ATRIAL FIBRILLATION AND ATRIAL VULNERABILITY IN THE WOLFF-PARKINSON-WHITE SYNDROME

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To explore the etiology of paroxysmal atrial fibrillation (AF) in the Wolff-Parkinson-White (WPW) syndrome, we examined the rates of AF episodes and performed electrophysiologic studies in 58 patients with WPW syndrome. They were classified into three patient groups depending on the property of antegrade conduction over accessory pathways: manifest WPW, intermittent WPW, and concealed WPW. Atrial vulnerability was defined as the inducibility of AF or repetitive atrial responses. The three groups were: 24 patients in manifest WPW, aged 42 ± 15 yrs, 38% with AF; 12 patients in intermittent WPW, aged 40 ± 15 yrs, 25% with AF; 22 patients in concealed WPW, aged 44 ± 16 yrs, 9% with AF. There were no significant differences in the mean age between the groups. The incidences of atrial vulnerability detected in electrophysiologic studies in each group were 54%, 42%, and 27% respectively. The incidence of AF was well correlated with that of atrial vulnerability (p < 0.01). The effective refractory periods (ERP) of the atrium and the retrograde ERP of the accessory pathway did not differ significantly between the three groups. Atrial conduction delay was more prominent in manifest WPW than in concealed WPW. The incidence of AF and atrial vulnerability was highest in the manifest WPW group, intermediate in the intermittent WPW group, and lowest in those patients with concealed WPW. The difference in incidence between the manifest WPW group and the concealed WPW group was significant (p < 0.05). Therefore, the property of antegrade conduction over accessory pathways may be related to the genesis of AF in the WPW syndrome.

Paroxysmal atrial fibrillation (AF) occurs frequently in patients with Wolff-Parkinson-White (WPW) syndrome. This arrhythmia may have life-threatening consequences by precipitating ventricular fibrillation when accompanied by conduction via an accessory pathway in a rapid succession. The mechanism of the genesis of AF in the WPW syndrome has not been clarified. Several studies have dealt with this problem but have not yet determined whether or not susceptibility to AF may be attributed to the function of accessory pathways. To address this question, we compared the rates of complication of AF and electrophysiologic findings, including atrial vulnerability, in three patient groups: manifest WPW, intermittent WPW, and concealed WPW. The major variable associated with the three categories is antegrade conduction via accessory atrio-ventricular (AV) pathways. Our concern was whether this variable may be related to the incidence of

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Concealed WPW syndrome

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TABLE I  PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Location of AP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>female</td>
</tr>
<tr>
<td>Manifest</td>
<td>24</td>
<td>42±15</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Intermittent WPW</td>
<td>12</td>
<td>40±15</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Concealed WPW</td>
<td>22</td>
<td>44±16</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>

AP: accessory pathway, L: left sided, S: septum, R: right sided The ages are in the form of mean±S.D.

AF and to the atrial vulnerability revealed by electrophysiologic examinations. Electrophysiologic parameters related to atrial vulnerability were also statistically analyzed in the three groups and in patients with antegrade conduction over accessory pathways in a search for useful parameters for predicting clinical AF in the WPW syndrome.

METHODS

Patient selection
We examined 58 consecutive patients having accessory AV connections. They entered this institution between 1981 and 1988 following palpitations with explained or unexplained causes. The patients had no apparent organic heart diseases and no serious complications. On admission, each patient had a sinus rhythm. The 58 patients were classified into three groups depending on the characteristic of the antegrade conduction through the accessory pathways: manifest WPW, intermittent WPW, and concealed WPW. The three groups comprised 24, 12, and 22 cases, respectively. Intermittent preexcitation was defined as intermittent loss of delta wave with concomitant prolongation of the P-R interval on at least one occasion.

The existence of a history of AF was confirmed by electrocardiographic records and physicians' medical records (Table I).

Electrophysiologic studies
Electrophysiologic studies were performed with the patients in the nonsedated and postabsorptive state after antiarrhythmic medica-
tions had been discontinued for at least 72h. Written informed consent was obtained from each patient. Generally, two quadripolar electrodes were positioned in the high right atrium and the coronary sinus to record the adjacent electrical activity. The His bundle electrogram was obtained by a tripolar electrode just across the tricuspid valve. The right atrium and ventricle were paced by two bipolar electrodes. Electrocardiographic leads I, aVF, and V1 (V5) were recorded simultaneously on an 8-channel Siemens Mingograph at a standard paper speed of 100 mm/sec. Programmed stimulation was performed using a square wave at twice diastolic threshold. The stimulation protocol included atrial or ventricular extrastimulus at basic cycle lengths of 545 and 667 msec and atrial or ventricular incremental pacing up to 260 beats per minute. The data from the extrastimulus method were compared in the same basic cycle length such as 545 msec. Atrial vulnerability was defined as inducibility of AF and repetitive atrial responses to single atrial extrastimuli. Atrial functions were defined as follows and are represented schematically in Fig. 1. In a spontaneous sinus cycle, the intra-atrial conduction time was defined as the interval from the onset of the P wave to the atrial activity on the His bundle electrogram and the interatrial conduction time was defined as the interval from the P wave to the atrial activity on the coronary sinus electrogram. Whether or not PA intervals reflect real intra-atrial or interatrial conduction time is controversial. However, these measurements are considered to be valuable at least for comparing the conduction properties of the atrium in the three groups, provided there are no organic heart deseases causing atrial enlargement. By the atrial extrastimulus method, atrial conduction delay was considered to exist if the S2A2 interval exceeded the S1A1 interval by more than 20 msec on the His bundle electrogram. Fragmented atrial activity was defined as the occurrence of disorganized activity in >150% of the A1 duration of the local atrial activity of the basic beats on the high right atrial electrogram. Repetitive atrial responses were defined as the production of more than two atrial activations by one extrastimulus. The interval between responses was less than 300 msec. Changes in atrial activation sequence, lack of criteria for sinus node interpolation or re-entry were additional criteria. The conduction delay zone was defined as the range of S1-S2 intervals resulting in conduction delay after atrial extrastimulus. Zone of fragmented activity was similarly defined as a range of S1-S2 intervals resulting in fragmented activity. The location of an accessory pathway was determined by the earliest atrial activation of the retrogradely-conducted orthodromic circus movement impulses over the pathway. However, if such a movement did not occur, it was determined by the method of Gallagher et al using surface electrocardiograms.

Statistics

Statistical analysis was performed using

TABLE II INCEDEANCE OF AF AND INCREASED ATRIAL VULNERABILITY

<table>
<thead>
<tr>
<th>History of AF</th>
<th>Atrial vulnerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manifest WPW</td>
<td>38%</td>
</tr>
<tr>
<td>Intermittent WPW</td>
<td>25%</td>
</tr>
<tr>
<td>Concealed WPW</td>
<td>9%</td>
</tr>
</tbody>
</table>

*p<0.05, AF: atrial fibrillation, Atrial vulnerability: positive atrial vulnerability detected in electrophysiologic study.

TABLE III RELATION BETWEEN ATRIAL VULNERABILITY AND CLINICAL AF

<table>
<thead>
<tr>
<th>Clinical AF</th>
<th>(+)</th>
<th>(-)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Vulnerability (+)</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>(-)</td>
<td>2</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

Subjects: total 58 patients, Chi square value = 13.3, p<0.01 sensitivity of atrial vulnerability to clinical AF: 86% Specificity of atrial vulnerability to clinical AF: 73%
Fig. 2. Comparison of electrophysiologic study between the three groups. Abbreviations as follows. M: manifest WPW syndrome, I: intermittent WPW syndrome, C: concealed WPW syndrome, cSRT: corrected sinus recovery time, ACT: atrial conduction time, AERP: effective refractory period of the atrium, CL/CMT: cycle length of circus movement tachycardia, AP-ERP retro: retrograde effective refractory period of the accessory pathway, CDZ: conduction delay zone, FAZ: fragmented activity zone. The individual data are presented in Table IV.

Student's t test for unpaired data and chi square test when appropriate. All data are in the form of mean ± standard deviation (S.D.). Statistical significance was considered to be present if the p value was less than 0.05, but p values below 0.1 are also presented for consideration.

RESULTS

Patient characteristics

Fifty-eight patients without serious organic heart diseases were divided into three categories according to WPW class. There were no significant differences between the three groups either in terms of mean age or sex ratio (Table I). Regarding the location of the accessory connection, right-sided pathways were rarer in cases of concealed WPW syndrome than in manifest or intermittent WPW syndromes: 5% (1/22) vs 25% (9/36), (p<0.05).
**TABLE IV** COMPARISON OF ELECTROPHYSIOLOGIC DATA BETWEEN THREE GROUPS

<table>
<thead>
<tr>
<th></th>
<th>Manifest WPW</th>
<th>Intermittent WPW</th>
<th>Concealed WPW</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cSRT</strong></td>
<td>279±112</td>
<td>253±98</td>
<td>253±98</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Intra-ACT</strong></td>
<td>45±11</td>
<td>47±13</td>
<td>46±15</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Inter-ACT</strong></td>
<td>80±18</td>
<td>79±16</td>
<td>78±13</td>
<td>NS</td>
</tr>
<tr>
<td><strong>AERP</strong></td>
<td>*201±29</td>
<td>201±33</td>
<td>*218±30</td>
<td>*p&lt;0.1</td>
</tr>
<tr>
<td><strong>AH interval</strong></td>
<td>75±16</td>
<td>81±22</td>
<td>79±15</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CL/CMT</strong></td>
<td>*359±66</td>
<td>350±45</td>
<td>*325±39</td>
<td>*p&lt;0.05</td>
</tr>
<tr>
<td><strong>AP-ERP ante</strong></td>
<td>279±41</td>
<td>336±16</td>
<td>——</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>AP-ERP retro</strong></td>
<td>275±82</td>
<td>259±40</td>
<td>265±41</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CDZ</strong></td>
<td>*23±18</td>
<td>15±16</td>
<td>*14±15</td>
<td>*p&lt;0.05</td>
</tr>
<tr>
<td><strong>FAZ</strong></td>
<td>*23±22</td>
<td>15±17</td>
<td>*14±18</td>
<td>*p&lt;0.1</td>
</tr>
</tbody>
</table>

*(mean ± S.D. msec)*

**AP-ERP ante:** antegrade effective refractory period of the accessory pathway. Other abbreviations are defined in Fig. 2.

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Fig. 3. Relation between atrial vulnerability and other factors. I and II stand for group I and group II, respectively. Abbreviations as in Fig. 2 and Table IV. The individual data are presented in Table V.

**Past history of AF and atrial vulnerability**

A history of AF was found more frequently in patients with manifest WPW than in concealed WPW patients (38% vs 9%, p<0.05, Table II). The incidence of atrial vulnerability detected in the electrophysiologic study was also higher in the manifest WPW group than in the concealed WPW group (54% vs 27%, p<0.05). On the other hand, the intermittent preexcitation group showed intermediate incidences of both AF and atrial vulnerability. The rank order for
TABLE V  RELATION BETWEEN ATRIAL VULNERABILITY AND OTHER FACTORS

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-ACT</td>
<td>49±15</td>
<td>44±15</td>
<td>NS</td>
</tr>
<tr>
<td>Inter-ACT</td>
<td>85±19</td>
<td>75±13</td>
<td>p&lt;0.1</td>
</tr>
<tr>
<td>AERP</td>
<td>196±30</td>
<td>212±30</td>
<td>p&lt;0.1</td>
</tr>
<tr>
<td>AP-ERP ante</td>
<td>283±38</td>
<td>300±46</td>
<td>NS</td>
</tr>
<tr>
<td>AP-ERP retro</td>
<td>275±65</td>
<td>283±91</td>
<td>NS</td>
</tr>
<tr>
<td>CL/CMT</td>
<td>368±69</td>
<td>351±47</td>
<td>NS</td>
</tr>
<tr>
<td>CDZ</td>
<td>30±19</td>
<td>11±10</td>
<td>p&lt;0.005</td>
</tr>
<tr>
<td>FAZ</td>
<td>28±25</td>
<td>12±9</td>
<td>p&lt;0.1</td>
</tr>
</tbody>
</table>

Subjects: 30 patients with preexcitation, group I: 17 patients with atrial vulnerability, group II: 13 patients without atrial vulnerability. Abbreviations as in Fig. 2 and Table 4.

both factors in the groups was therefore: manifest WPW>intermittent WPW>concealed WPW. As shown in Table III, there was a fair correlation between atrial vulnerability and clinical AF (p<0.05). In all 58 patients, the sensitivity and specificity of atrial vulnerability to clinical AF was 86% and 73% respectively.

Electrophysiologic data

The electrophysiologic consequences in each group are compared in Fig. 2 and Table IV. Corrected sinus node recovery times did not differ significantly among the three groups. The atrial effective refractory periods (AERP) in the manifest WPW group were somewhat shorter than those in the concealed WPW group (201±29 vs 218±31 msec, p<0.1), although statistically not significant. No significant differences were found in either intra-atrial conduction times or interatrial conduction times. However, conduction delay zones in cases of manifest WPW were longer than those in cases of concealed WPW (23±18 vs 14±15 msec, p<0.05). There was a similar trend in the findings for the length of the fragmented activity zones (23±22 vs 14±18 msec, p<0.1). Neither the AH intervals nor effective refractory periods of the AV node differed between the three groups, nor did the retrograde refractory periods of the accessory pathways. Circus movement tachycardias were induced in 18 patients with manifest WPW, in 9 patients with intermittent WPW, and naturally, in all those with concealed WPW. The mean cycle lengths of the circus movement tachycardias in the manifest WPW group were longer than those in the concealed WPW group (359±66 vs 325±39 msec, p<0.05). The intermittent WPW group tended to have values for width of atrial conduction delay zones and fragmented activity zones intermediate to those for the manifest and concealed WPW groups, as for the past history of AF and atrial vulnerability described above.

Relation between atrial vulnerability and parameters for atrial function

To test the significance of parameters for atrial functions, these parameters were compared with atrial vulnerability in those patients with preexcitation, i.e. the 24 cases of manifest WPW and 6 cases of intermittent WPW who showed delta waves during electrophysiologic studies. These patients were divided into two groups, patients with atrial vulnerability (group I) and without it (group II). As shown in Table IV and Fig. 3, the mean AERP in group I was slightly shorter than in group II (196±30 vs 212±30 msec, p<0.1). Intra-atrial conduction times and interatrial conduction times were longer in group I, but the difference was not significant. On the other hand, conduction delay zones were significantly wider in group I than in group II (30±19 vs 11±10 msec, p<0.005). The difference in fragmented activity zone width between the manifest WPW and the concealed WPW groups, however, was less than that in conduction
delay zones (28±25 vs 12±9 msec, p < 0.1). There were no significant differences in AH intervals, cycle lengths of circus movement tachycardia, or effective refractory periods of the accessory pathway in either antegrade or retrograde conduction.

DISCUSSION

Paroxysmal atrial fibrillation occurs frequently in the WPW syndrome. The incidence of AF associated with this condition has been reported to be between 10 and 38%.1–7 The incidence of AF in the present study was 38% in the manifest WPW group and 25% in the intermittent WPW group, which was consistent with the previous reports.

Spontaneous atrial fibrillation and atrial vulnerability

The relationship between clinically documented AF and atrial vulnerability, including repetitive atrial responses in an electrophysiologic study in one patient, is still controversial15,16 whereas our present study demonstrated a fair correlation between them (Table V). Rinne et al reported that patients with WPW syndrome presenting with AF had a higher incidence of atrial vulnerability than patients with WPW syndrome presenting with only atrio-ventricular tachycardia.16 Sung et al reported that the genesis of atrial fibrillation in the WPW syndrome may be related to the the presence of atrial vulnerability.9 It should be useful to discriminate between patients with atrial vulnerability and those without it in the WPW syndrome and to study these entities.

Role of the accessory pathway in the genesis of atrial fibrillation in the WPW syndrome

It was reported that susceptibility to AF was eliminated after interruption of the accessory pathway by surgical division or transcatheter electrical ablation.3 Apparently, one of the reasons for the elimination of AF was that circus movement tachycardia or ectopy mediated by the accessory pathway was abolished. In the present study, the incidence of spontaneous AF in the manifest WPW group was higher than that in the concealed WPW group, whereas circus movement tachycardias were inducible in 75% of the manifest WPW group, instead of the 100% induction in the concealed WPW group. Therefore, the genesis of AF in the WPW syndrome cannot be attributed solely to the occurrence of circus movement tachycardia. Furthermore, the mean cycle length of circus movement tachycardias in the present study was shorter in patients with concealed WPW than in those with manifest WPW, which does not explain the lower incidence of AF in the concealed WPW group, since shortening of cycle lengths was reported to increase atrial vulnerability.18 There have been no comparative studies of the cycle length of reciprocating tachycardia in manifest and concealed WPW syndromes. The cycle length of reciprocating tachycardia in manifest WPW ranged in several reports from 307 to 343 msec.16,17 Farshidi et al reported that the mean cycle length of reciprocating tachycardia in concealed WPW syndrome was 337±32 msec, which was shorter than the mean cycle length of tachycardias utilizing the AV node.19 The cause of the difference in the cycle length of reciprocating tachycardias between the manifest and concealed WPW groups in the present study is not known. However, intra-atrial or interatrial conduction disturbance may be a possible explanation for the longer cycle length of tachycardias in the manifest WPW group. On the other hand, circus movement tachycardia may potentiate susceptibility to AF, because of increased sympathetic activity, hypoxia, or atrial stretch. Therefore, circus movement tachycardia may be involved in the genesis of AF in the WPW syndrome. A patient with concealed WPW was reported as having AF by spontaneous ventricular premature beats.20 In this case, ventricular premature beats may have resulted in premature atrial activation via ventriculo-atrial conduction through an accessory pathway, possibly initiating AF when it occurred during the atrial vulnerable phase. However, we did not experience such an instance. Such a phenomenon could also occur in manifest WPW, but its prevalence was not recorded in the three WPW groups, and its contribution to the genesis of AF in the WPW syndrome could not be clarified.

The existence of a functional accessory pathway may be a major determinant in the genesis of AF in the patient without organic
heart disease even if circus movement tachycardias and ventricular premature beats are not the direct cause. From this point of view, the 58 cases were divided into three categories, depending on the property of antegrade conduction of the accessory pathway: manifest, intermittent, and concealed WPW. The rank order of both past history of AF and positive atrial vulnerability was as follows: manifest WPW > intermittent WPW > concealed WPW. As the number of patients was limited in our present study, patient selection may have biased the data. However, the incidences of AF in the manifest WPW and intermittent WPW groups were consistent with the previous reports, so comparisons between the data were considered to be reliable, provided the differences were statistically significant. In experimental studies of the canine-heart model of the WPW syndrome, structural differences in the accessory pathways apparently affected the effective refractory periods and the conduction properties of the pathway. Anatomical studies of the preexcitation syndrome have concerned mostly the accessory AV connection. Until recently, no detailed data for the human heart have been available concerning the structure of atrial tissues around the accessory pathway. It was postulated that the accessory AV connections are the result of an embryologic fault in the formation of fibrous tissue separating the atria and the ventricles. So developmental abnormalities may also be present in the atrial tissues adjacent to the connections. It is conceivable that in the three patient categories there are anatomical differences, possibly in atrial tissues around the accessory connection, which may affect the functional differences in the characteristics of the atrium close to accessory pathways. Either anatomical or functional properties of the tissues of the atrium may play a role in the genesis of AF and may contribute the difference in the incidences of AF and atrial vulnerability. It is postulated that the presence of anatomical and functional variations in the tissues of the atrium around the accessory pathway produce the differences in the incidence of AF between the three groups, since dispersion of the refractory periods and conduction disturbances apparently occur around the interconnection between different tissues such as the atrium and the accessory pathway. It is conjectural that these arrhythmogenic substrates contribute to the basis for one or more foci which generate AF, as the mechanism of the genesis of AF in general has not been clearly established.

Parameters for atrial function related to atrial vulnerability

As described in the results, the patients with preexcitation were divided into two groups: with and without atrial vulnerability. Widening of the conduction delay zone was best correlated with increased vulnerability of the atrium. The fragmented activity zone was also widened in group I, although the degree of widening was less than that in the conduction delay zone. Cosio et al reported that patients with AF had a wider conduction delay zone than patients without AF. The slow conduction of early extrastimulus may be due to conduction during partial recovery of myocardial excitability, and increased atrial conduction delay in patients with AF could be a manifestation of abnormal cellular electrophysiology in diseased atrial muscle. The fragmented activity zone was also reported to be widened in patients with AF and atrial vulnerability. The cause of fragmented atrial activity has not been clarified, but it may represent local continuous activity in response to premature beats. Ohe and co-workers suggested that the widening of the fragmented activity zone indicates the ease with which a premature beat occurs in response to atrial extrastimulation. The intra-atrial and interatrial conduction intervals did not differ significantly. Among these parameters for atrial function, the conduction delay zone appeared to be the most useful for prediction of atrial vulnerability. The sensitivity and specificity to atrial vulnerability of the conduction delay zone ≥ 30 msec were 63% and 85% respectively. The reproducibility of the detection of atrial vulnerability was not always high, whereas zones for conduction delay and fragmented activity were reproduced by the extrastimulus method. Therefore, the parameters for atrial function were thought to be helpful in detecting atrial vulnerability, although individual parameters were not highly sensitive.

Conclusions and clinical implications

Both the incidence of AF and of atrial vulnerability were observed to be higher in the manifest WPW syndrome than in the concealed WPW syndrome, while the incidences in the intermittent WPW syndrome group was intermediate. Patients with intermittent preexcitation may have better prognoses than those with manifest preexcitation. Widening of the conduction delay zone was one of the predictors for atrial vulnerability, which was well correlated with clinical AF. AERP and retrograde ERP of the accessory pathway did not differ significantly between the three groups. The existence of a functioning accessory pathway may play an important role in the genesis of AF. Accordingly, the property of antegrade conduction over the accessory pathway appears to be responsible for the mechanism of the genesis of AF in the WPW syndrome.

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