Atrial electrophysiologic properties of patients with asymptomatic Wolff–Parkinson–White syndrome

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To evaluate the existence of a peculiar atrial electrophysiologic substrate, we studied 18 patients with asymptomatic Wolff–Parkinson–White (WPW) syndrome. These patients were compared with 10 age-matched normal subjects (N). Effective and functional refractory periods were determined at two right atrial sites (high and low in the lateral wall), during atrial pacing (100 min^{-1}) and at twice diastolic threshold. Disperson (D) of effective (ERP) and functional (FRP) refractoriness was evaluated as the difference between refractory periods at the two atrial sites. WPW patients showed significantly lower mean values of effective and functional refractoriness at both atrial sites and significantly higher mean values of D-ERP and D-FRP. Moreover, in calculating the highest normal values of D-ERP and D-FRP (as mean values of N plus 2SD) it was observed that WPW with abnormal values of D showed a statistically (χ^2 test) higher incidence (100%) of induced atrial fibrillation (AF). These findings indicate the existence of both an abnormal atrial electrophysiologic substrate and of a higher vulnerability in WPW. Finally, AF was induced generally at the site with the lower refractoriness (i.e. low lateral site). This should be taken into account when considering how atrial fibrillation can be induced more easily.

Introduction

A relatively high incidence (up to 32%) of atrial fibrillation (AF) in patients with the Wolff–Parkinson–White syndrome has been described[1–4]. Previous studies indicate the existence in these patients of a 'primary' atrial vulnerability to fibrillation[5–8]. This could indicate the possible existence of a diverse and peculiar atrial electrophysiologic substrate. Previous studies of clinical electrophysiology have shown how it is possible to perform a better evaluation of atrial excitability by determining refractoriness and its dispersion[9–13]. We, therefore, decided to undertake an analogous study in patients with cardiac pre-excitation (but without associated cardiopathy) to verify the existence of this diverse electrophysiologic substrate. In order to perform a correct evaluation[12], the data obtained were compared with those of age-matched normal subjects. Finally, to avoid the influence of the different heart rate, we measured refractoriness during paced rhythm[11–14].

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Methods

PATIENT SELECTION

Two groups of subjects were studied. The first group (WPW) consisted of 18 patients (16 male and two female), mean age 35 ± 19 years (range 13–65 years) with electrocardiographic evidence of an accessory atrio-ventricular pathway (Wolff–Parkinson–White type). All were symptom free. The standard ECG showed a stable pre-excitation pattern in 15; three patients had intermittent pre-excitation.

The second group (N) consisted of 10 age-matched normal subjects (nine male and one female), mean age 38 ± 11 years (range 17–55 years). These patients underwent an electrophysiological study for unexplained dizziness or atypical chest pain.

CLINICAL EVALUATION

No subject had evidence of concomitant cardiac disease. All subjects provided a satisfactory medical history and underwent physical examination, chest roentgenography, 12-lead electrocardiography, 24-h Holter monitoring, exercise testing, and cross-sectional echocardiography.

ELECTROPHYSIOLOGIC STUDY

Electrophysiologic evaluation was carried out in the postabsorptive, non-sedated state. Informed written consent was obtained from every patient. All were in sinus rhythm when they entered the catheterization laboratory. A quadripolar catheter (6F USCI) was inserted into an antecubital vein and first positioned in the high right atrium (HRA), near its junction with the superior vena cava. The distal pair of electrodes was used to stimulate the atrium and the proximal pair to record a right atrial electrogram. This electrogram and four surface electrocardiographic leads were simultaneously displayed on a Hewlett-Packard eight-channel oscilloscope and recorded on a Elema-Schönander Mingograph 62-6 channel ink-jet at a paper speed of 100 mm s^{-1}. Overdrive and premature programmed atrial stimulation were performed using an electrically isolated battery-powered Medtronics 5325 stimulator. The pulse width was 2 ms and the amplitude was adjusted to twice diastolic threshold.

Atrial extrastimuli were applied at 5–10-ms decrements after each eighth beat of atrial pacing at a paced cycle length of 600 ms, until atrial refractoriness was determined. The stimulating poles were then fluoroscopically repositioned, the threshold re-evaluated, and atrial stimulation performed at another right atrial site in the lateral wall: low right atrium (LRA). By the same method the effective refractory period of the accessory pathway (ERP-AP) was determined. The atrial functional refractory period (FRP) was the shortest coupling interval recorded on the right atrial electrogram. The atrial effective refractory period (ERP) was the longest interval between the stimulus artifact (atrial pacing) and the extrastimulus failing to propagate. Dispersion (D) of effective (ERP) and functional (FRP) refractoriness was determined as the difference between the refractory periods measured at the two right atrial sites. The ERP-AP was defined as the longest A_1–A_2 interval at which the atrial premature response was not conducted through the accessory pathway. In five patients the ERP-AP could not be measured because the atrium became refractory before it occurred. In such patients the ERP-AP was expressed as being equal to or less than FRP. Incremental right atrial overdrive pacing was performed to a minimum paced cycle length of 250 ms to determine: (1) sinus node recovery time, and (2) the shortest atrial overdrive cycle length at which there was a 1:1 conduction through the accessory pathway. Finally, WPW patients were investigated to see whether they could develop AV re-entrant paroxysmal tachycardia or atrial fibrillation. In all cases the following stimulation protocol was performed: (a) premature atrial stimulation with single and double extrastimuli during sinus rhythm and atrial pacing at 600 and 400 ms cycle lengths; (b) burst of atrial pacing of 15 s duration at rates from 160 min^{-1} to 250 min^{-1}. The protocol was interrupted when a sustained (> 1 min), or at least two episodes of non-sustained (lasting less than 1 min but more than 3 s), AF were induced. AF was defined as a rapid irregular atrial activity, with inconstant relationships between atrial depolarizations[15].

Values were expressed in milliseconds and as mean ± 1 s.d. Group comparisons with respect to numerical data were made by *t*-test for unpaired data. Group comparisons with respect to the presence or absence of specific attributes were made by two χ^2 analysis with Yates correction.

Results

The two groups of subjects were age-matched. The sinus mode function was normal in each case. In fact, no subject showed abnormal values of heart rate (in previous electrocardiograms or during electrophysiologic study) or of corrected sinus node recovery time (NV < 500 ms in our laboratory).

Single values and mean values (± 1 s.d.) of ERP and of FRP at HRA and LRA and of D-ERP and of D-FRP are reported in Table 1. Mean ERP values of WPW and N at HRA were 246 ± 20 ms and 264 ± 21 ms, respectively, and at LRA 212 ± 32 ms and 249 ± 28 ms, respectively. The WPW patients showed significantly lower mean values than did those of N at both atrial sites: HRA, $P < 0.05$; LRA, $P < 0.05$. Mean values of FRP of WPW and of N were: at HRA, 264 ± 24 ms and 286 ± 22 ms, respectively; and at LRA, 228 ± 35 ms and 269 ± 18 ms, respectively. Even in this case WPW showed significantly lower mean values than those of N: HRA, $P < 0.01$; LRA, $P < 0.005$. Mean values of D-ERP and of D-FRP were in WPW 46 ± 22 ms and 45 ± 26 ms, respectively, and in N 24 ± 16 ms and 19 ± 13 ms, respectively. Mean values of WPW proved to be significantly higher than those of N: D-ERP, $P < 0.02$; D-FRP, $P < 0.01$. Conversely to N, WPW showed mean values of refractoriness at HRA significantly higher than those at LRA (ERP, $P < 0.001$; FRP, $P < 0.005$). AF was induced in 13 WPW patients (72%), generally at the atrial site (i.e. LRA) with the shortest refractoriness and particularly (92%) through programmed atrial stimulation

Table I Single and mean values (ms) of atrial refractoriness and its dispersion

	ERP		FRP		D-ERP	D-FRP
	HRA	LRA	HRA	LRA		
WPW case						
1	220	210	220	210	10	10
2	240	250	240	260	10	20
3	240	220	260	240	20	20
4	210	240	260	260	30	0
5	220	250	240	260	30	20
6	260	220	280	230	40	50
7	250	190	260	200	60	60
8	250	180	270	200	70	70
9	260	190	280	205	70	75
10	270	200	290	225	70	65
11	240	160	270	170	80	100
12	260	300	280	320	40	40
13	260	200	270	220	60	50
14	260	200	270	210	60	60
15	240	210	260	230	30	30
16	240	200	250	220	40	30
17	290	220	330	260	70	70
18	220	180	230	190	40	40
$\bar{x}$	246	212	264	228	46	45
±s.d.	20	32	24	35	22	26
N case						
1	260	260	280	270	10	10
2	250	230	270	250	20	20
3	240	220	270	250	20	20
4	240	230	260	260	10	0
5	250	280	270	285	30	15
6	260	210	270	250	50	20
7	290	280	300	290	10	10
8	300	250	320	270	50	50
9	280	290	320	300	10	20
10	270	240	300	270	30	30
$\bar{x}$	264	249	286	269	24	19
±s.d.	21	28	22	18	16	13

ERP, effective refractory period; FRP, functional refractory period; D-ERP, dispersion of effective refractoriness; D-FRP, dispersion of functional refractoriness; HRA, high right atrium; LRA, low right atrium; N, normal subjects; WPW, patients with asymptomatic Wolff–Parkinson–White syndrome.

(one or two extrastimuli). In order to evaluate the relationship between inducibility and D we calculated the highest normal values of D-ERP and of D-FRP. These were obtained as mean values of N+2 s.d.: 56 ms for D-ERP, 45 ms for D-FRP. On this basis WPW were then divided. Ten patients (56%) showed normal values and eight patients (44%) abnormal values of D-ERP. Nine patients (50%) showed normal values and nine (50%) abnormal values of D-FRP. AF was induced in 100% of patients with abnormal values and in 50% of those with normal values of D-ERP. AF was induced in 100% of patients with abnormal values and in 44% of those with normal values of D-FRP.

In both cases the difference was statistically (χ^2 test) significant (D-ERP, $P<0{\cdot}006$; D-FRP, $P<0{\cdot}003$). These results indicate a higher incidence of inducibility of AF in WPW subjects with abnormal values of D. Patients with normal and abnormal values were also compared in terms of refractoriness. This was possible because the mean age did not differ statistically. Mean values of ERP

of WPW patients with abnormal and normal values of D-ERP at HRA were 260 ± 15 ms and 235 ± 17 ms respectively and, at LRA, 192 ± 18 ms and 228 ± 34 ms respectively. WPW patients with abnormal values showed significantly higher mean values at HRA ($P < 0.01$) and significantly lower mean values at LRA ($P < 0.02$). Mean values of FRP for WPW patients with abnormal and normal values of D-FRP were 280 ± 21 ms and 249 ± 18 ms at HRA, respectively, and 213 ± 25 ms and 243 ± 38 ms at LRA, respectively. WPW patients with abnormal values of D-FRP showed significantly higher mean values at HRA ($P < 0.005$).

The shortest R–R intervals during induced AF lay between 380 and 240 ms. This parameter was evaluated in 10 patients because eight had no pre-excited R–R in AF, or AF was not inducible. The R–R interval was less than 250 ms in only one patient (10%). The maximal duration of induced AF was evaluated in each patient and lay between 21 min and 12 h. This parameter was not correlated either with values of D or with refractoriness of the two atrial sites. ERP–AP, when measurable, ranged between 200 and 380 ms. It was possible to evaluate this parameter in only 15 patients because in three, the WPW morphology was absent during the electrophysiologic study. ERP-AP was lower than 270 ms in seven patients (47%). Mean values of D-ERP and D-FRP were not statistically different between these two groups. The rate of atrial pacing required to produce second-degree A-V block in patients with WPW morphology was always higher than 200 beats min^{-1}, if we exclude one patient for whom it was 140 beats min^{-1}. This patient showed the highest values of ERP-AP (i.e. 380 ms).

Discussion

Our results indicate the existence in WPW patients of both lower mean values of effective and functional refractoriness at the two tested right atrial sites and of higher mean values of D-ERP and D-FRP. This is noteworthy considering that: (a) previous reports[16,17] consider these electrophysiologic properties as indicators of a higher atrial vulnerability and of an easier arrhythmogenesis; and (b) superimposable findings were reported in patients with paroxysmal atrial fibrillation but without cardiac pre-excitation[11,18].

The peculiar electrophysiologic substrate observed in WPW patients could help explain the relatively high incidence of spontaneous AF in patients with ventricular pre-excitation[1-4]. The pathophysiological pattern of WPW may not only comprehend the presence of an accessory pathway, but also of diverse atrial electrophysiologic characteristics as previously suggested[6,8,19] (this even in the absence of an associated cardiopathy). On the basis of the modality of induction of AF in WPW, we are tempted to attribute the peculiar electrophysiologic substrate to intra-atrial factors rather than to an abnormality of the atrium at the site of the atrial insertion of the accessory pathway. In fact, AF was induced in all cases, except one, by programmed atrial stimulation (one or two extra-stimuli) and not as a consequence of atrial 'echoes' or of AV re-entrant paroxysmal tachycardia. In this respect, one should consider that values of ERP-AP did not show any relationship with values of D and with incidence or duration of induced AF. However, we cannot exclude that the presence of the bypass tract contributes to the atrial vulnerability as previously indicated[19].

It is noteworthy that in the present study AF was generally induced at LRA. Moreover, refractoriness at this site proved to be almost always lower than that of HRA. Previous studies[11,18] indicated that, if an early extrastimulus is delivered at the site of short refractoriness, it can be conducted along the atrial fibres with a lower velocity and without regularity. A favourable substrate for the induction of AF would be produced. An identical behaviour has been described in patients with paroxysmal atrial fibrillation, but without pre-excitation[11]. We can, therefore, suggest that evaluation of refractoriness at more than one atrial site could be useful in WPW in order to locate the site where refractoriness is lower, so as to perform the induction of AF more easily.

As in previous studies[8,20,21], AF was not induced in all WPW cases. However, we must stress again that this arrhythmia was induced in all WPW patients with abnormal values of D-ERP and D-FRP. Thus, it is possible to indicate that WPW patients with abnormal values of D have a higher atrial vulnerability. Our results indicate that in the evaluation of patients with WPW syndrome, a more accurate determination of atrial electrophysiologic properties should be obtained.

The maximal duration of induced AF did not show a relationship with values of D. It has previously been reported[17] that D, even if it conditions atrial vulnerability, is not the unique electrophysiologic factor which determines the duration of AF. Moreover, it should be remembered that AF can produce haemodynamic changes and, conse-