INTRA-ATRIAL CONDUCTION DELAY AND FRAGMENTED ATRIAL ACTIVITY IN PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION

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To examine the electrophysiologic characteristics of paroxysmal atrial fibrillation (PAF), we studied intra-atrial conduction delay and fragmented atrial activity during premature stimulation of high right atrium in the following four groups: Group I (n = 25), patients without PAF and without sick sinus syndrome (SSS); Group II (n = 22), patients with PAF but without SSS; Group III (n = 10), patients without PAF and with SSS; Group IV (n = 6), patients with PAF and SSS. Intra-atrial conduction delay was the increase in the interval (from the stimuli to the coronary sinus electrogram) observed with early premature beats ≥ 20 ms compared with that of basic rhythm. Fragmented atrial activity was defined as disorganized atrial activity ≥ 150% of the duration of high atrial activity of basic beats recorded. The conduction delay zone (CDZ) and fragmented atrial activity zone (FAZ) were significantly wider in Groups II, III and IV than in Group I. There were no significant differences in either CDZs or FAZs among Groups II, III and IV. Thus, the widening of CDZs and/or FAZs are characteristic of PAF and SSS. CDZ and FAZ may be good indices of development of PAF in patients without SSS.

Intra-atrial conduction delay1–3 and marked fragmentation of atrial activity4–5 have recently been suggested to be characteristic of paroxysmal atrial fibrillation (PAF). Repetitive atrial firing has also been suggested by some investigators to be a sign of predisposition to atrial fibrillation6–8 but others have found it to be a nonspecific phenomenon2,9,10.

The patient populations in the above studies included patients with and without sick sinus syndrome (SSS). Pathological examination of SSS patients without PAF has shown abnormality not only in the sinus node but also in the atrium.11 However, no assessment of electrophysiological parameters suggestive of a propensity to PAF has been made based on the presence or absence of SSS.

To assess the electrophysiologic parameters in atrial muscle that might be predictive of the development of PAF in patients with or without SSS, we examined intra-atrial conduction delay, fragmented atrial activity and repetitive atrial firing in such patients.

METHODS

Patient population: The subjects were 63 consecutive patients who had had electrophysiologic tests between July 1986 and September 1987, and had no significant organic heart

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Fig. 1. Recording from a patient in Group II. The basic atrial drive cycle length is 500 ms. Electrocardiographic lead I, aVF and V1, the high right atrial electrogram (HRA), the coronary sinus distal portion (CSd) and the His bundle electrogram (HBE) are shown. An extrastimulus with a S1-S2 interval of 250 ms prolongs intra-atrial conduction from 120 ms to 190 ms in CSd, and prolongs the duration of the atrial activity from 100 ms (D1) to 230 ms (D2) in HRA. S2 produces an intra-atrial conduction delay at the CSd and disorganized fragmented activity of the atrium at HRA. Repetitive atrial firing follows. All values in milliseconds.

disease or overt congestive heart failure at the time of study. The patients were divided into 4 groups.

Group I consisted of 25 patients with associated arrhythmia, but without a history of SSS and without atrial fibrillation. Ages ranged from 14 to 80 years (mean ± standard deviation, 42 ± 22). Associated arrhythmias included the Wolff-Parkinson-White syndrome in 12, atrioventricular block in 8, idiopathic ventricular tachycardia in 3 and atrioventricular nodal reentrant tachycardia in 2.

Group II consisted of 22 patients with PAF, but without SSS. Ages ranged from 31 to 77 years (mean 53 ± 15). Associated arrhythmias included Wolff-Parkinson-White syndrome in 8. Idiopathic PAF was identified in 14.

Group III consisted of 10 patients with SSS, but without PAF. Their ages ranged from 46 to 77 years (mean 63 ± 10).

Group IV consisted of 6 patients with SSS and PAF (the tachycardia-bradycardia syndrome). Ages ranged from 61 to 76 years (mean 71 ± 7).

SSS was diagnosed using the recordings of a previous ECG, ambulatory Holter ECG (at least two), and bedside monitoring, according to the classification of Rubenstein.12

All patients were assigned to PAF groups documented electrocardiographically to have paroxysmal atrial fibrillation. To judge whether or not patients had a history of atrial fibrillation, previous ECGs, ambulatory Holter ECG (at least two) and bedside monitoring were used. Patients defined as having PAF had had more than 2 documented episodes of paroxysmal atrial fibrillation, and the last episode occurring within 3 months before the electrophysiological study was performed.

The ages in Group III and Group IV were significantly higher than that in Group I (III vs I, p < 0.05: IV vs I, p < 0.05). In order to cancel the possible influence of age on the electrophysiologic parameters of the atrial muscle, we selected from among the four groups only 38 patients who were more than 50 years old. The data obtained from these 38 patients were analyzed separately. Group I consisted of 11 patients without PAF and without SSS. Group II' consisted of 12 patients with PAF but without SSS. Group III' consisted of 9 patients with
SSS but without PAF. Group IV' consisted of 6 patients with SSS and PAF.

Electrophysiologic studies: All cardioactive medications were discontinued at least 3 days before the study. Quadrupolar catheter electrodes with a 1 cm interelectrode distance were used. The intracardiac signals were filtered to record frequencies of 50 to 700 Hz with a MIC-8800T Fukudenshi polygraph. Recordings were made at a paper speed of 100 mm/s with simultaneous inscription of 3 surface electrograms on an ink-jet recorder (Siemens-Elema).

Catheters were advanced into the lateral high right atrium (HRA), RA appendage, coronary sinus and right ventricle. The distal portion of the catheter within the coronary sinus was placed at a lateral or posterolateral position in the left atrium. Right atrial electrograms were recorded from the distal pair of electrodes at the HRA near its junction with the superior vena cava. His bundle activity was recorded from a distal pair of electrodes placed across the tricuspid valve. Atrial stimulation was performed at an intensity twice the threshold and 2 ms in duration through the distal electrodes in the RA appendage, using a SEC-2102 Nihonkoden pulse generator.

A premature stimulus (S2) was delivered after eight beats of drive pacing (S1) at a cycle length of 500 ms (59 patients) or 700 ms (4 patients). The S1–S2 interval was decreased in 10 ms steps until the effective refractory period of RA was reached. The first deflection in amplified recordings of the atrial electrograms was taken as the onset of atrial depolarization.

Measurements and Definitions: S1 and A1 refer to the driving stimulus and the atrial
deflection of the basic rhythm. S2 and A2 refer to the extrastimulus and the atrial deflection resulting from it. The effective refractory period was defined as the longest S1–S2 interval at which a stimulus failed to propagate a response.

Intra-atrial conduction time was measured as the interval from the stimulus to the atrial deflection at the coronary sinus distal portion. Intra-atrial conduction delay was arbitrarily defined as an increase in S2A2 ≥ 20 ms compared to S1A1 of the basic drive (Fig. 1).

Fragmented atrial activity was defined as the occurrence of disorganized atrial activity ≥ 150% of the duration of the local atrial activity in basic beats recorded on the right atrial electrogram. Repetitive atrial firing was defined as the occurrence of two or more premature atrial complexes with a return cycle (A2–A3) of 250 ms or less and a subsequent cycle length of 300 ms or less. Atrial conduction delay zones, fragmented atrial activity zones, and repetitive atrial firing zones were the difference between the longest and the shortest S1–S2 intervals producing atrial conduction delay, fragmented atrial activity, and repetitive atrial firing, respectively.

The sinus node recovery time was measured after atrial overdrive pacing for 1 min at pacing rate of 70, 90, 110, 130, 150, 180 and 210 beats per minute, the longest value being reported. The sinoatrial conduction time was estimated by Strauss’ method, and a corrected value of 130 ms or longer was considered abnormal.

Statistical analysis: The results were expressed as the mean ± 1 standard deviation. The statistical significance of the differences were analyzed by Student’s t test for unpaired values. Prevalence was compared using the chi-square test.

RESULTS

Driving cycle length and effective refractory periods in the right atrium: There were no significant differences among the 4 groups in the driving cycle length used in the measurement of the electrophysiologic parameters. The effective refractory periods were 203 ± 30 ms in Group I, 195 ± 27 ms in Group II, 226 ± 35 ms in Group III and 231 ± 31 in Group IV. The figures for Groups III and IV were significantly longer than those for Groups I and II (III vs I or II, p < 0.05; IV vs I or II, p < 0.05).

Conduction delay zone: All patients had intra-atrial conduction delay. The conduction delay zone was significantly wider in Group II (54 ± 23 ms), Group III (54 ± 18 ms) and Group IV (84 ± 45 ms) than in Group I (25 ± 14 ms). However, conduction delay zones were not significantly different among Groups II, III and IV (Fig. 2).

Fragmented atrial activity zone: Fragmented atrial activities were recorded in 16 patients in Group I, in 17 patients in Group II, 8 patients in Group III and 6 patients in Group IV. There were no significant differences among the 4 groups in the prevalence of fragmented atrial activity resulting from atrial extrastimulation. The fragmented atrial activity zone was significantly wider in Group II (51 ± 27 ms), Group III (73 ± 32 ms) and Group IV (62 ± 35 ms) than in Group I (18 ± 15 ms). However, fragmented atrial activity zones were not significantly different among Groups II, III and IV (Fig. 3).

Repetitive atrial firing zone: Repetitive atrial firings were recorded in 7 patients in Group I (28%), 11 patients in Group II (50%), 5 patients in Group III (50%) and 3 patients in Group IV (50%). The incidence of repetitive atrial firing was not significantly different among the four groups. Repetitive atrial firing zones were 6 ± 11 ms in Group I, 35 ± 29 ms in Group II, 24 ± 25 ms in Group III and 43 ± 58 ms in Group IV. The repetitive atrial firing zone was significantly wider in Group II than in Group I (p < 0.05). There were no significant differences among Groups II, III and IV.

Sinus node function, conduction delay zones and Fragmented atrial activity zones in the patients with sick sinus syndrome: Group III consisted of four patients in type I (consistent bradycardia) and 6 patients in type II (sinoatrial block and sinus arrest) of Rubenstein’s classification. There were no significant differences between types I and II in terms of conduction delay zone, fragmented atrial activity zone or repetitive atrial firing zone.

The maximum sinus node recovery time ranged in all patients with SSS from 1.2 to 9.3 sec (2.7 ± 2.2). In 7 Group III patients and 5 Group IV patients, the maximum sinus node recovery time was longer than 1.6 sec. Other patients showed frequent sinoatrial block or at least one episode of sinus arrest longer than 2.0 sec by Holter electrocardiography. A maximum sinus node recovery time of more than 5.0 sec was observed in 2 Group IV patients. Sinoatrial conduction time was longer than 130 ms in only

TABLE 1 THE ELECTROPHYSIOLOGIC PARAMETERS IN 38 PATIENTS MORE THAN 50 YEARS OLD

<table>
<thead>
<tr>
<th>Group I'</th>
<th>Group II'</th>
<th>Group III'</th>
<th>Group IV'</th>
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<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Age</td>
<td>62 ± 9</td>
<td>64 ± 7</td>
<td>65 ± 9</td>
</tr>
<tr>
<td>ERP</td>
<td>212 ± 19</td>
<td>203 ± 32</td>
<td>224 ± 36</td>
</tr>
<tr>
<td>DCZ</td>
<td>29 ± 14</td>
<td>52 ± 24§</td>
<td>58 ± 15¶</td>
</tr>
<tr>
<td>FAZ</td>
<td>23 ± 14 (n = 9)</td>
<td>58 ± 31 (n = 8)*</td>
<td>73 ± 32 (n = 7)¶</td>
</tr>
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</table>

Group I': patients more than 50 years old without paroxysmal atrial fibrillation (PAF) and without sick sinus syndrome (SSS), Group II': patients more than 50 years old with PAF and without SSS, Group III': patients more than 50 years old without PAF and with SSS, Group IV': patients with PAF and with SSS. 

n: number of patients in group, (n = ...): number of patients who had fragmented atrial activity in group. ERP: effective refractory period in atrium (ms). CDZ: conduction delay zone (ms). FAZ: fragmented atrial activity zone (ms). §: Group I vs Groups II, III or IV p < 0.01; *: Group I vs Groups II, III or IV, p < 0.02; ¶: Group I vs Groups II, III or IV, p < 0.005. Values: mean ± standard deviation.

one patient out of 9 who were measurable. There was no relationship between the maximum sinus node recovery time and the conduction delay zone, fragmented atrial activity zone or repetitive atrial firing zone.

The influence of age on conduction delay zone and fragmented atrial activity zone: To cancel the possible influence of age on the atrial muscle’s electrophysiologic parameters, 38 patients more than 50 years of age were studied according to the previous protocol. The repetitive atrial firing zone was not examined, because the number of patients showing repetitive atrial firing was not large enough to analyse statistically. These 38 patients were divided into 4 groups as before (Table I). There were no significant intergroup differences in age or in atrial effective refractory periods (Table I).

Conduction delay zones were 29 ± 14 ms in Group I’ (n = 11), 52 ± 24 ms in Group II’ (n = 12), 58 ± 15 ms Group III’ (n = 9) and 82 ± 45 ms in Group IV’ (n = 6). Fragmented atrial activity zones were recorded in 9 patients in Group I’, 8 patients in Group II’, 7 patients in Group III’ and 6 patients in Group IV’. Fragmented atrial activity zones were 23 ± 14 ms in Group I’, 58 ± 31 ms in Group II’, 73 ± 32 ms in Group III’ and 63 ± 34 ms in Group IV’. The conduction delay zone and fragmented atrial activity zone were significantly wider in Groups II, III and IV than in Group I (Table I). However, conduction delay zones and fragmented atrial activity zones were not significantly different among Groups II, III and IV (Table I). These results were similar to those obtained with patients less than 50 years of age.

DISCUSSION

It has been reported that intra-atrial slow conduction and fragmented atrial activity can be observed in normal subjects, though the intensity of these phenomena in such people is reduced compared with that seen in patients with paroxysmal atrial fibrillation. It is conceivable that the widening of these electrophysiologic indices could be a manifestation of abnormal cellular electrophysiology, as it may be found in diseased atrial muscle.

We have presumed that the abnormal the electrophysiologic parameters are observable in patients with sick sinus syndrome even if paroxysmal atrial fibrillation is not present. In our present study, therefore, we examined the conduction delay and fragmented atrial activity zones in patients with and without sick sinus syndrome. Additionally, we further subdivided patients with sick sinus syndrome and compared the conduction delay zone in patients with and in those without paroxysmal atrial fibrillation.

In the present study, Group I was not truly a control group. Almost 50% of the patients had the Wolff-Parkinson-White syndrome and this may have influenced the pattern of electrophysiologic parameters. Others had atrioventricular block or atrioventricular nodal reentrant tachycardia. This might be a cause for serious consideration. However, there were no significant differences in the conduction delay and fragmented activity zones between patients with and without the Wolff-Parkinson-White syndrome in Groups I and II. Patients with atrioventricular block or atrioventricular nodal reentrant tachy-
cardia did not have abnormal values for conduction delay or fragmented atrial activity zones. Therefore, in our study, it was probable that the Wolff-Parkinson-White syndrome, atrioventricular block and atrioventricular nodal reentrant tachycardia had no influence on the conduction delay and fragmented atrial activity zones.

**Paroxysmal atrial fibrillation and conduction delay zone:** Without intracellular recordings at the site of stimulation, it is difficult to rule out the possibility that the S2−A2 delays were caused by a latency resulting from local tissue polarization caused by stimuli applied during the absolute refractory period. Thus, the S2−A2 delay may reflect latency or intra-atrial conduction delay or both. However, Cosio et al postulated that the latency explanation was very unlikely.

In our study, patients with idiopathic paroxysmal atrial fibrillation had wider conduction delay zones than did control subjects. This suggests that patients with atrial fibrillation had a higher tendency than control subjects to develop slow intra-atrial conduction. Similar opinions have been reported by some investigators.\(^1\)−\(^3\)

**Paroxysmal atrial fibrillation and fragmented atrial activity zone:** In our study, patients with idiopathic paroxysmal atrial fibrillation had wider fragmented atrial activity zones than did control subjects. This suggests that the widening of the fragmented atrial activity zone is closely related to spontaneous atrial fibrillation. Similar opinions have been reported by some investigators.\(^3\)−\(^5\)

In patients in our present study with sick sinus syndrome, there was no significant difference in the fragmented atrial activity zone between patients with and without paroxysmal atrial fibrillation. On the other hand, Ohe et al\(^4\) who divided 57 patients into four groups in experiments similar to our study, reported that patients with sick sinus syndrome who also exhibited paroxysmal atrial fibrillation had a wider fragmented atrial zone than did patients with sick sinus syndrome but without paroxysmal atrial fibrillation. It is possible that these discrepancies in electrophysiologic parameters can be explained by the different pacing sites (high lateral right atrium in their study vs right atrial appendage in our study) used in the two studies, or differences in the selected groups of patients.

**Paroxysmal atrial fibrillation and repetitive atrial firing zone:** The incidence of repetitive atrial firing was not significantly different in patients with idiopathic PAF and control subjects. Some investigators have reported that repetitive atrial firing is a nonspecific response of atrial muscle, and therefore is not a reliable parameter of a tendency to spontaneously develop atrial fibrillation.\(^1\)\(^2\)\(^9\)\(^10\) However, the repetitive atrial firing zone showed a significant difference between patients with idiopathic paroxysmal atrial fibrillation and control subjects in our study. The widening of the repetitive atrial firing zone could therefore be used by some as an index of a tendency toward spontaneous atrial arrhythmias in patients without sick sinus syndrome. Similar opinions have been reported by some investigators.\(^6\)−\(^8\)

**Paroxysmal atrial fibrillation and atrial effective refractory period:** In our study which canceled the possible influence of age, there was no significant difference in atrial effective refractory periods between patients with and without paroxysmal atrial fibrillation. A similar finding has been reported by Brauenfeind et al\(^6\) However, some investigators have emphasized that patients with paroxysmal atrial fibrillation have a shorter atrial refractory period\(^1\)\(^8\)\(^17\) and that there is a significant relationship between the vulnerable zone and the atrial refractory period\(^9\) Simpson et al\(^2\) has suggested that the atrial refractory period varies with paced cycle length and electrode position, and is probably not useful as a method of distinguishing normal from diseased atria.

**Fragmented atrial activity zone, conduction delay zone, repetitive atrial firing zone and atrial effective refractory period:** In the present study, fragmented atrial activity and atrial conduction delay induced by a premature stimulation were always induced by earlier premature stimulations, until the atrial effective refractory period was reached. Thus, the inner margins of the fragmented atrial activity zone and conduction delay zone were the atrial effective refractory period.\(^1\)\(^4\) The range of coupling intervals used to produce repetitive atrial firing has previously been established as the repetitive atrial firing zone or vulnerable zone.\(^9\) However, in the present study the inner margin of the repetitive atrial firing zone was not always the atrial effective refractory period, because the repetitive atrial firing was occasionally caused by a premature stimulation did not necessarily result in repetitive atrial firing.\(^4\)\(^9\)

**Sick sinus syndrome and paroxysmal atrial fibrillation**

fibrillation: Our study showed that there were no significant differences in conduction delay zones and fragmented atrial activity zones between patients with idiopathic paroxysmal atrial fibrillation and those with sick sinus syndrome but without paroxysmal atrial fibrillation. It is possible that sinus nodal function influences the occurrence and the duration of paroxysmal atrial fibrillation. Nadeau et al \(^\text{18}\) studied atrial fibrillation produced by application of methacholine chloride. This fibrillation was more readily initiated and persisted for a longer period of time in the presence of an intact sinus node than after its suppression. Similar findings have been reported by other investigators \(^\text{19,20}\).

On the other hand, some investigators have reported that bradycardia may induce an increase in the dispersion of excitability recovery and facilitate reentrant arrhythmias \(^\text{5,20,21}\). Cosio et al \(^\text{1}\) reported that sinus nodal dysfunction was frequently found in patients with paroxysmal atrial fibrillation, but that it was not essential for the occurrence of atrial fibrillation. \(^\text{1}\) Thus, the relationship between paroxysmal atrial fibrillation and sick sinus syndrome is still not clear.

Influence of age on conduction delay zone and fragmented atrial activity zone: In our study, the mean age in patients with sick sinus syndrome was significantly higher than that in either patients with paroxysmal atrial fibrillation or control subjects. Thus, it was necessary to consider the influence of age on the electrophysiologic characteristics of atrial muscle. We selected 38 patients out of the four groups who were more than 50 years old, and studied them separately according to the previous protocol. The results were similar to those obtained with patients under 50 years of age. This suggests that the influence of age was not a major factor contributing to the differences in either the conduction delay or fragmented atrial activity zones.

Limitations: Some limitations to this study should be considered. Group I is not truly a control group. The patients in our study had a variety of clinical and electrophysiologic abnormalities, and this may have influenced the results in unpredictable ways. It is not easy to make a precise judgment of whether or not a patient has a history of atrial fibrillation by taking a history, previous ECGs, ambulatory Holter ECGs and bedside monitoring. The electrophysiologic reaction of atrial muscle to premature stimuli is effected by various factors, including basic driving cycle length \(^\text{1,23}\) the site and strength of stimuli \(^\text{3}\) the functional neurologic factors \(^\text{24,25}\) and structural complexities \(^\text{26}\).

Conclusions: 1) The widening of the conduction delay zones and/or the fragmented atrial activity zones is characteristic of paroxysmal atrial fibrillation and sick sinus syndrome. 2) The conduction delay zones and/or the fragmented atrial activity zone are no different in patients with either PAF but without sick sinus syndrome, or patients with sick sinus syndrome. 3) The conduction delay and/or fragmented atrial activity zone may be good indices of a propensity for paroxysmal atrial fibrillation in patients without sick sinus syndrome.

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