Importance of Retrograde Atrial Activation in Atrial Fibrillation Genesis in the Initiation of Atrial Fibrillation in Wolff-Parkinson-White Syndrome

Comparison of Atrial Electrophysiologic Parameters between Patients with Different Atrial Fibrillation Genesis (Initiation Sites) in Atria

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SUMMARY

The changes in the duration of atrial electrograms during different atrial activation sequences from a sinus rhythm were evaluated to test the hypothesis that the prolongation of atrial electrogram duration caused by the different atrial activation sequence is more prominent at the site of atrial fibrillation (Afib) genesis (initiation site) than other areas.

In 39 patients with single retrograde left-sided accessory connection who had inducible transient atrial fibrillation during an electrophysiologic study, the site of Afib genesis was determined and classified into three groups, i.e., 1) high right atrial genesis (HRA), 2) low right atrial genesis (LRA), and 3) left atrial genesis (LA). Single premature extrastimuli after 8 basic drive trains (600 ms) were delivered at the HRA and the right ventricular apex. Three atrial electrophysiologic parameters were evaluated at three atrial sites, i.e., 1) HRA, 2) LRA, and 3) coronary sinus. The atrial vulnerability parameters were as follows; 1) %A2/A1: % prolongation of atrial electrogram duration during premature beat (A2) in comparison with basic drive (A1), 2) wavelength index (WLI): calculated as [effective refractory period]/[A2], and 3) retrograde activation index (RAI): calculated as [A1 during retrograde activation; i.e., RVA pacing]/[A1 during antegrade activation, i.e., HRA pacing], shown as a percentage.

The Afib genesis was HRA in 20, LRA in 12 and LA in 7 patients. At the HRA recording site, %A2/A1 and RAI were the largest and WLI the shortest

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in the HRA genesis group in comparison with the other two groups. Similarly, at the LRA and LA recording sites, %A2/A1 and RAI were the largest and WLI the shortest in the groups with Afib genesis at these recording sites.

In patients with inducible Afib, %A2/A1 and RAI were the highest and WLI the shortest at the atrial recording site close to the site of Afib genesis. Atrial wave prolongation during retrograde atrial activation, possibly the anisotropic conduction, was considered to play a role in initiating Afib as well as a conduction delay during the atrial premature beat. (Jpn Heart J 1999; 40: 281–293)

Key words: Atrial fibrillation, Accessory pathway, Anisotropic conduction, Electrophysiologic study

ALTHOUGH atrial fibrillation is a relatively common form of arrhythmia, it may result in life-threatening conditions in patients with Wolff-Parkinson-White (WPW) syndrome when the effective refractory period of antegrade conduction through an accessory pathway is critically short.^{1–6)} Interestingly, the incidence of atrial fibrillation in patients with WPW syndrome is higher than that in the total population,^{7–10)} but the mechanism of the occurrence of atrial fibrillation in WPW syndrome is unclear. It has recently been suggested 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 slowing of conduction caused by premature excitation or anisotropic conduction most likely produces areas of slow conduction, and a collision of the activation wave fronts of the sinus rhythm and a premature beat produces block lines, which may then result in multiple random reentry, i.e., atrial fibrillation.^{10,11,13,15)} However, it has been shown that the local atrial muscle close to the atrial breakthrough of the accessory pathway rarely plays a role of “genesis”, i.e., initiation site, of atrial fibrillation.^{16,17)} In the present study, we hypothesized that the atrial vulnerability for atrial fibrillation is higher at the atrial fibrillation genesis compared to other areas. To test this hypothesis, atrial vulnerability, i.e., prolongation of the atrial wave duration caused by premature excitation or retrograde atrial activation was evaluated, as was the local wavelength at selected areas in atria in WPW patients with atrial fibrillation induced during an electrophysiologic study.

METHODS

Patients: The study population consisted of 39 patients with single retrograde left-sided accessory connection (22 manifest and 17 concealed WPW syndrome) who showed induced atrial fibrillation during an electrophysiologic study. Sub-

Table I. Clinical Characteristics of the Patients

Age	41 ± 15 years
Sex	17 female, 22 male
Antegrade conduction of accessory pathway	yes 22, no 17
Afib history	yes 9, no 30
Afib genesis	HRA 20, LRA 12, LA 7
Afib induction mode	HRA pacing 16 RVA pacing 5 AVRT 18

Afib = atrial fibrillation; HRA = high right atrium; LRA = low right atrium; LA = left atrium, AVRT = atrio-ventricular reentrant tachycardia; RVA = right ventricular apex.

jects were 39 of 246 consecutive patients with WPW syndrome who underwent an electrophysiologic study at our hospitals between May 1994 and July 1998. Nine of the 39 patients had an episode of spontaneous electrocardiographically documented atrial fibrillation. No structural heart disease was present in any of the 39 patients. The mean age was 41 ± 15 years (range from 16 to 64); 22 were male and 17 were female (Table I). 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 the fasting and non-sedated state after obtaining informed consent from each patient. All antiarrhythmic drugs were discontinued at least 5 half-lives before the procedure. Through the femoral vein, two 6F quadripolar electrode catheters (Josephson multipurpose catheter, USCI Division of C.R. Bard, Billerica, MA, USA) were positioned against the high right atrium (HRA) close to the sinus node and the right ventricular apex. The catheters were used for the stimulation and recording of the intracardiac electrograms. To record the His bundle electrogram (HBE), one 6F tripolar electrode catheter (C.R. Bard) was introduced through the same site. The atrial electrogram recorded through this HBE catheter was used for the measurement of atrial wave duration of the low right atrium (LRA). 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 to confirm the left-sided accessory connection. Electrical stimulation was delivered by a programmable cardiac stimulator (BCO30, Fukuda-Denshi Co., Tokyo, Japan) at twice diastolic threshold with a 2 msec rectangular pulse. Intracardiac electrograms were recorded on an ink-jet recorder (Mingograf 7 or 82, Siemens Elema Co., Solna, Sweden) with three surface leads, i.e., I, II, and V1, 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., Tokyo), and were

retrieved on a thermal recorder (Thermal recorder RF-85, Fukuda-Denshi).

Electrophysiologic parameters: To complete the regular electrophysiologic study, single extrastimuli with two basic drive cycle lengths (400 and 600 msec) and transient pacing with fixed cycle length (from 667 to 286 msec) were delivered at each of the HRA and RVA pacing sites. When atrial fibrillation was induced by stimulation or reciprocating atrioventricular reentrant tachycardia, the site of atrial fibrillation genesis (initiation site) was determined as the atrial recording site that first showed a continuous fragmented atrial electrogram at the time the atrial fibrillation occurred.

The measurement of the following atrial electrophysiologic parameters was performed with the basic drive cycle length of 600 msec. The atrial effective refractory period (AERP) was determined as the longest delivered coupling interval of atrial extra stimulus that failed to capture the atrium and was determined at each of the three atrial recording sites, i.e., HRA, LRA and CS sites. The atrial wave duration was measured at all three atrial sites. At these recording sites, a bipolar atrial electrogram was recorded between 10 mm spacing electrodes on the electrode catheter. The control atrial wave duration (A1) was measured during the basic atrial stimuli at a cycle length of 600 msec. The atrial wave duration during atrial extrastimulation was also measured, and the longest duration of atrial wave obtained during the atrial extrastimulation was defined as A2 and was always observed during the extrastimulus with the shortest delivered coupling interval. The maximal prolongation of the atrial wave duration during the atrial extrastimulation was represented by the %A2/A1 ratio.^{18,19)} At these three recording sites, the atrial wave duration during the retrograde atrial activation (Ar) produced by the basic right ventricular stimulus was also measured. The wavelength index (WLI) was determined as the AERP/A2 ratio.²⁰⁻²²⁾ The retrograde activation index (RAI) was calculated as [A1 duration during retrograde activation; i.e., ventricular pacing]/[A1 duration during antegrade atrial activation; i.e., HRA pacing] and is expressed as a percentage. This index was considered to express comparative prolongation of the atrial wave duration during retrograde atrial activation. The occurrence of atrial fibrillation was determined by the appearance of a continuous fragmented atrial electrogram at one of the three atrial recording sites.

The 39 patients were divided into three groups in accordance with the atrial fibrillation genesis, i.e., the HRA genesis group, the LRA genesis group, and the left atrial (LA) genesis group. The three electrophysiologic parameters for atrial vulnerability for atrial fibrillation, i.e., %A2/A1, WLI and RAI were compared among these three groups at each of the three atrial recording sites.

Statistics: All values are expressed as mean $\pm$ standard deviation. Statistical analysis was performed with one-way ANOVA or Pearson's chi-square test. A *p*

value of < 0.05 was considered significant.

RESULTS

In the electrophysiologic study, atrial fibrillation was initiated during atrio-ventricular reentrant tachycardia in 18 patients, during atrial pacing at the HRA pacing site in 16 patients, and during ventricular pacing at the right ventricular apex pacing site in 5 patients. All episodes of atrial fibrillation in each patient terminated spontaneously after lasting 3 to 17 minutes.

Figure 1 shows a representative example of the initiation of atrial fibrillation during atrial pacing at the HRA pacing site. In this patient, atrial pacing was delivered during a 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. The surface ECG leads showed wide QRS morphologies as a result of manifest atrioventricular conduction through the accessory pathway. Immediately after the atrial premature beat, a continuous fragmented atrial elec-

Figure 1. Initiation of atrial fibrillation during HRA pacing. 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, i.e., low right atrium (LRA), because the fragmented atrial electrogram was first observed at this site (indicated by arrow heads). See text for discussion.

I, II, V₁ = 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.

Figure 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 the pacing stopped (represented by long horizontal arrow). The site of atrial fibrillation genesis was localized at the CS site, i.e., left atrium (LA), because the fragmented atrial electrogram was first observed at this site (indicated by four arrowheads). Following this, a fragmented atrial electrogram appeared at the HRA and HBE sites. See text for discussion. RVA = right ventricular apex; CL = cycle length. See Figure 1 legend for other abbreviations.

Table II. Relationship between the Afib Induction Mode and Afib Genesis

Afib induction mode	Afib genesis
HRA pacing (<i>n</i> = 16)	HRA 6, LRA 16, LA 2
RVA pacing (<i>n</i> = 5)	HRA 2, LRA 1, LA 2
AVRT (<i>n</i> = 18)	HRA 10, LRA 5, LA 3
	<i>p</i> = 0.680

Abbreviations are the same as Table I.

trogram first appeared at the HBE recording site, and then atrial fibrillation was initiated. In this patient, the site of atrial fibrillation genesis was considered to be the HBE site, i.e., LRA.

Figure 2 shows a representative example of the initiation of atrial fibrillation during atrioventricular reentrant tachycardia. Ventricular pacing with a fixed cycle length of 240 msec was delivered at the right ventricular apex pacing site. From the first beat to the fifth beat in this figure, the QRS morphology gradually

changed in the surface ECG leads, indicating that paced ventricular beats fusing with tachycardia beats via the His-Purkinje system captured a gradually larger area of both ventricles and then finally fully captured the ventricles at the fifth beat. Up to the fourth beat, the atrial wave could be identified at all of the HRA, HBE and CS recording sites. At the fifth beat, a continuous fragmented atrial electrogram first appeared at the CS recording site, and then similar atrial fragmented electrograms appeared at the HRA and HBE recording sites from the sixth beat. After the ventricular pacing was stopped, atrioventricular reentrant tachycardia was not observed but the atrial fibrillation continued, although not shown in the figure. In this patient, the site of the atrial fibrillation genesis was considered to be the CS site, i.e., LA.

Atrial fibrillation genesis: The clinical characteristics and atrial fibrillation genesis data from all 39 patients are summarized in Tables I & II. In total, atrial fibrillation was initiated during atrioventricular reentrant tachycardia in 18, during the HRA pacing in 16 and during right ventricular apex pacing in 5 patients. The site of atrial fibrillation genesis was localized at the HRA in 20, at the LRA in 12 and at the LA in 7 patients. In 6/39 patients (15%), the atrial pacing site itself, i.e., the HRA site, was the atrial fibrillation genesis.

Measurement of atrial wave duration: Figure 3 shows a representative ex-

Figure 3. Measurement of atrial wave duration during HRA pacing. Single extra stimulus with a coupling interval of 270 msec was delivered at the HRA pacing site after 8 basic beats at a cycle length of 600 msec. Surface leads showed normal QRS configurations during atrial pacing because the accessory pathway in this case did not show antegrade conduction. Each number in the figure shows measured atrial wave duration at each recording site. See text for discussion. RVA = right ventricular apex, S = atrial stimulation artifact, A = atrial wave, V = ventricular electrogram. See Figure 1 for other abbreviations.

Figure 4. Measurement of atrial wave duration during RVA pacing. Single extra stimulus with a coupling interval of 270 msec was delivered at the RVA pacing site after 8 basic beats at a cycle length of 600 msec. Retrograde atrial activation first appeared at the CS site because of retrograde conduction via left-sided accessory pathway. Each number in the figure shows measured atrial wave duration at each recording site. See text for discussion. Abbreviations are explained in Figures 1 and 3.

ample of measurement of atrial wave duration during atrial pacing at the HRA pacing site. A single extrastimulus with a coupling interval of 270 msec was delivered at the HRA pacing site after 8 basic beats at a cycle length of 600 msec. The surface ECG leads showed normal QRS configurations because this patient did not show antegrade conduction through the accessory pathway. Each number in the figure shows the measured atrial wave duration at each recording site. Note that the atrial wave duration during the premature beat was prolonged in comparison with that during the basic atrial stimulation at each recording site. In this patient, the AERP was 260 msec at the HRA site, 220 msec at the HBE site, and 230 msec at the CS site. The wavelength index (WLI) was 1.90 cm at the HRA site, 1.69 cm at the HBE site, and 6.57 cm at the CS site. The %A2/A1 values were 150% at the HRA site, 200% at the HBE site, and 117% at the CS site.

Figure 4 shows a representative example of the measurement of the atrial wave duration during ventricular pacing at the RVA pacing site in the same patient shown in Figure 3. A single extra stimulus with a coupling interval of 270 msec was delivered at the RVA pacing site after 8 basic beats at a cycle length of 600 msec. The numbers in the figure show the measured atrial wave duration at each recording site. Note that the atrial wave duration during the premature beat

Table III. Comparison of Atrial Electrophysiologic Parameters between Different Types of Afib Genesis

	HRA genesis (<i>n</i> = 20)	LRA genesis (<i>n</i> = 12)	LA genesis (<i>n</i> = 7)	Total (<i>n</i> = 39)	<i>p</i> value
HRA recording					
%A2/A1 (%)	158 ± 22	142 ± 17	144 ± 16	150 ± 20	0.062
WLI (cm)	2.2 ± 0.5	3.0 ± 0.9	3.0 ± 0.6	2.6 ± 0.8	0.002*
RAI (%)	124 ± 15	116 ± 14	107 ± 11	119 ± 15	0.018*
HBE recording					
%A2/A1 (%)	135 ± 22	159 ± 34	127 ± 14	141 ± 28	0.016*
WLI (cm)	3.0 ± 0.6	2.1 ± 0.4	3.4 ± 1.2	2.8 ± 0.8	0.001*
RAI (%)	121 ± 16	138 ± 32	112 ± 15	125 ± 24	0.033*
CS recording					
%A2/A1 (%)	120 ± 21	110 ± 12	144 ± 25	121 ± 22	0.004*
WLI (cm)	4.7 ± 0.9	5.1 ± 1.4	3.6 ± 0.6	4.5 ± 1.1	0.014*
RAI (%)	114 ± 14	108 ± 13	130 ± 27	115 ± 18	0.031*

Afib = atrial fibrillation; HRA = high right atrium; LRA = low right atrium; LA = left atrium; WLI = wave-length index; RAI = retrograde activation index.

was prolonged in comparison with that during the basic atrial stimulation at each recording site. The atrial wave duration during retrograde atrial activation, Ar, was 70 msec at the HRA site, 65 msec at the HBE site, and 30 msec at the CS site. The retrograde activation index (RAI) was 100% at the HRA site, 138% at the HBE site, and 117% at the CS site.

Comparison of parameters of atrial vulnerability for atrial fibrillation:

Table III summarizes the results of the statistical comparison of the atrial electrophysiologic parameters for atrial fibrillation, i.e., %A2/A1, WLI, and RAI, among the groups with different atrial fibrillation genesis in atria. At each atrial recording site, the atrial vulnerability was always highest, i.e., large %A2/A1, short WLI, and large RAI, in the group with the atrial fibrillation genesis close to that of the recording site, although the difference was not always significant. For example, at the HBE recording site, the %A2/A1 was largest in the LRA genesis group ($159 \pm 34\%$), i.e., the group in which the atrial fibrillation genesis was considered to be close to the HBE recording site. Similarly, at the HBE recording site, the WLI was shortest in the LRA genesis group, i.e., 2.1 ± 0.4 cm, and the RAI was largest in the LRA group, i.e., $138 \pm 32\%$.

DISCUSSION

The mechanism of the initiation of atrial fibrillation has been investigated in several studies, often by examining patients with atrioventricular accessory connection.¹⁻¹⁵⁾ It has been suggested that the retrograde conduction through the accessory pathway may play an important role in the initiation of atrial

fibrillation as a result of inhomogeneous depolarization in both atria.¹¹⁻¹⁴⁾ A short effective refractory period of the accessory pathway was also suggested to be related to the occurrence of atrial fibrillation.^{11,13)} However, the electrophysiologic specificity and abnormalities in a local atrial area are not well understood. Actually, the atrial "genesis" of atrial fibrillation is considered to be in different atrial areas in individual patients,^{16,17)} so that the electrophysiologic parameters at the local atrial muscle should be evaluated at several atrial areas in each patient. In the present study, we evaluated the local atrial electrogram during atrial pacing at three representative atrial recording sites to test the hypothesis that the atrial vulnerability for atrial fibrillation is highest at the atrial fibrillation "genesis" in comparison with the other atrial areas.

Atrial fibrillation genesis in the atria: It has recently been documented that the initiation site of atrial fibrillation, i.e., atrial fibrillation genesis, was in different atrial areas in individual patients.^{16,17)} In the present study, when the atria were divided into three representative areas, i.e., HRA, LRA, and LA areas, HRA genesis was observed in 20/39 patients, LRA genesis in 12/39 and LA genesis in 7/39 patients. The HRA area was thus the most common area as the atrial fibrillation genesis in these WPW syndrome patients, and this incidence is similar to that in previous reports concerning atrial fibrillation genesis.¹⁶⁾ In 6 of the 16 present patients with HRA atrial fibrillation genesis, transient atrial fibrillation appeared during atrial pacing at the HRA pacing site (Table II). Because of the conduction delay of the atrial activation during the atrial premature beat, a shorter coupling interval of paced atrial beat could be achieved at the area close to the pacing site, which might have then resulted in the HRA becoming the atrial fibrillation genesis due to critical local conduction delay. However, in the remaining 10 of the 16 patients with HRA genesis, transient atrial fibrillation was induced not during HRA pacing but rather during a different activation sequence.

Parameters of atrial vulnerability for atrial fibrillation: In the present study, three parameters of atrial vulnerability for atrial fibrillation were employed. The %A2/A1 represented a local conduction delay at each atrial recording site as a result simply of premature atrial activation.^{18,19)} The WLI (wavelength index), which was calculated from the effective refractory period and activation time in the fixed recording site, i.e., A2 duration in 1 cm distance, represented the minimum length of the reentrant circuit at that site.²⁰⁻²²⁾ The RAI (retrograde activation index) represented a local conduction delay at each atrial recording site as a result of a change in the direction of the atrial activation sequence. Because a larger delay and shorter wavelength make it easier to produce multiple small reentrant circuits, a larger %A2/A1 or RAI and shorter WLI indicate higher atrial vulnerability for atrial fibrillation. We found that the values

of these three parameters of atrial vulnerability were always highest at the atrial recording site in the area of atrial fibrillation genesis in each individual patient (Table III).

Mechanism of conduction delay in atrial activation: According to the “multiple random reentry theory” as a mechanism of atrial fibrillation, a local conduction delay is necessary to form a relatively small reentrant circuit in either atrium. The relationship between a history of transient atrial fibrillation and the fragmented atrial electrogram during the atrial premature beat was emphasized in several reports.^{18,19} The atrial electrogram was physiologically prolonged during the premature beat at all sites of the atria, but a prominent prolongation in the duration of the atrial electrogram, i.e., fragmentation, was observed in patients with transient atrial fibrillation or sick sinus syndrome.^{18,19} The mechanism of the appearance of fragmented activity is thought to be local conduction delay as a result of phase 3 block, anisotropic conduction, or cell-to-cell uncoupling.^{11,21,22} These electrophysiologic changes result in a shortening of the spatial wavelength, then produce the basic structure for the multiple small reentrant circuits of atrial fibrillation.^{21–26} In accordance with the results of the present study, a more prominent difference in atrial vulnerability parameters between patient groups with different atrial fibrillation genesis was observed in %A2/A1 in comparison with RAI. Prolongation of the conduction time during retrograde atrial activation, which might be the result of anisotropic conduction, was thought to play a role in the initiation of atrial fibrillation as well as conduction delay during the atrial premature beat, although its participation was relatively small.

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, i.e., the HRA, HBE, and CS sites, so that the actual site of atrial fibrillation genesis might have been misinterpreted. Additionally, the number of patients was also limited. These problems would be solved by obtaining high density recordings in the atria and inducing atrial fibrillation several times in the same patients in a larger population. The clinical significance of induced atrial fibrillation in an electrophysiologic study also remains unclear. This question may be answered by the long-term follow-up of the individual patients evaluated in this study.

Conclusions: The site of atrial fibrillation genesis and electrophysiological parameters at three atrial recording sites were evaluated in 39 patients with single left-sided retrograde connection and with atrial fibrillation induced in an electrophysiologic study. HRA genesis was observed in 20/39 patients, LRA genesis in 12/39 patients, and LA genesis in 7/39 patients. The %A2/A1 and RAI were highest and the WLI was shortest at the atrial recording site close to

the atrial fibrillation genesis. Atrial wave prolongation during retrograde atrial activation, possibly the anisotropic conduction, was considered to play a role in initiating atrial fibrillation as well as a conduction delay during the atrial premature beat.

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