Atrial Conduction Curves in Patients With and Without Atrial Fibrillation

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In order to quantify underlying atrial conduction properties in patients with atrial fibrillation (AF) using clinical electrophysiology techniques, atrial conduction curves relating intra-atrial conduction times to extrastimulus prematurities during programmed atrial stimulation were drawn. Based on the presence or absence of AF episodes, 95 subjects were divided into 2 groups: control (n=42); and AF (n=53). During programmed stimulation introduced from the right atrial appendage, an atrial conduction curve was drawn for each patient. For most of the control subjects, when the extrastimulus prematurity was increased by 10-ms steps, the intra-atrial conduction times also increased gradually; the maximum stepwise prolongation in intra-atrial conduction time was 11.0 ± 3.4 msec. For patients with AF, a 10-msec increase in extrastimulus prematurity often produced a sudden marked prolongation in the intra-atrial conduction time; the maximum stepwise prolongation of intra-atrial conduction time was 21.4 ± 5.9 msec. In contrast to the gradual atrial conduction curves recorded in control subjects, the sudden prolongation of intra-atrial conduction time was remarkable on the curves obtained in patients with AF. Statistical significance was clearly established ($p < 0.0001$). This difference could be related to differences in the underlying conduction properties in patients with and without AF. (*Jpn Circ J* 1998; 62: 289–293)

Key Words: Atrial fibrillation; Intra-atrial conduction curve; Programmed atrial stimulation

Atrial fibrillation (AF) is a diverse disease. Following various extensive experimental laboratory and clinical studies,^{1–6} it has become clear that many forms of AF have a re-entrant origin, and that the initiation of AF is related to a sufficient degree of inhomogeneity in atrial conduction. In sections of rabbit atrium, Allesie et al^{7,8} and Lammers et al⁹ demonstrated this special inhomogeneous conduction during extrastimulation. It was reported that, before a circus movement, propagation of the premature impulse was in 1 direction only. When it occurred in other directions the propagation failed completely or occurred with such severe decrement that the impulse died out. However, in clinical electrophysiologic tests, direct evaluation of inhomogeneous atrial conduction is difficult because the total number of recording channels is limited. We devised an indirect method for quantifying the conduction features that may lead to AF in humans. We drew atrial conduction curves relating intra-atrial conduction time to each extrastimulus prematurity during programmed atrial stimulation. These curves show distinctly how intra-atrial conduction responds to early stimuli of consecutively increasing prematurity. The difference between patients with and without AF in the atrial conduction response to the extrastimulation may reflect a difference in atrial conduction properties between patients with and without

electrophysiologic substrates for AF.

Methods

Patient Population

The subjects were 95 patients (62 men and 33 women) who underwent electrophysiologic tests for paroxysmal AF or other arrhythmias between 1992 and 1996 at Nagasaki University Hospital. Written informed consent was obtained from all patients for the electrophysiology studies. Patients with the following conditions were excluded from the study: organic heart disease or congestive heart failure; thyroid diseases; enlarged cardiac silhouette on chest radiography (cardiothoracic ratio $> 50\%$); or atrial enlargement on echocardiography (left atrial dimension ≥ 40 mm). The 95 patients were divided into 2 groups depending on whether or not episodes of paroxysmal AF were documented on electrocardiography (ECG) or 24-h Holter recordings and/or electrically induced sustained AF lasting more than 30 sec occurred during programmed atrial stimulation. All data are given as means $\pm$ SD.

Forty-two patients (26 men and 16 women) with neither episodes of paroxysmal AF nor electrically induced AF served as control group. The mean age in this group was 46.8 ± 17.3 years. Cardiac arrhythmias found in this group were Wolff-Parkinson-White syndrome (WPW) in 22 patients, atrioventricular block (AVB) in 7, atrioventricular node re-entrant tachycardia (AVNRT) in 9, and idiopathic ventricular tachycardia (IVT) in 4 patients.

Fifty-three patients (34 men and 19 women) with episodes of paroxysmal AF and/or electrically induced sustained AF served as the experimental AF group. The

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Fig 1. Electrocardiographic lead V₁, the right atrial appendage (RAA), and the left atrial electrogram recorded from the distal coronary sinus (CSd) are shown. The basic atrial drive cycle length of S1–S2 is 500 msec, and the basic intra-atrial conduction time of RAA1–CSd1 is 110 msec. When an extrastimulus (S2) is introduced at a coupling interval of 250 msec, the corresponding intra-atrial RAA2–CSd2 conduction time is 150 msec.

Table 1 Population Characteristics

	Control group	AF group
No of patients	42	53
Men/women	26/16	34/19
Age (years, mean $\pm$ SD)	46.8 $\pm$ 17.3	52.9 $\pm$ 15.6
Diseases (n)	WPW (22)	Lone PAF (18) SSS (2)
	AVB (7)	WPW (7)
	AVNRT (9)	SSS+PAF (8) AVB (2)
	IVT (4)	WPW+PAF (12) AVNRT (2)
		IVT (4)

AF, atrial fibrillation; AVB, advanced atrioventricular block; AVNRT, atrioventricular nodal re-entrant tachycardia; IVT, idiopathic ventricular tachycardia; PAF, paroxysmal atrial fibrillation; SD, standard deviation of the mean.

SSS, sick sinus syndrome (Rubenstein's classification: group I, group II).

WPW, Wolff-Parkinson-White syndrome.

mean age in this group was 52.9 ± 15.6 years. The electrical induction of AF was not an aim of the programmed atrial stimulation; rather it was a result of a routine stimulation protocol. In this group, 18 patients had only paroxysmal AF, 8 had paroxysmal AF and sick sinus syndrome (SSS), and 12 had paroxysmal AF and WPW. Of the remaining 15 patients who had electrically induced AF but no previous history of paroxysmal AF, 7 patients had WPW, 2 had SSS, 2 AVB, 2 AVNRT, and 2 IVT. The study population is detailed in Table 1.

Electrophysiology Studies

Amiodarone was not used in any patient, and other cardioactive medications were discontinued at least 3 days before electrophysiological studies. With patients under local anesthesia, 10-mm-spaced quadripolar electrode catheters were advanced into the right atrial appendage (RAA), high lateral right atrium (HLRA), and coronary sinus (CS). The distal pair of electrodes of the CS catheter (CSd) was placed under fluoroscopic guidance in a posterolateral position behind the left atrium. Atrial stimulation was performed at an intensity twice the diastolic threshold and 2 msec in duration through the distal pair of electrodes of the RAA catheter using a SEC-2012 Nihon Koden pulse generator. The atrial endocardial electrograms were filtered at 50–1,000 Hz, and surface ECGs (I, aV_F and V₁) were recorded simultaneously at a paper speed of 100 mm/sec on a 12-channel, ink-jet recorder (Siemens-Elema 804, Siemens-Elema, Solna, Sweden). A premature stimulus was delivered after 8

Fig 2. Atrial conduction curves of intra-atrial conduction time (RAA2–CSd2) related to extrastimulus prematurity (RAA1–RAA2). Left: an example from the control group. Right: an example from the AF group. Maximum sudden prolongation: the maximum stepwise prolongation in the RAA2–CSd2 interval for each 10-msec decrease in RAA1–RAA2 interval.

beats of drive pacing at a cycle length of 500 msec. The extrastimulus prematurity was increased gradually in 10-msec steps until the effective atrial refractoriness was reached.

Measurements and Definitions

RAA1 is defined as the atrial deflection recorded at the RAA during S1 drive pacing, and the basic intra-atrial conduction time of RAA1–CSd1 is defined as the interval between the beginning of RAA1 and the corresponding atrial deflection recorded at the CSd. RAA2 is defined as the atrial deflection of the premature S2 extrastimulus recorded at the RAA, and the corresponding intra-atrial conduction time of RAA2–CSd2 is defined as the interval between the beginning of RAA2 and the corresponding atrial deflection recorded at the CSd. The effective refractory period (ERP) at the pacing site is defined as the shortest extrastimulus coupling interval (S1–S2) at which S2 fails to result in an atrial response. The range of relative refractoriness at the pacing site is defined as the range of the S1–S2 interval that began with the initial local delay (RAA1–RAA2 > S1–S2) and ended with the ERP.

A sample measurement is shown in Fig 1. In this case, the basic intra-atrial RAA1–CSd1 conduction time is 110 msec. When an atrial extrastimulus is introduced at a coupling interval of 250 msec, the corresponding intra-atrial RAA2–CSd2 conduction time is 150 msec. In order to avoid artificial errors, the measurements were performed before knowing the classification of the study

patients.

Atrial conduction curves of RAA2–CSd2 times related to each RAA1–RAA2 interval were obtained during extrastimulation before the relative refractoriness at RAA was reached. As shown in Fig 2, when the RAA1–RAA2 interval was decreased in 10-msec steps, the RAA2–CSd2 time changed both in patients with (Fig 2, right) and without (Fig 2, left) AF. The stepwise prolongations in the RAA2–CSd2 time related to each 10-msec decrease in RAA1–RAA2 intervals were measured manually, and the maximum stepwise prolongation induced by a 10-msec decrease in RAA1–RAA2 interval was defined as the “maximum sudden prolongation” in the atrial conduction curve.

In theory, prolongation of the RAA2–CSd2 interval can be caused by 2 factors: an increase in intra-atrial conduction between the RAA and CSd or an increase in local conduction in the proximity of the RAA pacing site. In order to distinguish between these 2 factors, we also measured the corresponding change in RAA2–HLRA2 interval during the RAA1–RAA2 interval when the maximum sudden prolongation in the RAA2–CSd2 time occurred.

Statistical Analysis

Data are expressed as means $\pm$ 1 standard deviation. The differences observed between the control and AF groups were analyzed using Student's unpaired t test. The relationship between the CSd and HLRA recording sites in the prolongation of conduction time was calculated using Pearson's product moment correlation coefficient. Significance was established at a p value of <0.05 .

Results

The results are summarized in Table 2.

Age

Although the 2 groups were not strictly age matched, no significant difference in age was found between patients with and without AF (52.9 ± 15.6 years vs

46.8 ± 17.3 years).

RAA1–CSd1 Time During Drive Pacing

The RAA1–CSd1 time measured during drive pacing was about the same in patients with and without AF (106.1 ± 19.8 vs 104.0 ± 16.2 msec).

ERP at RAA

For control subjects, the mean ERP at RAA was 205.2 ± 21.0 msec. For patients with AF, the mean ERP at RAA was 200.2 ± 21.0 msec. No significant difference was found between them.

Maximum Sudden Prolongation in RAA2–CSd2 interval on the Atrial Conduction Curves

In control patients, when the RAA1–RAA2 interval approached the refractory period, the RAA2–CSd2 intra-atrial conduction time increased accordingly, resulting in a gradual atrial conduction curve. The maximum sudden prolongation of RAA2–CSd2 interval measured in these patients was 11.0 ± 3.4 msec. By contrast, in the conduction curves obtained from patients with AF, a 10-msec decrease in the RAA1–RAA2 interval often caused a sudden marked prolongation of the RAA2–CSd2 interval. The maximum sudden prolongation of RAA2–CSd2 interval in these patients was 21.4 ± 5.9 msec, which is significantly greater than that in the control subjects ($p < 0.0001$) (Fig 3). No relationship is found between RAA1–CSd1 interval measured during drive pacing and maximum sudden prolongation of RAA2–CSd2 interval on the atrial conduction curves ($r = 0.020$, $p = 0.85$).

At the RAA1–RAA2 interval when the maximum sudden prolongation in RAA2–CSd2 time was produced, the corresponding prolongation in the conduction time from RAA2 to HLRA2 was measured. In control subjects, the corresponding prolongation of the RAA2–HLRA2 interval was 0.5 ± 1.5 msec. For the AF group, the corresponding prolongation in RAA2–HLRA2 interval was 3.5 ± 6.2 msec. No relationship was found between the prolongation of conduction time in the CSd and HLRA recording sites in either group.

Discussion

The maximum sudden prolongation of intra-atrial conduction time was higher in patients with AF than that in control subjects. As to what extent the anatomic and electrophysiologic properties of the atrium contribute to the initiation and maintenance of AF, Konings et al² clearly illustrated that in patients with WPW syndrome multiple re-entrant wave fronts are present in the right atrium, and that these might be perpetuated if a sufficient degree of conduction block is present. In other studies by Allessie et al^{7,8} and Lammers et al⁹ it was shown that, in

Table 2 Summary of the results

	Control group	AF group
Age (years)	46.8 ± 17.3	52.9 ± 15.6
RAA1–CSd1 time (msec)	104.0 ± 16.2	106.1 ± 19.8
ERP at RAA (msec)	205.2 ± 21.0	200.2 ± 21.0
Max sudden prolongation in RAA2–CSd2 time (msec)	11.0 ± 3.4	21.4 ± 5.9
Corresponding prolongation in RAA2–HLRA2 time (msec)	0.5 ± 1.5	3.5 ± 6.2

ERP at RAA, effective refractory period at right atrial appendage.

Fig 3. Maximum sudden prolongation of RAA2–CSd2 interval in the atrial conduction curves obtained from patients with and without atria fibrillation. The vertical bars represent means $\pm$ standard deviation.

sections of rabbit atrium, unidirectional conduction block or severe decremental conduction was needed to initiate a small functional re-entrant circuit. It is reasonable to assume that the underlying myocardial cause of AF is related to a sufficient degree of inhomogeneity in atrial conduction. In order to define such abnormal conduction properties using clinical electrophysiologic tests, many researchers¹⁰⁻¹⁵ have examined the slow conduction resulting from early impulses during these tests. It has been demonstrated repeatedly that in patients with AF the atrial excitation induced by extrastimuli tends to be conducted with delays. However, atrial conduction delay introduced by extrastimulation is not a phenomenon unique to patients with AF; it can also be observed in normal subjects. Fewer data are available on whether or not the delayed conduction is physiologic. In the present study, we investigated the response of intra-atrial conduction time to consecutively increased extrastimulus prematurity by drawing atrial conduction curves. It is conceivable that the difference in the response of atrial conduction to extrastimulation between patients with and without AF may reflect a difference in the underlying conduction properties in atria with and without electrophysiologic substrates for AF.

In control patients, when the RAA1–RAA2 interval approached the refractory period, the RAA2–CSd2 intra-atrial conduction time increased gradually. The stepwise prolongations of intra-atrial conduction time with each 10-msec increase in atrial prematurity were relative small, resulting in a gradual atrial conduction curve that is somewhat similar to the decremental conduction seen physiologically in the normal atrioventricular node. According to Moe's hypothesis, if a control atrium could be treated as a homogeneous sheet of muscle with uniform properties in all directions, a premature impulse would travel smoothly in all directions, although some degree of decrement may be observed. It is reasonable to assume that these gradual increases in the RAA2–CSd2 time are related to physiologic decrements in atrial conduction.

In contrast to the gradual atrial conduction curves obtained from control subjects, maximum sudden prolongation of RAA2–CSd2 interval is high in the conduction curves obtained in patients with AF. Without intracellular recordings at the site of stimulation, it is difficult to rule out the possibility that these large sudden prolongations are caused by local conduction delay around the RAA pacing site. However, as was described by Cosio et al¹⁰ and Buxton et al¹² if local latency were the reason for the marked prolongation of RAA2–CSd2 interval, a similar prolongation would present simultaneously in other directions. In fact, at the RAA1–RAA2 interval at which the maximum sudden prolongation in RAA2–CSd2 interval occurred, the corresponding prolongation of the RAA2–HLRA2 interval was only 0.5 ± 1.5 msec in control subjects and 3.5 ± 6.2 msec in the AF group. It seems that the influence of latency is minimal, although we cannot exclude the influence of local conduction delay around the pacing site on the measured RAA2–CSd2 interval.

As impulses always travel along the shortest possible route,¹⁶ the sudden prolongation of intra-atrial conduction time could have resulted from 1 of the following 2 factors: a severe conduction delay somewhere on the long conduction route between the RAA and CSd during

partial recovery of myocardial excitability or a pathway change when conduction in the original direction failed completely or occurred with such severe decrement that the impulse died out. In animal experiments, Allesie et al^{7,8} and Lammers et al⁹ demonstrated such severe conduction delay and unidirectional block by high-density mapping. In the present study, we could not locate the critical site for severe conduction delay or unidirectional block. However, the sudden prolongation of the RAA2–CSd2 interval suggests an existing inhomogeneous conduction somewhere on the long conduction route between the RAA and the CSd. This inhomogeneous conduction may be fundamental, but early extrastimulation is needed for it to be evident on the conduction curves. If the gradual atrial conduction curve obtained in control patients is assumed to be characteristic of the underlying conduction properties in atria without electrophysiologic substrates for AF, then the sudden prolongation found in the patients with AF may be a manifestation of the underlying myocardial mechanism leading to AF in these patients.

Some researchers¹⁰ have reported that patients with AF have shorter right atrial refractory periods than control patients and that increases in atrial conduction time may be due purely to the shorter refractory periods observed. However, surely short refractory periods make early extrastimulation possible, which would in turn critically intensify potential inhomogeneous atrial conduction. For initiation of AF, however, a short refractory period in itself is insufficient if the atrial conduction property is homogeneous. In agreement with Simpson et al¹⁴ and other investigators,^{12,13} we found no significant difference in the effective RAA refractory periods in patients with and without AF.

In this study, 15 patients had an electrically induced sustained AF without any previous AF history. It is possible that the potential causes of AF were present at to a sufficient degree during the electrophysiologic study to initiate AF. We cannot predict whether these patients will develop AF in the future. On the other hand, AF was not electrically induced in some patients who had a history of paroxysmal AF. This suggests that other unmeasured factors (eg the frequency of premature atrial beats or abnormalities of autonomic tone^{17,18}) help determine if and when patients with atrial abnormalities develop AF.

Limitations

We obtained atrial conduction curves for intra-atrial conduction time from RAA to CSd only. To quantify the conduction properties of the whole atrium, it would be necessary to investigate conduction in the entire atrial region at different stimulation sites. Although it is unclear whether the critical site of the conduction defect is located in the right or left atrium, we believe that our observation of a long conduction route between the RAA and the CSd is a feasible representation of the total atrial conduction system. It is conceivable that the longer the distance, the higher the chance that with some form of prematurity a change takes place in the conduction route and thus in the conduction time. Furthermore, the control group in this study was simply a group without AF but not healthy volunteers. Associated arrhythmias in the control group, such as AVB, WPW, AVNRT, may have influenced the electrophysiology of the atria in

unpredictable ways. To understand the normal electrophysiologic feature in atrium, true control subjects should be studied.

Conclusion

Atrial conduction curves show distinctly how intra-atrial conduction responds to early extrastimulation of increasing prematurity. The sudden marked prolongations in the atrial conduction curves in patients with AF may be a characteristic presentation of the underlying abnormal conduction properties that tend to develop into atrial fibrillation in these patients.

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