12	62±21
Male (%)	57	50
Organic heart disease (%)	14	17
Left atrial diameter (mm)	37±9	35±5
LV end-diastolic diameter (mm)	47±7	47±4
LV ejection fraction (%)	72±8	80±2
Diameter of inferior vena cava (mm)	12±3	15±4
RA area (cm ²)	14±6	15±4
E wave (m/s)	0.41±0.07	0.48±0.12
A wave (m/s)	0.39±0.17	0.35±0.09
E/A	1.23±0.62	1.45±0.54
CSNRT (ms)	2,887±2,826	2,179±562
SACT (ms)	184±40	174±69
Sinus cycle length (ms)	1,063±137	1,188±237

Triangular/rectangular, shape of MAPD recorded at the crista terminalis. MAPD, monophasic action potential duration. Other abbreviations as for Table 1. There were no significant differences in the profiles of the 2 groups.

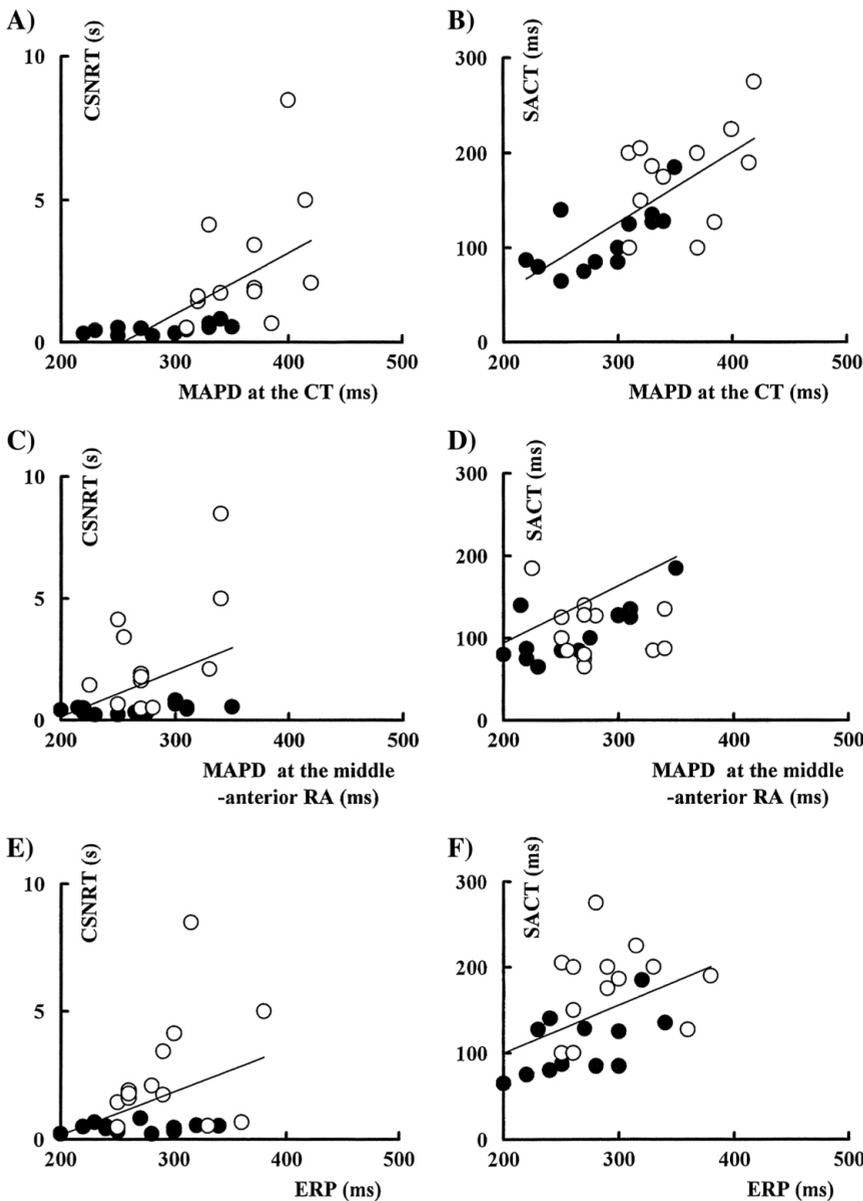


Fig 5. Correlation between (A) corrected sinus node recovery time (CSNRT) and the monophasic action potential duration (MAPD) at the crista terminalis (CT) ($r=0.61$, $p<0.001$), (B) sino-atrial conduction time (SACT) and MAPD at the CT ($r=0.72$, $p<0.001$), (C) CSNRT and the MAPD at the middle–anterior right atrium (RA) ($r=0.41$, $p<0.05$), (D) SACT and MAPD at the middle–anterior RA ($r=0.52$, $p<0.05$), (E) CSNRT and effective refractory period (ERP) ($r=0.38$, NS) and (F) SACT and ERP (and $r=0.44$, $p<0.05$). Closed and open circles indicate the control and sinus node disease groups, respectively.

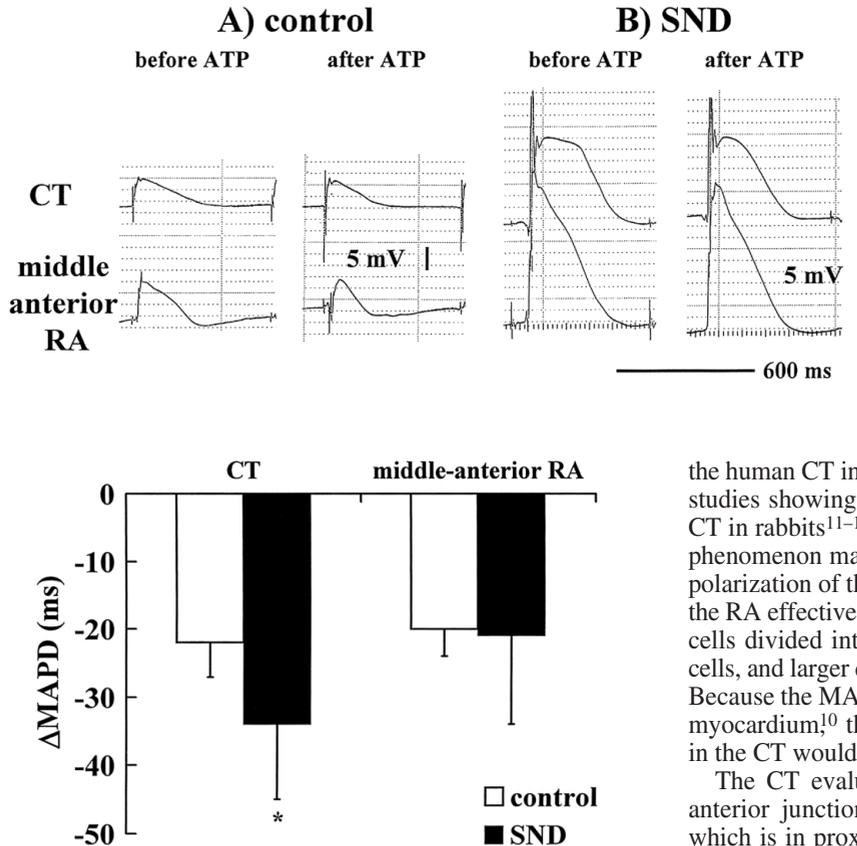


Fig 7. Differences (D) in the monophasic action potential duration (MAPD) at the crista terminalis (CT) and middle-anterior right atrium (RA) before and after a bolus injection of 10 mg adenosine triphosphate. Open and black bars indicate control and sinus node disease (SND) groups, respectively. * $p < 0.05$ vs CT in the control group and middle-anterior RA in the both groups. Error bar = SD.

significantly greater than those at the middle-anterior RA in the SND group ($-21 \pm 13\%$) and at the CT and middle-anterior RA in the control group ($-22 \pm 5\%$ and $-20 \pm 4\%$, respectively).

Discussion

We developed a novel method of evaluating the repolarization of the CT and used it to demonstrate that in SND patients (1) the MAPD at the CT is prolonged compared with that at the middle-anterior RA, and is augmented, (2) both CSNRT and SACT correlate with the MAPD at the CT better than the other indices of repolarization of the RA, and (3) adenosine triphosphate-induced shortening of the MAPD was pronounced at the CT.

The MAPD measured by our method certainly reflected the repolarization of atrial cells because of the close correlation with ERP (Fig 2). The ratio of ERP to MAPD was 0.83 ± 0.03 at the CT and 0.88 ± 0.05 at the middle-anterior RA, consistent with a previous study of the human RA.⁹ Experimentally, MAP reflected the transmembrane action potential duration not of the superficial endocardial cells (1–2 cell layers), but of the underlying deeper muscle cells.¹⁰ Thus, MAPD can be estimated as a surrogate of the action potential duration several layers below the superficial endocardial cells.

This study is the first to show prolonged repolarization at

the human CT in the clinical setting. There are experimental studies showing prolonged action potential duration at the CT in rabbits^{11–13} and dogs,¹⁴ consistent with our data. This phenomenon may be related to matching the end of the repolarization of the CT and atrial muscle in order to contract the RA effectively. Avanzino et al demonstrated that the CT cells divided into small superficial cells, resembling atrial cells, and larger deep cells with extended T-tubule systems.¹⁵ Because the MAPD reflects the repolarization of the deeper myocardium,¹⁰ the action potential of the larger deep cells in the CT would contribute to the generation of MAP.

The CT evaluated in this study was positioned at the anterior junction of the wall of the superior vena cava, which is in proximity to the sinus node cells set along the anterior to lateral junction of the CT and vena cava.¹⁶ Therefore, the MAP at the CT might be electrotonically affected by the sinus node cells. However, the pacemaker site in the SND patients shifted caudally along the CT,¹⁷ suggesting that less electrotonic interaction contributed to the MAP of the SND patients.

We first demonstrated that the prolongation of the MAP at the CT was pronounced in SND patients. In addition, the shape of the MAP at the CT appeared to be rectangular in 6 of the 13 SND patients, which was never observed in the control patients (Fig 3B). However, the MAPD did not depend on the shape of the MAP, indicating that a number of mechanisms may have contributed to these observations. The MAPD at the CT correlated with the function of the sinus node better than that at the middle-anterior RA and ERP in the high RA (Fig 5). These observations, of which the clinical meaning remains unknown, suggest that the abnormal action potential of the CT cells is associated with the pathophysiology of SND.

The functional and anatomical properties of the RA in SND patients might contribute to prolongation of the MAPD at the CT. Pressure and/or volume overload of the RA induces mechano-electrical feedback, affecting repolarization of the RA.¹⁸ However, the transtricuspid flow patterns and the diameter of the inferior vena cava did not differ between the 2 groups, indicating comparable levels of load to the RA. If hypertrophy of atrial myocytes occurs in SND patients, the MAPD would also alter. This is, however, unlikely because neither the MAPD at the middle-anterior RA nor the ERP differed between the 2 groups (Fig 4A), and also because the RA area did not differ between the 2 groups. Thus, mechano-electrical feedback and hypertrophy of atrial myocytes cannot explain our results.

The difference in the percentage of patients with second-degree AV block in the SND (23%) and control (62%)

Fig 6. Representative recordings of the response of the monophasic action potential (MAP) at the crista terminalis (CT) and middle-anterior right atrium (RA) to bolus injection of adenosine-triphosphate (ATP) in (A) the control and (B) sinus node disease (SND) patients.

groups may have affected our results. In SND patients, electrophysiological abnormalities may exist not only in the sinus node but also in the AV node,¹⁹ although this is unlikely because the MAPD at both the CT and middle–anterior RA did not differ between the patients with and without second-degree AV block.

An enhancement of adenosine triphosphate-induced shortening in the MAPD at the CT characterized SND. Adenosine, the degradation product of adenosine triphosphate, mainly activates the acetylcholine-sensitive outward potassium current (I_{K-ach}) with only a small inhibition of the cyclic-adenosine monophosphate-dependent inward calcium current (I_{Ca}).²⁰ It is unlikely that inhibition of I_{Ca} by adenosine contributed to the response of the MAPD at the CT to adenosine triphosphate in SND because the density and the kinetics of I_{Ca} do not differ between CT and atrial cells.¹¹ Therefore, either the function of the I_{K-ach} receptors or their sensitivity to adenosine in the CT cells may be altered in SND. The ability of adenosine to induce sinus arrest was enhanced in the patients with SND²¹ and I_{K-ach} contributes to the negative chronotropic effect of rabbit sinoatrial cells²² consistent with the above hypothesis. Another possibility is a vagal-dependent negative chronotropic effect of adenosine triphosphate mediated by P_{2x} -purinoreceptors.²³ An abnormal vagal input to the CT cells or abnormal function of the P_{2x} -purinoreceptors in the CT cells may contribute to CT-specific abnormal repolarization in SND patients.

Study Limitations

Because pharmacological autonomic blockade was not used in this study, the effect of the autonomic tone in the SND patients is unclear. The present study did not clarify how the prolonged repolarization at the CT contributed to the cause of SND. To answer this question, further studies to record the MAP with sinus node electrogram and an activation map of the RA are required. This study did not show whether the heterogeneous repolarization of the RA contributed to the occurrence of reentrant atrial tachyarrhythmias, including atrial fibrillation. Simultaneous recording of the MAP was restricted to 2 sites because MAPs recorded for more than 15 min have not been validated. This small number of recording sites made it difficult to estimate the dispersion of the repolarization of the RA.²⁴ In addition, we did not study the origin of focal atrial fibrillation, such as the pulmonary veins or inferior vena cava, because we did not intend showing the complex relationship between the substrates and triggers of atrial fibrillation.

Conclusion

Our novel method of estimating the MAP at the CT revealed that prolongation of the MAPD and augmentation of adenosine triphosphate-induced shortening of the MAPD at the CT characterizes SND.

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