Atrial Electrophysiologic Abnormalities in Patients with Wolff-Parkinson-White Syndrome but without Paroxysmal Atrial Fibrillation

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Summary

Background: Paroxysmal atrial fibrillation (PAF) frequently occurs in patients with Wolff-Parkinson-White (WPW) syndrome.

Hypothesis: The purpose of this study was to analyze the atrial electrophysiologic abnormalities and vulnerability to develop atrial fibrillation (AF) in patients with WPW syndrome but with no previous history of PAF.

Methods: We investigated atrial electrophysiologic abnormalities and vulnerability to AF in patients with WPW syndrome but without PAF. An electrophysiologic study was performed in 28 patients with WPW syndrome, 23 with atrioventricular nodal reentrant tachycardia (AVNRT) and 25 with other arrhythmias (control), all of whom had no history of PAF. The following atrial excitability parameters were assessed: effective refractory period (ERP), spontaneous or paced (A1) and extrastimulated (A2) atrial electrogram widths, percent maximum atrial fragmentation (%MAF; $A2/A1 \times 100$), wavelength index (WLI; $ERP/A2$), and inducibility of AF.

Results: The ERP tended to be shorter in patients with WPW syndrome and in those with AVNRT than in the control group. The %MAF increased (154 ± 33 vs. $137 \pm 23\%$, $p < 0.05$) and WLI decreased (2.7 ± 0.8 vs. 3.4 ± 1.0 , $p < 0.05$) significantly in patients with WPW syndrome compared with the control group; however, these parameters in patients with AVNRT showed intermediate values. Atrial fibrillation was more in-

ducible in patients with WPW syndrome ($4/28$ [14.3%]) than in those with AVNRT (4.3% [1/23]) and the control group (0/25 [0%]). With respect to patients with WPW syndrome and with and without inducible AF, the %MAF increased (195 ± 23 vs. $148 \pm 30\%$, $p < 0.01$) and the WLI decreased (2.2 ± 0.3 vs. 2.9 ± 0.9 , $p < 0.05$) in subjects with inducible AF.

Conclusions: Atrial electrophysiologic abnormalities, especially atrial conduction delays, are more prominent in patients with WPW syndrome, even if they had no previous history of PAF. These abnormalities may play an important role in determining the vulnerability to AF.

Key words: Wolff-Parkinson-White syndrome, atrial fibrillation, electrophysiology, atrial vulnerability, atrioventricular nodal reentrant tachycardia

Introduction

Paroxysmal atrial fibrillation (PAF) is a relatively common arrhythmia in patients with Wolff-Parkinson-White (WPW) syndrome,¹ and the atrial electrophysiologic abnormalities have been identified in those with associated PAF.² However, atrial electrophysiologic abnormalities in patients with WPW syndrome but without PAF are not fully elucidated, especially when compared with normal individuals. Several investigators have reported that ventricular fibrillation induced by PAF can be the first clinical event of the WPW syndrome.^{3,4} This study analyzes the atrial electrophysiologic abnormalities and vulnerability to develop atrial fibrillation (AF) in patients with WPW syndrome but with no previous history of PAF.

Methods

Patient Population

Seventy-six consecutive patients, who underwent electrophysiologic studies for syncope or tachycardia at our institute and who did not meet exclusion criteria, were enrolled in this study. Of these patients, 28 had WPW syndrome with documented atrioventricular reentrant tachycardia, 23 had docu-

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Received: August 8, 2003

Accepted with revision: October 27, 2003

mented atrioventricular nodal reentrant tachycardia (AVNRT) with dual atrioventricular nodal pathways, and the remaining 25 had other arrhythmias (idiopathic ventricular tachycardia [$n = 8$], atrioventricular nodal block [$n = 10$], and neurally mediated syncope [$n = 7$]). These 25 patients were matched with the other study patients with respect to age and gender and served as the control group. All patients underwent physical examination, resting electrocardiography (ECG), chest radiography, echocardiography, and routine hematologic and biochemical testing to exclude structural heart disease and conditions with potential effects on cardiac hemodynamic or electrophysiologic function. Exclusion criteria for the study were documented PAF, structural heart disease, congestive heart failure, hypertension, diabetes, electrolyte abnormalities, or a history of smoking, because these factors are known to influence vulnerability to develop AF.⁵ Written informed consent was obtained from all patients before enrollment in the study. The study was carried out during routine electrophysiologic study and, when necessary, before catheter ablation of the tachycardia.

Electrophysiologic Studies

All antiarrhythmic drugs were discontinued prior to the studies for at least five half-lives for each drug. Patients were studied in the fasting, nonsedated state, as previously described.⁶ A 5 Fr quadripolar electrode catheter with 5-mm spacing (DAIG) was inserted through the right femoral vein and positioned against the high right atrium. Atrial stimulation was delivered from the first and atrial electrograms recorded from the second electrode pair. Before initiating the stimulation protocol, 5000 IU of heparin was injected intravenously, followed by a continuous infusion of heparin at a rate of 1000 IU/h.

Stimulation was performed using 2-ms square wave impulses at an intensity twice the threshold level. Stimuli were delivered by a programmable stimulator (SEC-3102, Nippon Kodan, Inc., Tokyo, Japan). Intracardiac electrograms were recorded (gain: 2 mV/cm, filter: 30 to 500 Hz) with the use of an electrophysiologic recording system (Prucka Cardiolab 7000, GE Medical Systems Information Technologies, Inc.,

Milwaukee, Wis., USA). To determine the atrial vulnerability index as described below, programmed electrical stimulation using eight basic stimuli at a cycle length of 500 ms followed by extrastimuli was delivered. Basic stimuli and the corresponding atrial deflections were designated S1 and A1, respectively; S2 and A2 represent a single extrastimulus and the provoked atrial deflection, respectively. The S1–S2 interval was decreased by 10 ms until the extrastimulation failed to capture the atrium. In addition, programmed electrical stimulation with two extrastimuli (S2 and S3) was delivered to assess the inducibility of AF when AF was not induced by a single extrastimulus.

The following electrophysiologic indices of atrial vulnerability were assessed:⁶ (1) Percent maximum atrial fragmentation (%MAF) was calculated as the maximum width of A2 / width of A1 $\times$ 100. The width of A2 increases when the premature stimulation is given earlier in the cardiac cycle. The maximum width of A2 is therefore obtained at the shortest S1–S2 interval that can provoke A2.^{7,8} (2) Right atrial effective refractory period (ERP) was defined as the longest S1–S2 interval that does not provoke A2 in the high right atrium.⁸ (3) Wavelength index (WLI) was defined as the ratio of ERP / maximum width of A2.^{8–10} (4) Inducibility of AF was assessed by utilizing progressively more aggressive stimulation protocols using single or double extrastimulation and was defined as the development of AF with a duration of at least 1 min. When AF persisted for > 5 min (or degenerated into ventricular fibrillation), electrical cardioversion was performed.¹¹

Statistical Analysis

Continuous data are expressed as the mean $\pm$ SD and were analyzed by Student's *t*-test. Comparisons of categorical variables were performed using the chi-square test. A value of $p < 0.05$ was considered statistically significant.

Results

As shown in Table I, the clinical characteristics were similar among the patients with WPW syndrome, those with AVNRT, and the control group.

TABLE I Demographics and clinical characteristics of the study population

Variable	WPW (n = 28)	AVNRT (n = 23)	Control (n = 25)
Age (years)	50 $\pm$ 11 (22–72)	55 $\pm$ 18 (14–77)	53 $\pm$ 18 (15–84)
Male / female	14/14	11/12	14/11
CTR (%)	48 $\pm$ 5	47 $\pm$ 4	48 $\pm$ 4
LAD (mm)	34 $\pm$ 5	32 $\pm$ 6	33 $\pm$ 6
LVDd (mm)	48 $\pm$ 5	47 $\pm$ 6	46 $\pm$ 6
EF (%)	72 $\pm$ 7	73 $\pm$ 6	71 $\pm$ 5
PAC (beats/day)	91 $\pm$ 96	96 $\pm$ 106	89 $\pm$ 93

Values are reported as the mean $\pm$ SD (range) or number of patients (%).

Abbreviations: WPW = Wolff-Parkinson-White syndrome, AVNRT = atrioventricular nodal reentrant tachycardia, CTR = cardiothoracic ratio, LAD = left atrial diameter, LVDd = left ventricular end-diastolic diameter, EF = ejection fraction, PAC = premature atrial complex.

TABLE II Electrophysiologic characteristics of the study population

Variable	WPW (n = 28)	AVNRT (n = 23)	Control (n = 25)
Atrial vulnerability index			
A1 (ms)	62 ± 14	60 ± 18	60 ± 18
Max A2 (ms)	95 ± 26	86 ± 27	82 ± 27
%MAF (%)	154 ± 33 ^a (108–225)	145 ± 35 (106–262)	137 ± 23 (108–186)
ERP (ms)	242 ± 26 (180–280)	241 ± 44 (200–390)	256 ± 42 (180–360)
WLI	2.7 ± 0.8 ^a (1.8–4.7)	3.1 ± 0.9 (1.6–5.3)	3.4 ± 1.0 (1.9–6.2)
Induction of AF	4 (14.3)	1 (4.3)	0 (0)

Values are reported as the mean ± SD (range) or number of patients (%).

^a p < 0.05 versus control.

Abbreviations: %MAF = percent maximum atrial fragmentation, ERP = right atrial effective refractory period, WLI = wavelength index, AF = atrial fibrillation. Other abbreviations as in Table I.

The atrial electrophysiologic characteristics of the patients are summarized in Table II. The ERP tended to be shorter in patients with WPW syndrome and in those with AVNRT than in the control group (242 ± 26, 241 ± 44, 256 ± 42 ms, respectively); however, the difference was not statistically significant. The %MAF increased (154 ± 33 vs. 137 ± 23%, p < 0.05) and the WLI decreased (2.7 ± 0.8 vs. 3.4 ± 1.0, p < 0.05) in patients with WPW syndrome compared with the control group. However, these parameters in patients with AVNRT showed intermediate values (145 ± 35 and 3.1 ± 0.9%, respectively) between those with WPW syndrome and the control group. Atrial fibrillation was induced in four patients with WPW syndrome (14.3%), one patient with AVNRT (4.3%), and none of the patients in the control group, and was induced more frequently in patients with WPW syndrome than in those with AVNRT and the control group.

The 28 patients with WPW syndrome were classified into two groups based on the induction of AF (Table III). With respect to patients with and without inducible AF, the %MAF in-

creased (195 ± 23 vs. 148 ± 30%, p < 0.01) and WLI decreased (2.2 ± 0.3 vs. 2.9 ± 0.9, p < 0.05) in subjects with inducible AF, while the ERP showed no difference.

Discussion

Atrial Vulnerability Index in Patients with WPW Syndrome without Paroxysmal Atrial Fibrillation

The propensity for developing AF has been expressed electrophysiologically as atrial vulnerability, and several parameters, including the atrial refractory period, fragmented atrial activity, atrial conduction delay, repetitive atrial firing, WLI, and inducibility of AF, have been proposed as indices of atrial vulnerability.^{7–13} The %MAF and WLI have been reported to reflect the presence of conduction abnormalities⁸ and the minimum length of the reentrant circuit at that site,¹⁰ respectively. These parameters have also been reported to predict the occur-

TABLE III Comparison of WPW syndrome patients with and without inducible AF

Variable	WPW		p Value
	Inducible AF (n = 4)	Noninducible AF (n = 24)	
Age (years)	53 ± 16	49 ± 11	NS
Male / female	3 / 1	15 / 9	NS
LAD (mm)	35 ± 3	34 ± 5	NS
Electrophysiologic study			
Left-sided APs	1 (25)	11 (46)	NS
ERP of AP (ms)			
(anterograde)	281 ± 26	262 ± 44	NS
(retrograde)	264 ± 44	24 ± 42	NS
A1 (ms)	56 ± 17	62 ± 14	NS
Max A2 (ms)	110 ± 25	92 ± 26	NS
%MAF (%)	195 ± 23	148 ± 30	< 0.01
ERP of right atrium (ms)	240 ± 43	243 ± 24	NS
WLI	2.2 ± 0.3	2.9 ± 0.9	< 0.05

Values are reported as the mean ± SD (range) or number of patients (%).

Abbreviation: AP = accessory pathway. Other abbreviations as in Tables I and II.

rence of AF, although it is unclear whether the ERP predicts the occurrence of AF.^{7, 12, 14, 15} In patients with WPW syndrome and associated PAF, electrophysiologic abnormalities of the atrial muscle and atrial vulnerability have been identified.² However, it has not been determined whether these indices also reflect the inherent electrophysiologic properties of patients with WPW syndrome without PAF, especially compared with normal individuals.

In this study, the ERP tended to be shorter in patients with WPW syndrome without PAF than in the control group, while the %MAF increased and WLI decreased significantly, and AF was more likely to be induced. Thus, the electrical abnormalities of the atrium and the vulnerability to develop AF exist in patients with WPW syndrome, even those who have not experienced spontaneous AF. In those patients, atrial conduction delays are more prominent and could be a predisposing factor for the development of AF. The WLI can be divided into two components: conduction velocity and refractory period.¹⁶ The present study demonstrated that atrial conduction abnormalities contribute to the decrease in the WLI in patients with WPW syndrome without PAF. In comparison between patients with WPW syndrome with and without inducible AF, the %MAF increased and WLI decreased significantly in those with inducible AF, while there was no difference with respect to the ERP. These results indicate that the atrial conduction abnormalities are more important for the development of AF in patients with WPW syndrome without PAF. Previous studies have demonstrated that atrial conduction delays, but not the atrial refractory period, play an important role in the vulnerability to AF in patients with WPW syndrome with PAF,² which is consistent with our results.

Pathogenesis of Atrial Vulnerability in Patients with Wolff-Parkinson-White Syndrome without Paroxysmal Atrial Fibrillation

Several potential mechanisms are responsible for PAF in the setting of WPW syndrome. As previously reported, the accessory pathway plays an important role in the development of AF but may not be the only mediator because PAF is abolished in some patients, but not in others, after successful ablation.² It has been reported that accessory pathway-dependent and -independent atrial vulnerability exists in patients with WPW syndrome with PAF.² In addition, reciprocating tachycardia-induced hemodynamic changes may be responsible for increased atrial vulnerability.^{17, 18} In this study, we could not determine the exact pathogenesis of atrial vulnerability in patients with WPW syndrome without PAF, because we did not analyze the atrial vulnerability after ablation of the accessory pathways. However, atrial vulnerability was more prominent in patients with WPW syndrome without PAF than in the control group, but was not more prominent in patients with AVNRT, which suggests that the accessory pathway plays an important role in the development of atrial vulnerability. The persistent interaction between the normal AV pathway and the accessory pathway has been reported to result in asynchronous activation of the atria, which might

affect the development of atrial vulnerability.¹⁹ On the other hand, it is interesting that atrial vulnerability in patients with AVNRT showed an intermediate value between patients with WPW syndrome and the control group, which suggests that reciprocating tachycardias may also be responsible for some of the increasing atrial vulnerability.

Study Limitations

In this study, it was impossible to determine the long-term clinical significance of increased atrial vulnerability in patients with accessory pathways but without PAF, because successful radiofrequency catheter ablation was performed in all patients with WPW syndrome. However, our electrophysiologic findings suggest that patients with accessory pathways, even those who had no PAF, are at greater risk for developing AF.

The control group in this study had different types of arrhythmias or neurally mediated syncope. Although the effects of the underlying diseases on atrial vulnerability may not be negligible, this is a limitation common to many invasive studies.^{6, 7, 9, 10} It might be possible to have a control group of healthy people with noninvasive studies and parameters. The best would be to compare the invasive and noninvasive parameters; however, this was not feasible in our study.

Conclusions

To the best of our knowledge, this study provides the first comparison of atrial electrophysiologic abnormalities among patients with WPW syndrome, those with AVNRT, and normal individuals, all of whom had no previous PAF. Atrial electrophysiologic abnormalities, especially atrial conduction delays, were more prominent in patients with WPW syndrome but without PAF, and it may play an important role in determining the vulnerability to AF. Thus, patients with WPW syndrome are at greater risk for developing AF, even if they had no previous PAF.

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