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The Mechanism of Atrial Fibrillation in Patients with Wolff-Parkinson-White Syndrome —Importance of Atrial Vulnerability in the Right Atrium—

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Summary. **The sites of atrial fibrillation genesis and electrophysiological parameters of the atria were evaluated in 24 patients with Wolff-Parkinson-White (WPW) syndrome with induced atrial fibrillation in an electrophysiologic study. The twenty-four patients, 8 females and 16 males had a mean age of 42±16 years. Atrial electrogram was recorded at three atrial sites during the initiation of atrial fibrillation: the high right atrium (HRA), the His bundle electrogram recording site (HBE), and the coronary sinus (CS). The site of atrial fibrillation genesis was determined as the recording site that first showed fragmented atrial electrogram at the time atrial fibrillation occurred. Atrial fibrillation was generated from the HRA site in 15/24 patients, the HBE site in 6/24 patients, and the CS site in 3 patients. Atrial effective refractory period (AERP), atrial wave duration at the HRA site (A1), prolongation of atrial wave during premature beat at the HRA site (%A2/A1), prolongation of atrial wave duration at the CS site during retrograde excitation of the atrium (% Cret/Cant), antegrade and retrograde effective refractory period of the accessory pathway (Kant-ERP, Kret-ERP), and wavelength index (WLI) were evaluated in each patient. Only the %A2/A1 and WLI were significantly different among the groups with different sites of atrial fibrillation genesis. Atrial vulnerability of the HRA site was highest in patients with HRA genesis of atrial fibrillation as represented by the largest %A2/A1 and shortest WLI at the HRA recording site. Although different types of atrial fibrillation might occur, the HRA site is considered to play an important role in initiating atrial fibrillation in patients with WPW syndrome.**

Key words—atrial fibrillation, WPW syndrome, atrial vulnerability, atrial fibrillation genesis.

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INTRODUCTION

Atrial fibrillation may result in life-threatening conditions causing ventricular fibrillation in patients with Wolff-Parkinson-White (WPW) syndrome, especially in cases with a critically short effective refractory period of antegrade atrio-ventricular conduction via an accessory pathway.[1-6] The incidence of atrial fibrillation in patients with WPW syndrome is reportedly higher than that in the total population[7-10] but the mechanism of occurrence for atrial fibrillation in WPW syndrome is unclear. It has been reported that retrograde conduction through the accessory pathway plays an important role in initiating atrial fibrillation because the occurrence of atrial fibrillation is frequently observed during atrioventricular reciprocating tachycardia or after premature ventricular contractions.[11-14] The following mechanisms account for this: 1) anisotropic conduction in the local atrial muscle close to the atrial breakthrough of the accessory pathway, i.e., different conduction properties during sinus rhythm and reciprocating tachycardia; and 2) collision of the atrial excitation wave front of the sinus rhythm with another atrial excitation wave front from the accessory connection.[10,11,13,15] These conditions may cause inhomogeneous atrial depolarization and repolarization, which may result in random atrial reentry, i.e., atrial fibrillation. However, it has been shown that the accessory connection itself may modify the atrial electrophysiologic properties, e.g, shorten the atrial wavelength, although the mechanism is uncertain.[16,17] However, in either explanation, the "site of genesis" of atrial fibrillation remains uncertain.[18] In the present study, the initia-

tion site of atrial fibrillation was evaluated in patients with induced atrial fibrillation during an electrophysiologic study to investigate whether the atrial muscle close to the atrial connection of the accessory pathway plays a role in the "genesis" of atrial fibrillation in WPW syndrome.

METHODS

Patients

The study population consisted of 24 patients with WPW syndrome who showed induced atrial fibrillation during the electrophysiologic study. Subjects were 24 of 127 consecutive patients with WPW syndrome who underwent electrophysiologic study at our hospital between May 1992 and June 1996. Patients with an episode of spontaneous electrocardiographically documented atrial fibrillation (13/127 patients) were not included among the 24 patients because they were considered to have potentially higher atrial vulnerability than patients without spontaneous atrial fibrillation. No structural heart disease was present in any of the 24 patients. The mean age was 42 ± 16 years (range from 16 to 67), and 16 were male and 8 were female. Of the 24 patients, 18 showed manifest antegrade accessory pathway conduction, i.e., classical WPW syndrome, with left sided accessory connection (type A) in 9 patients and right sided (type B) in 9 patients. The remaining 6 patients had concealed WPW syndrome (Table 1). A later electrophysiologic study revealed that all 6 patients with concealed WPW syndrome had left sided accessory pathways. All patients had at least one episode of supra-ventricular tachycardia with narrow QRS configuration and regular rhythm on a surface twelve-lead electrocardiogram.

Electrophysiologic study

Electrophysiologic studies were performed in both fasting and non-sedated states after obtaining informed consent from each patient. All antiarrhythmic drugs were discontinued at least 5 half-lives before th procedure. Through the femoral vein, two 6F quadripolar electrode catheters (Josephson multipurpose catheter, USCI Division of. C.R. Bard, Billerica, Mass.) were positioned against the high right atrium (HRA) close to the sinus node and the right ventricular apex. They were used for stimulation and recording of the intracardiac electrograms. To record His bundle electrogram (HBE), one 6F tripolar electrode catheter (USCI Division of C.R. Bard, Billerica, Mass.) was introduced through the same site. An additional 6F quadripolar electrode catheter was introduced through the right internal jugular vein and was positioned in the coronary sinus (CS) to record atrial and ventricular electrograms of the left posterior side of the heart. This CS catheter was used for mapping the accessory pathway location in the left posterior area of the heart in patients with left-sided accessory connection. Even in patients with right-sided accessory connection, this CS catheter was applied to exclude the existence of an additional accessory connection on the left side of the heart. Electrical stimulation was delivered by a programmable cardiac stimulator (BCO20, Fukuda-Denshi Co., Ltd., Tokyo. Japan) at twice the diastolic threshold with a 2 msec rectangular pulse. Intracardiac electrograms were recorded on an ink-jet recorder (Mingograf 82, Siemens Elema Co., Ltd., Solna, Sweden) with three surface leads, i.e., I, II, V_1, at a paper speed of 100 or 200 mm/sec. The band-pass filter was set at 50 to 300 Hz. These data were simultaneously recorded on magnetic tape by a data recorder (XR-5000, TEAC Co., Ltd., Tokyo, Japan), and were retrieved on a thermal recorder (Thermal recorder RF-85, Fukuda-Denshi Co., Ltd.).

Electrophysiologic parameters

Atrial effective refractory period (AERP) was determined as the longest delivered coupling interval of atrial extrastimulus that failed to capture the atrium. Single atrial extrastimuli were delivered at the HRA site after an 8-beat atrial train at a cycle length of 600 msec. *Duration of atrial wave* was measured at HRA and CS sites (Fig. 1). At the HRA site, bipolar atrial electrogram was recorded between 10 mm spacing electrodes on the electrode catheter. Control atrial wave duration *(A1)* was measured during basic atrial stimuli at a cycle length of 600 msec. Atrial wave duration during atrial extrastimulation was also measured, the longest duration of atrial wave obtained during atrial extrastimulation being defined as *A2*, and always observed during the extrastimulus with the shortest delivered coupling interval. Maximal prolongation of the atrial wave at the HRA site during atrial extrastimulation was represented by *% A2/A1* ratio.[19,20] At the CS site, atrial wave duration during antegrade excitation *(Cant)* was measured during the basic atrial stimulation at the HRA site at a cycle length of 600 msec. Recording of the atrial electrogram at this CS site was performed between the electrodes closest to the accessory pathway location. In patients with right-sided accessory connection, atrial electrogram recording at the CS site was performed between the distal pair of electrodes on

Table 1. Clinical characteristics of patients

No.	Sex/Age	Type of AcP	Atrial Genesis	Pacing site or Tachycardia
1	F/46	A-WPW	CS	AVRT
2	M/53	A-WPW	HRA	AVRT
3	M/45	A-WPW	HRA	AVRT
4	M/49	A-WPW	HRA	AVRT
5	F/53	A-WPW	HBE	AVRT
6	F/16	A-WPW	HBE	HRA
7	M/16	A-WPW	HRA	HRA
8	M/62	A-WPW	CS	AVRT
9	F/22	A-WPW	HRA	HRA
10	M/47	B-WPW	HRA	HRA
11	M/34	B-WPW	HRA	HRA
12	M/31	B-WPW	HRA	HRA
13	F/67	B-WPW	HRA	HRA
14	M/45	B-WPW	HRA	HRA
15	M/64	B-WPW	HBE	HRA
16	M/37	B-WPW	HBE	HRA
17	M/38	B-WPW	HBE	HRA
18	M/47	B-WPW	HBE	HRA
19	M/17	C-WPW	HRA	HRA
20	M/54	C-WPW	HRA	HRA
21	F/19	C-WPW	HRA	AVRT
22	F/58	C-WPW	HRA	AVRT
23	M/36	C-WPW	CS	RVA
24	F/61	C-WPW	HRA	AVRT
	42±16 years	A-WPW 9	HRA 15	AVRT 9
	8 Female	B-WPW 9	HBE 6	HRA 14
	16 Male	C-WPW 6	CS 3	RVA 1

Acp, accessory pathway; A-WPW, type A WPW; B-WPW, type B WPW; C-WPW, concealed WPW; HRA, high right atrium, HBE; His bundle electrogram recording site; CS, coronary sinus; AVRT, atrioventricular reentrant tachycardia; RVA, right ventricular apex.

the electrode catheter. Atrial wave duration during retrograde excitation *(Cret)* was measured during reciprocating atrioventricular tachycardia or ventricular pacing through the catheter positioned at the right ventricular apex. The prolongation of the atrial wave at the CS recording site caused by anisotropic conduction during retrograde ecxcitation was represented by *%Cret/Cant* ratio. The effective refractory period of antegrade conduction through the accessory pathway *(Kant-ERP)* was determined as the longest recorded atrial coupling interval that failed to conduct through the accessory pathway. The atrial coupling interval was measured at the atrial recording site closest to the accessory pathway location. Effective refractory period of retrograde conduction through the accessory pathway *(Kret-ERP)* was determined as the longest ventricular coupling interval that failed to conduct retrogradely through the accessory pathway. The ventricular coupling interval was measured at the CS recording site in patients with left-sided accessory pathway. In patients with right-sided accessory pahtway, the delivered ventricular stimulus coupling interval was used as the ventricular coupling interval. Wavelength index *(WLI)* at the HRA site was determined as the AERP/A2 ratio.[21-23] Occurrence of atrial fibrillation

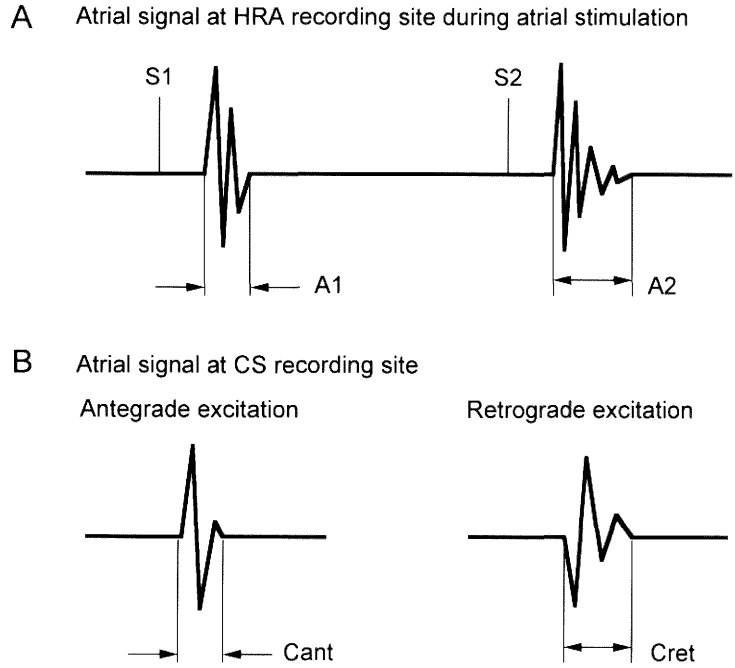

Fig. 1. Measurement of atrial wave duration. Panel A shows a schematic representation of the measurement of atrial wave duration at the HRA site. S1 ad S2 indicate basic and premature atrial stimulation. Prolongation of atrial wave duration during premature stimulus was calculated as %A2/A1. Panel B shows a schematic representation of the measurement of atrial wave duration at the CS site. "Cant" and "Cret" indicate atrial wave duration during antegrade and retrograde excitation, respectively. Prolongation of atrial wave duration during retrograde excitation was calculated as % Cret/Cant. See text for discussion.

was determined by the appearance of continuous fragmented atrial electrogram at one of three atrial recording sites, i.e., HRA, HBE, and CS. *The site of atrial fibrillation genesis* was determined as the atrial recording site that first showed fragmented atrial electrogram at the time atrial fibrillation occurred.

Comparison of electrophysiologic parameters

The twenty-four patients were divided into three groups according to the type of accessory pathway: 1) manifest WPW syndrome with left-sided accessory connection; 2) manifest WPW syndrome with right-sided accessory connection; or 3) concealed WPW syndrome (The accessory pathway being located in the left side of the heart in all cases in this study). The electrophysiologic parameters described above were then compared among the three groups. Additionally, these 24 patients were divided into three groups according to the "site of atrial fibrillation genesis": 1) HRA gensis, 2) HBE genesis, or 3) CS genesis, and parameters were compared among these groups.

Statistics

All values were expressed as mean±standard deviation. Statistical analysis was performed with one-way ANOVA test or with χ^2 test. A p value of <0.05 was considered significant.

RESULTS

In the electrophysiologic study, atrial fibrillation was initiated during atrioventricular reentrant tachycardia in 9 patients, during atrial pacing at the HRA pacing site in 14 patients, and during ventricular

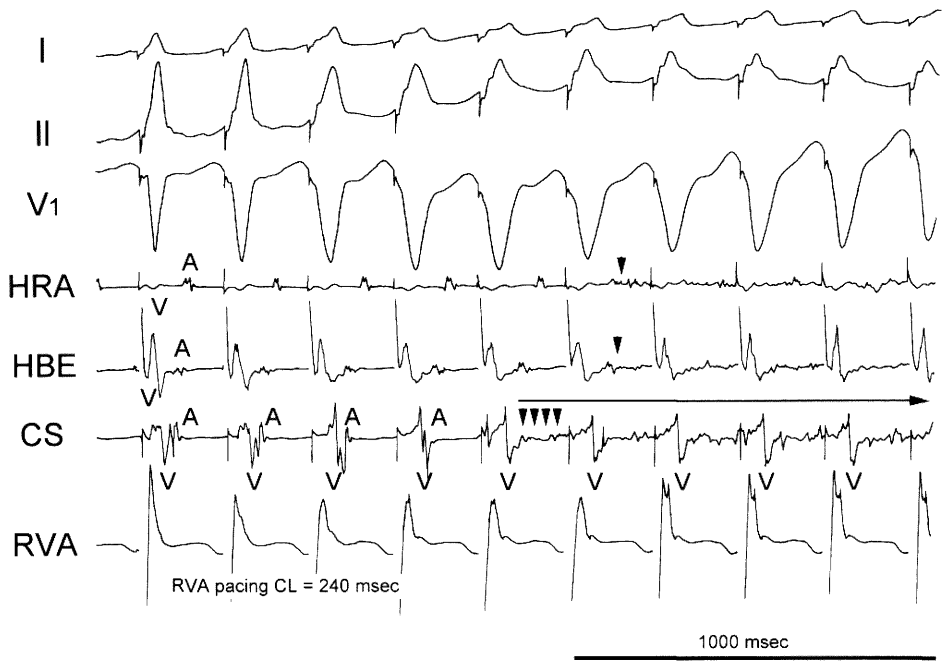

Fig. 2. Initiation of atrial fibrillation by ventricular pacing during atrioventricular reentrant tachycardia. Ventricular pacing at a cycle length of 240 msec was performed during atrioventricular reentrant tachycardia with a cycle length of 260 msec. Atrial fibrillation appeared during pacing and lasted even after pacing stopped (represented by the long horizontal arrow). The site of atrial fibrillation genesis was localized at the CS site because a fragmented atrial electrogram was first observed at this site (indicated by four arrow heads). Following this, fragmented atrial electrogram appeared at the HRA and HBE sites. See text for discussion. I, II, V_1, surface electrocardiogram leads; HRA, high right atrium; HBE, His bundle electrogram recording site; CS, coronary sinus; A, atrial wave; V, ventricular electrogram; RVA, right ventricular apex; CL, cycle length.

pacing at the right ventricular apex pacing site in 1 patient. All episodes of atrial fibrillation in each patient spontaneously terminated after lasting 3 to 17 min. The site of atrial fibrillation genesis was localized at the HRA site in 15 patients, at the HBE site in 6 patients, and the CS site in 3 patients (Table 1).

Fig. 2 shows a representative example of the initiation of atrial fibrillation during atrioventricular reentrant tachycardia (case 1 in Tables 1 and 2). Ventricular pacing with a fixed cycle length of 240 msec was performed at the right ventricular apex pacing site. From the first beat to the fifth beat in this Figure, the QRS morphology gradually changes in the surface ECG leads, indicating that paced ventricular beats fusing with tachycardia beats via the His-Purkinje system gradually captured a larger area of both ventricles, and then finally fully captured the ventricles at the fifth beat. Up to the fourth beat, atrial wave could be identified at all of the HRA, HBE and CS recording sites. At the fifth beat, a fragmented atrial electrogram appeared at the CS recording site (indicated by four arrow heads), then a similar atrial fragmented electrogram appeared at the HRA and the HBE recording sites from the sixth beat. After stopping the ventricular pacing atrioventricular reentrant tachycardia was not observed but atrial fibrillation continued, although not shown in the Figure. In this case, the site of atrial fibrillation genesis was considered the CS site because the fragmented atrial electrogram was first observed at the CS recording site.

Fig. 3 shows a representative example of the initiation of atrial fibrillation during atrial pacing at the HRA pacing site (case 6 in Tables 1 and 2). In this case, atrial pacing was performed during sinus rhythm with an eight-beat basic drive train at a cycle length of 400 msec followed by an atrial premature stimulus with a coupling interval of 180 msec. Sur-

Table 2. Electrophysiologic parameters of atrial excitation

No.	AERP (msec)	A1 (msec)	%A2/A1 (%)	%Cret/Cant (%)	Kant-ERP (msec)	Kret-EPR (msec)	WLI (cm)
1	200	55	145	111	250	280	2.50
2	230	75	167	130	280	320	1.84
3	220	70	164	125	270	300	1.91
4	230	75	147	120	240	270	2.09
5	210	60	142	87	280	290	2.47
6	200	90	122	117	290	340	1.82
7	250	80	131	117	290	330	2.38
8	210	45	156	118	290	300	3.00
9	240	75	153	117	240	290	2.09
10	230	60	175	91	270	280	2.19
11	230	70	157	109	250	290	2.09
12	210	70	142	121	240	260	2.10
13	190	55	173	91	230	240	2.00
14	220	40	213	150	260	290	2.59
15	280	85	124	90	270	340	2.67
16	210	95	105	94	280	330	2.10
17	270	60	142	89	250	280	3.18
18	220	80	131	108	270	290	2.10
19	220	75	140	133	-	290	2.10
20	190	80	138	110	-	320	1.73
21	200	75	167	111	-	270	1.60
22	240	75	160	143	-	310	2.00
23	220	80	125	92	-	300	2.20
24	240	65	177	130	-	280	2.09
	223	70	150	113	264	295	2.20
	±23	±13	±23	±18	±19	±25	±0.38

AERP; atrial effective refractory period; A1, A wave duration during basic drive train; %A2/A1, % prolongation of A wave duration during atrial extrastimulus; %Cret/Cant, % prolongation of A wave at coronary sinus recording site comparing between antegrade and retrograde excitation; Kant-ERP, effective refractory period of antegrade conduction via accessory pathway; Kret-ERP, effective refractory period of retrograde conduction via accessory pathway; WLI, wavelength index at HRA recording site. See text for discussion.

face ECG leads showed wide QRS morphologies, indicating that atrioventricular conduction through the accessory pathway captured a larger ventricular area in comparison wiht that through the atrioventricular node. Following the atrial premature beat, fragmented atrial electrogram appeared at the HBE recording site, with atrial fibrillation then initiated. In this case, the site of atrial fibrillation genesis was considered the HBE site because the fragmented atrial electrogram was first observed at the HBE recording site.

Data from all 24 patients are summarized in Tables 1 and 2. In total, atrial fibrillation was initiated during atrioventricular reentrant tachycardia in 9 patients, during the HRA pacing in 14, and during right ventricular apex pacing in 1. The site of atrial fibrillation genesis was localizes at the HRA site in 15, at the HBE site in 6 and at the CS site in 3. Atrial pacing site of atrial penetration of atrial fibrillation initiating pulses, i.e., the CS site during atrioventricular reentrant tachycardia or right ventricular pacing, coincided with the site of atrial fibrillation genesis in 12 patients, i.e., the HRA site in 10 and the CS site in 2 patients. Atrial effective refractory period (AERP) determined at the HRA site was 223±23 msec (range from 190 to 280). The duration of the

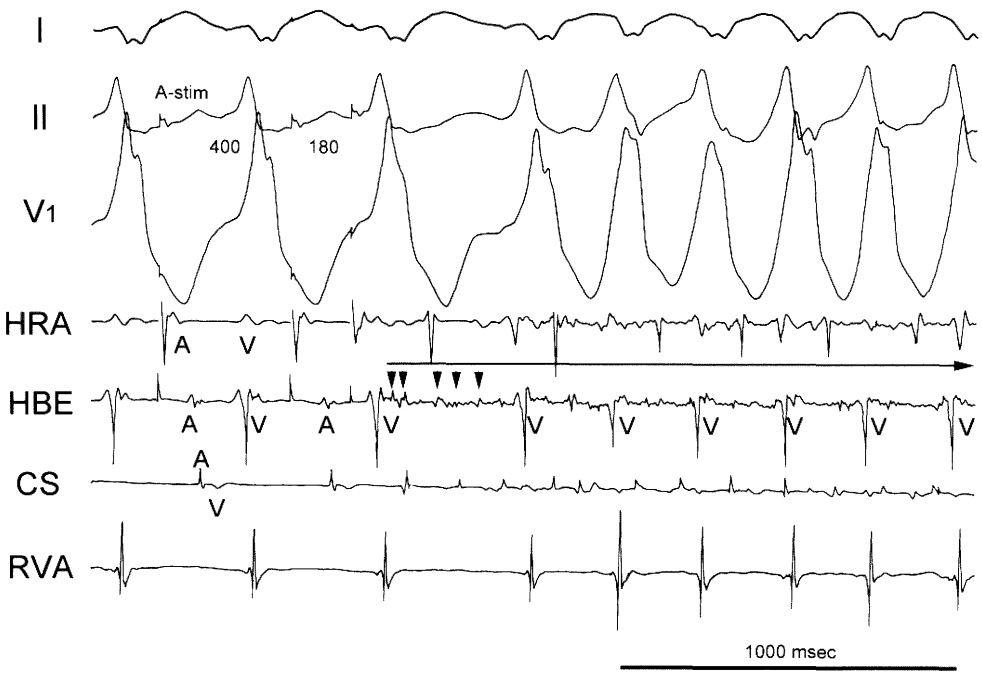

Fig. 3. Initiation of atrial fibrillation during atrial pacing at the HRA pacing site. Following programmed atrial stimulation at the HRA site (8 basic beats at a cycle length of 400 msec and a premature stimulus with a coupling interval of 180 msec), atrial fibrillation appeared (indicated by long horizontal arrow). The site of atrial fibrillation genesis was localized at the HBE site because fragmented atrial electrogram was first observed at this site (indicated by arrow heads). See text for discussion. I, II, V_1, surface electrocardiogram leads; HRA, high right atrium, HBE, His bundle electrogram recording site, CS, coronary sinus; A, atrial wave; V, ventricular electrogram; A-stim, atrial stimulation.

Table 3. Comparison of groups with different types of accessory pathway

	A-WPW	B-WPW	C-WPW	p value
Patient	9	9	6	
Sex	4 female/5 male	1 female/8 male	3 female/3 male	0.1175
Age (years)	40±5	46±13	41±20	0.7640
Genesis	HRA 5, HBE 2, CS 2	HRA 5, HBE 4	HRA 5, CS 1	0.1743
AERP (msec)	221±18	229±29	218±20	0.6496
A1 (msec)	69±14	68±17	75±5	0.6346
%A2/A1 (%)	147±15	151±32	142±18	0.9328
%Cret/Cant (%)	116±12	105±20	120±19	0.2251
Kant-ERP (msec)	270±21	258±16	-	0.1905
Kret-ERP (msec)	302±23	289±31	295±19	0.5527
WLI (cm)	2.23±0.39	2.33±0.39	2.10±0.49	0.1489

A-WPW, type A WPW; B-WPW, type B WPW; C-WPW, concealed WPW; HRA, high right atrium; HBE, His bundle electrogram recording site; CS, coronary sinus; AERP, atrial effective refractory period; A1, A wave duration during basic drive train; %A2/A1, % prolongation of A wave duration during atrial extrastimulus, %Cret/Cant; % prolongation of A wave at coronary sinus recording site comparing between antegrade and retrograde excitation; Kant-ERP, effective refractory period of antegrade conduction via accessory pathway; Kret-ERP; effective refractory period of retrograde conduction via accessory pathway; WLI, wavelength index at HRA recording site. See text for discussion.

Table 4. Comparison of groups with different genesis of atrial fibrillation

	CS	HBE	HRA	p value
Patient	3	6	15	
Sex	1 female/2 male	2 female/4 male	5 female/10 male	1.0000
Age (years)	48±13	43±16	41±17	0.8096
Type of AcP	A2, C1	A2, B4	A5, B5, C5	0.1743
AERP (msec)	210±10	232±34	223±18	0.4094
A1 (msec)	60±18	78±15	69±11	0.1317
%A2/A1 (%)	142±16	128±14	156±22	0.0049*
%Cret/Cant (%)	107±13	97±12	120±17	0.0518
Kant-ERP (msec)	270±28	273±14	257±20	0.2501
Kret-ERP (msec)	293±12	312±28	289±24	0.1873
WLI (cm)	2.57±0.40	2.39±0.49	2.11±0.34	0.0284*

ACP, accessory pathway; A, type A WPW; B, type B WPW; C, concealed WPW; HRA, high right atrium; HBE, His bundle electrogram recording site; CS, coronary sinus; AERP, atrial effective refractory period; A1, A wave duration during basic drive train; %A2/A1, % prolongation of A wave duration during atrial extrastimulus; %Cret/Cant, % prolongation of A wave at coronary sinus recording site comparing between antegrade and retrograde excitation, Kant-ERP, effective refractory period of antegrade conduction via accessory pathway, Kret-ERP, effective refractory period of retrograde conduction via accessory pathway, WLI, wavelength index at HRA recording site. *means statistically significant. See text for discussion.

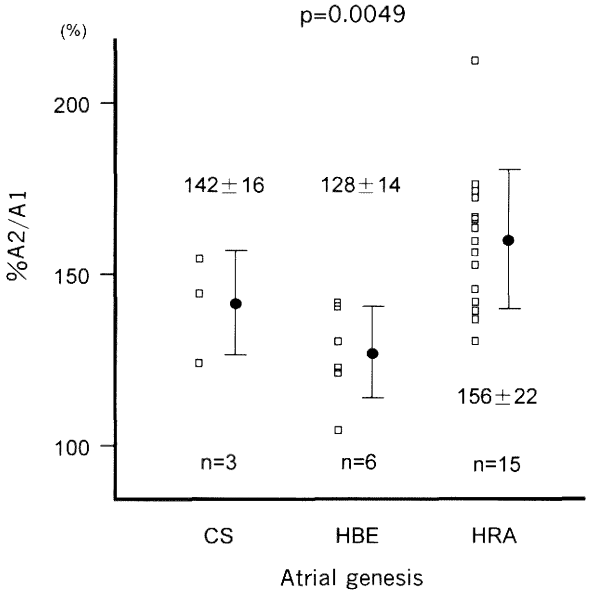

Fig. 4. Comparison of prolongation of atrial wave duration during atrial extrastimulus among the groups with different sites of atrial fibrillation genesis. Vertical axis indicates % prolongation of atrial wave duration during atrial extrastimulus (%A2/A1) at the HRA pacing site. Open squares represent %A2/A1 in each patient in each group. Mean ± standard deviation and number of patients in each group are shown in the Figure. %A2/A1 was larger in the HRA genesis group than in HBE genesis group (p=0.0049). See text for discussion. HRA, high right atrium, HBE, His bundle electrogram recording site, CS, coronary sinus. *indicates significance.

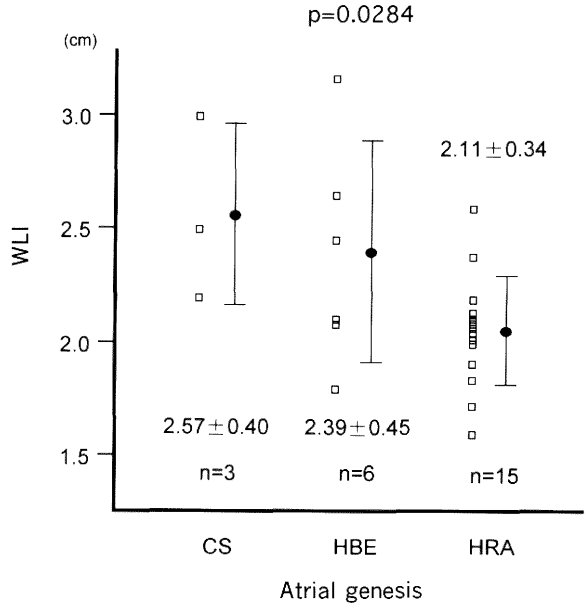

Fig. 5. Comparison of wavelength index among the groups with different sites of genesis of atrial fibrillation. Vertical axis indicates wavelength index (WLI) evaluated at the HRA pacing site. Open squares represent %A2/A1 in each patient in each group. Mean ± standard deviation and number of patients in each group are shown in the Figure. WLI was shortest in the HRA genesis group in comparison with the other two groups (p=0.0284). See text for discussion. HRA, high right atrium; HBE, His bundle electrogram recording site; CS, coronary sinus. *indicates significance.

atrial wave at the HRA site during the basic drive train (A1) was 70±13 msec (range from 40 to 95). The maximal prolongation of the atrial wave during premature stimulus at the HRA site (%A2/A1) was 148±23% (range from 105 to 213). The degree of atrial wave prolongation during premature stimulus was consistent with previously reported results in patients without documented episodes of spontaneous atrial fibrillation.[19,20] Prolongation of atrial wave duration at the CS site (%Cret/Cant) during retrograde excitation, i.e., during atrioventricular reentrant tachycardia or during ventricular pacing in comparison with that during antegrade excitation, i.e., during the sinus rhythm, was 113±18% (range from 87 to 150). Actually, atrial wave duration at the CS site was prolonged in 17 patients, and was shortened in the remaining 7 patients during retrograde excitation in comparison with that during antegrade excitation. The effective refractory period of antegrade conduction through the accessory pathway (Kant-ERP) was 264±19 msec (range from 230 to 290) in 18 patients with manifest WPW syndrome. Retrograde conduction through the accessory pathway was observed in all 24 patients. The effective refractory period of retrograde conduction through the accessory pathway (Kret-ERP) was 295±25 msec (range from 240 to 340). The wavelength index (WLI) at the HRA site was 2.24±0.41 cm (range from 1.60 to 3.18). These values of WLI approximately accorded with values in previous reports which used the same formula to calculate the WLI.[22]

Comparison among groups with different types of atrioventricular accessory connection

All data described above were compared among groups with different types of atrioventricular accessory pathways, and the results are summarized in Table 3. As shown in Table 3, none of the parameters showed significant differences among groups with different types of accessory connection. However, the site of atrial fibrillation genesis was not localized at the CS site in the B-WPW group, i.e., the patients with the right-sided accessory pathway.

Comparison among the groups with different sites of genesis of atrial fibrillation

All data studied were compared among the groups with different sites of atrial fibrillation genesis, and the results are summarized in Table 4. None of the parameters showed significant differences among the groups except for %A2/A1, i.e., % maximal prolongation of atrial wave duration during atrial premature stimulus, and wavelength index (WLI) at the HRA site.

Fig. 4 shows comparisons of %A2/A1 among groups with different sites of atrial fibrillation genesis. %A2/A1 was 142±16 msec in the group with CS genesis, 128±14 msec in the group with HBE genesis, and 156±22 msec in the group with HRA genesis. The group with HRA genesis showed the largest % A2/A1, this being significantly larger than that of the group with HBE genesis. This indicates that the HRA site has a higher atrial vulnerability in patients with HRA genesis of atrial fibrillation in comparison to that in patients with other sites of atrial fibrillation genesis.

Fig. 5 presents a comparison of WLI among the groups with different sites of atrial fibrillation genesis. WLI was 2.57±0.40 cm in the group with CS genesis, 2.39±0.45 cm in the group with HBE genesis, and 2.11±0.34 cm in the group with HRA genesis. The group with HRA genesis showed significantly shorter WLI than the other two groups. Similar to % A2/A1, this indicates that the HRA site in patients with HRA genesis of atrial fibrillation has an intrinsically higher atrial vulnerability related to atrial fibrillation than that in those patients with the other sites of atrial fibrillation genesis.

DISCUSSION

There are several reports which have evaluated factors relating to the occurrence of atrial fibrillation in patients with WPW syndrome.[1-15] It has been suggested that the retrograde conduction through the accessory pathway is important to initiate atrial fibrillation as a result of inhomogeneous depolarization in both atria.[11-14] Additionally, a short effective refractory period of the accessory pathway has also been suggested to be related to the occurrence of atrial fibrillation in those patients.[11,13] However, atrial "genesis" of atrial fibrillation was not studied in these reports. In the present study, we evaluated the site of atrial fibrillation genesis and its possible related parameters in patients with WPW syndrome.

Patient population

For the study population, we selected patients with WPW syndrome with an episode of induced atrial fibrillation in an electrophysiologic study, though patients with an episode of electrocardiographically documented spontaneous atrial fibrillation were excluded. For the present study, induced atrial fibrillation during the electrophysiologic study was neces-

sary to evaluate the site of atrial fibrillation genesis. As described in the methods, 13/127 patients with WPW syndrome had an episode of clinically documented atrial fibrillation, but atrial fibrillation was induced during electrophysiologic study in 8/13 patients. Although the site of atrial fibrillation genesis could also be determined in those 8 patients, we did not include them in our study population because patients with a spontaneous episode of atrial fibrillation could be expected to show a potentially higher atrial vulnerability to atrial fibrillation, i.e., a shorter wavelength and larger prolongation of atrial wave duration during premature atrial stimulation.[21,22] Thus we decided that they should not be assessed along with patients without a spontaneous episode of atrial fibrillation.

Electrophysiological characteristics of accessory pathway

It has been reported that the shorter effective refractory period of accessory pathway is associated with the initiation of atrial fibrillation in patients with WPW syndrome.[12,13] In the present study, the effective refractory period of the accessory pathway in patients with induced atrial fibrillation during the electrophysiologic study was not compared with that of patients without induced atrial fibrillation, but the mean effective refractory period of antegrade or retrograde conduction of the accessory pathway was comparable with that of other patients with WPW syndrome.[15,16] Actually, only 4 of 18 patients in this study showed a critically short effective refractory period of antegrade conduction of accessory pathway (<250 msec).

Electrophysiological characteristics of the site of atrial insertion of accessory pathway

It has been suggested that anisotropic conduction at the site of atrial insertion of the accessory pathway plays a role in initiating atrial fibrillation in patients with WPW syndrome.[10-14] If this is the case, the site of atrial insertion of accessory connection would be the site of atrial fibrillation genesis. However, the CS site, i.e., the recording site close to the site of atrial insertion of the accessory pathway in patients with type A WPW syndrome or patients with concealed WPW syndrome, proved to be as the site of genesis of atrial fibrillation in only 3/15 patients. Furthermore, %Cret/Cant, considered to reflect anisotropic conduction at the CS recording site, showed no significant difference among the groups with different sites of atrial fibrillation genesis (Table 4).

Importance of the HRA site in atrial fibrillation genesis

Of the three sites in the atria evaluated in the present study, i.e., HRA, HBE, and CS sites, the HRA site most frequently played a role in the genesis of atrial fibrillation in all groups with different types of accessory pathway, i.e., 5/9 with type A WPW syndrome, 5/9 with type B WPW syndrome, and 5/6 with concealed WPW syndrome (Table 3). This indicates that the HRA site may be the most vulnerable in initiating atrial fibrillation. It has to be mentioned that 9/15 patients with HRA genesis of atrial fibrillation showed their episodes of induced atrial fibrillation during atrial pacing at the HRA pacing site (Table 1). However, in the remaining 6 patients with HRA genesis of atrial fibrillation, atrial fibrillation was induced during pacing at the different sites, or during atrioventricular reentrant tachycardia, so that the HRA site seems to have the highest vulnerability in relation to the occurrence of atrial fibrillation. According to the results of our study, wavelength index (WLI) was shorter and prolongation of atrial wave duration during atrial premature beat (%A2/A1) was greater at the HRA recording site in patients with HRA genesis of atrial fibrillation in comparison to those in patients with other sites of genesis. These findings also suggest that the HRA site is most vulnerable in patients with HRA genesis of atrial fibrillation. In reports from other investigators, the specific vulnerability of the HRA site was suggested.[17] In a canine model of atrial fibrillation, it has been shown that the HRA site or the central area of the right atrial free wall worked as the genesis of atrial fibrillation during pacing at either site in the both atria or during preceding atrial tachycardia.[24-27] Because of the anatomical basis, i.e., the existence of pectinate muscles and crista terminalis, the HRA area or the central area of the right atrium shows a highly different anisotropic conduction during ectopic atrial beats compared to that during normal sinus rhythm.[24-27] Additionally, ectopic atrial beats may easily cause a conduction block in this area, resulting in the formation of a small reentrant circuit which can initiate atrial fibrillation.

Limitations

In the present study, the episode of induced atrial fibrillation was evaluated only once in each patient, so that reproducibility in determining the site of atrial fibrillation genesis was not confirmed. Also, the number of atrial sites evaluated in the present study was limited to only the HRA, HBE, and CS sites, so

that the actual site of atrial fibrillation genesis might have been misinterpreted. These problems would be solved by obtaining high density recordings in the atria and inducing atrial fibrillation several times in the same patient. The clinical significance of induced atrial fibrillation only in an electrophysiologic study also remains unclear. We eliminated patients with clinically documented episodes of atrial fibrillation for the reason described above, but the site of atrial fibrillation genesis should be studied during the occurrence of spontaneous atrial fibrillation if possible.

CONCLUSIONS

The site of atrial fibrillation genesis and electrophysiological parameters of the atria were evaluated in 24 patients with WPW syndrome with induced atrial fibrillation in an electrophysiologic study. The HRA site appeared to be the site of atrial fibrillation genesis in 15/24 patients, the HBE site in 6/24 patients, and the CS site in 3/24 patients. The site of atrial insertion of the accessory pathway played a role in the genesis of atrial fibrillation in only 3/15 patients. Atrial vulnerability of the HRA site was highest in patients with HRA genesis of atrial fibrillation represented by the largest prolongation of atrial wave duration during premature stimulus (%A2/A1) and shortest WLI at the HRA recording site. Although there might be different types of atrial fibrillation occurrence, the HRA site is considered to play an important role in initiating atrial fibrillation in patients with WPW syndrome.

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