Effects of Flecainide on the Electrophysiological Properties of Atrial Vulnerability in Humans

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The aims of this study were to evaluate the changes in the electrophysiological characteristics of the right atrium after the administration of flecainide and to clarify whether flecainide has a selective effect on human atrial tissue. Electrophysiological measurements were made in 38 patients, before and after intravenous administration of flecainide (2 mg/kg per 10 min). The effective refractory period of the right atrium (ERP-A), maximum conduction delay (Max.CD), repetitive atrial firing zone (RAFZ), fragmented atrial activity zone (FAAZ), and conduction delay zone (CDZ) were studied in the patients who were divided into 2 groups based on whether repetitive atrial firing (RAF) was induced in the baseline study. Flecainide significantly prolonged the ERP-A (202±22 to 238±33 ms, p<0.001) and shortened Max.CD (77±17 to 63±32 ms, p<0.05) in the patients with RAF, but not in those without RAF in the baseline study. After flecainide administration, there were significant reductions in the RAFZ (43±22 to 13±19 ms, p<0.0001), FAAZ (51±22 to 28±26 ms, p<0.001) and CDZ (70±21 to 48±30 ms, p<0.01) in the patients with RAF. However, atrial fibrillation (AF) was induced by stimulation after flecainide in 2 patients without RAF in the baseline study. There was a significant negative correlation between the ERP-A in the baseline study and the change in the ERP-A upon flecainide administration (r=-0.45, p<0.01). Flecainide may preferentially activate the substrate for AF and RAF, but that action is mainly based on the electrophysiological characteristics found in the baseline study. (Circ J 2003; 67: 437–442)

Key Words: Atrial fibrillation; Atrial refractoriness; Atrial vulnerability; Flecainide

The antiarrhythmic drug, flecainide, suppresses the maximum rate of the rise (dV/dt) in the action potential, but does not prolong its duration. Therefore, flecainide is classified as a class Ic antiarrhythmic drug according to the Vaughan Williams classification. It has been well documented that flecainide has clinical antiarrhythmic effects in terminating atrial fibrillation (AF) and preventing its recurrence.1–3 but there is little information concerning the effects of flecainide on atrial vulnerability in humans.4–5 Class Ic antiarrhythmic drugs have selective effects on the substrate of ventricular tachycardia, relative to normal ventricular tissue,6–7 but it is unclear whether flecainide has selective effects on atrial tissue, similar to cibenzoline which we previously reported has selective effects on abnormal atrial tissue.8 Repetitive atrial firing (RAF) is well known as a parameter of atrial vulnerability.8–17 because its electrophysiologic characteristics, which include a shorter refractory period and longer conduction delay, are the same as those of paroxysmal AF (PAF). To clarify whether flecainide has selective effects on atrial tissue, we investigated its effect on the conduction, refractoriness and electrophysiologic parameters of human atrial tissue.

Methods

Patients
Between September, 1999 and December, 2000, 38 consecutive patients, referred for an electrophysiological study, were prospectively studied. The patient group [age (mean± standard deviation) 49±15 years; 28 males, 10 females] comprised 19 with Wolff-Parkinson-White (WPW) syndrome, 11 with atrioventricular nodal reentrant tachycardia (AVNRT), 3 with atrial flutter, 3 with sick sinus syndrome (SSS), 1 with ventricular tachycardia (VT), and 1 with idiopathic PAF; 10 of the 38 patients had a history of PAF, which was diagnosed by routine ECG, ambulatory Holter electrocardiogram (ECG), and bedside monitoring. In the patients with WPW syndrome, AVNRT and atrial flutter, we performed the electrophysiological studies 1 week after catheter ablation. No patient had received amiodarone. The electrophysiological studies were performed at least 72 h after the last dose of any antiarrhythmic medication.

Electrophysiological Studies
The study protocol was approved by the regional ethics committee and written informed consent to participate in the study was obtained from all patients. As described in our previous study,9 catheter electrodes with an interelectrode distance of 2 mm were placed at the high right atrium, coronary sinus, and His bundle area. Quadrupolar catheter electrodes with an interelectrode distance of 5 mm were
placed at the right atrial appendage (RAA).

With a programmable electric stimulator (Cardiac Stimulator BC-03, Fukuda Densi, Tokyo, Japan) with rectangular current pulses of 2-ms duration at twice the diastolic threshold, we delivered programmed, single, premature atrial stimuli (S2) after a train of 8 atrial paced beats (S1) at a cycle length of 300 ms from the RAA.

During this study, signals from ECG leads I, aVF, V1, and V5 were recorded simultaneously with the stimulus artifact from the pacing site and with bipolar electrograms from the other electrode sites. The electrograms were filtered at a bandpass of 0.1–500 Hz, and the endocardial electrograms between 30 and 400 Hz were recorded with a computing electric recorder (EPL00372-001-07, EP Lab, Quinton, Canada). The coupling interval between S1 and S2 was reduced in 10-ms steps until S2 was no longer captured.

Definitions

In the present study, S1 and A1 refer to the driving stimulus and the atrial deflection of the basic rhythm, respectively. S2 and A2 refer to the extrastimulus and the deflection resulting from it, respectively, as previously reported.8–20

The effective refractory period of the right atrium (ERP-A) was defined as the longest S1–S2 interval that did not elicit an atrial depolarization. The conduction time from the stimulus artifact to the distal electrode pair placed at the coronary sinus during the single premature stimulation to the RAA.

RAF was defined as the occurrence of 2 or more successive atrial complexes with a return cycle (A2–A3) ≤250 ms and a subsequent cycle length (CL) ≤300 ms (14). Fragmented atrial activity (FAA) was defined as the occurrence of disorganized atrial activity ≥150% of the duration of the local atrial activity in basic beats recorded on the right atrial electrogram.19

The intratrial conduction time (CT) at baseline was defined as the conduction time from the stimulus artifact to the distal electrode pair placed at the coronary sinus during the stimulation at a CL of 500 ms delivered to the RAA (S1A1). Intraatrial conduction delay (CD) was defined as the presence of an increase in S2A2 ≥20 ms as compared with the S1A1 for the basic drive, which was measured from the distal electrode pair placed at the coronary sinus (3 cm from the ostium of the coronary sinus).20

The zones of RAF (RAFZ), fragmented atrial activity (FAAZ), and conduction delay (CDZ) were defined as the range between the longest and the shortest S1–S2 intervals that elicit RAF, FAA, and CD, respectively. When RAF, FAA, or CD was induced at only 1 coupling interval, the zone was expressed as 10 ms.8–20

Each electrophysiologic index was measured before and after flecainide administration, and the plasma concentration of flecainide was determined immediately after the electrophysiologic studies following flecainide administration. A value of p<0.05 was considered to be significant.

Results

Electrophysiological Changes After Intravenous Flecainide

Flecainide significantly prolonged the ERP-A (213±31 to 240±35 ms, p<0.0001) and conduction time (124±22 to 154±28 ms, p<0.0001), but did not significantly change the Max.CD (64±24 to 62±29 ms, p=0.67). Flecainide significantly reduced the RAFZ (22±27 to 11±22 ms, p<0.05), but did not significantly affect the FAAZ (35±27 to 32±30 ms, p=0.64) or CDZ (56±25 to 48±27 ms, p=0.15) (Table 1). Flecainide significantly increased the atrial threshold (0.8±

| Table 1 | Change in the Electrophysiologic Parameters Before and After Flecainide |
|---------|-----------------|------|
| ERP-A (ms) | Before | After | p value |
| CT (ms) | 213±31 | 240±35 | <0.0001 |
| Max. CD (ms) | 64±24 | 62±29 | 0.67 |
| RAFZ (ms) | 22±27 | 11±22 | <0.05 |
| FAAZ (ms) | 35±27 | 32±30 | 0.64 |
| CDZ (ms) | 56±25 | 48±27 | 0.15 |

ERP-A, effective refractory period of atrium; CT, conduction time; Max. CD, maximum conduction delay; RAFZ, repetitive atrial firing zone; FAAZ, fragmented atrial activity zone; CDZ, conduction delay zone.
Effects of Flecainide on RAF

During the baseline study, RAF was induced in 18 [47%; age (mean±standard deviation) 55±9 years] of the 38 patients: 9 of the 19 patients with WPW syndrome, 4 of the 11 patients with AVNRT, 1 of the 3 patients with atrial flutter, 2 of the 3 patients with SSS, the 1 patient with VT, and the 1 patient with AF. RAF was induced in 6 (60%) of the 10 patients with AF and in 12 (43%) of the 28 patients without AF. Although there was a significant difference in age, there were no significant differences in the left ventricular ejection fraction or the left atrial dimension between the patients in whom RAF was or was not induced in the baseline study (Table 2).

After flecainide administration, RAF was abolished in 11 (61%) of the 18 patients with it (Fig 1), whereas RAF was newly induced in 5 (25%) of the 20 patients without RAF in the baseline study. The electrophysiological parameters were not measured in 2 of these 20 patients because sustained AF was induced by flecainide (Fig 2).

Atrial Refractoriness and Conduction Before and After Flecainide

The ERP-A was significantly shorter among the patients with RAF than among those who did not have RAF in the baseline study (202±22 vs 224±34 ms, p<0.05). The Max.CD was significantly longer among the patients with RAF than among those who did not have RAF (77±17 vs 51±23 ms, p<0.001). However, there was no significant difference in the CT of the basic CL between the patients who did or did not have RAF in the baseline study (127±26 vs 121±18 ms).

Flecainide significantly prolonged the ERP-A in the patients with RAF (202±22 to 238±33 ms, p<0.001), whereas it had no significant effect on the ERP-A in the patients without RAF (224±34 to 242±38 ms). Flecainide significantly prolonged the CT in both the patients with RAF (127±26 to 145±25 ms, p<0.0001) and those without RAF (121±18 to 145±25 ms, p<0.0001). Flecainide significantly reduced the Max.CD in the patients with RAF (77±17 vs 63±32 ms, p<0.05), but did not significantly affect Max.CD in the patients without RAF (51±23 to 60±26) (Fig 3).

Flecainide significantly increased the atrial threshold in the patients with RAF (0.9±0.1 to 1.0±0.3, p<0.05) and without RAF (0.8±0.2 to 1.0±0.2, p<0.001).

RAFZ, FAAZ, and CDZ Before and After Flecainide

The RAFZ (43±22 vs 0±0 ms, p<0.0001), FAAZ (51±22 vs 18±22 ms, p<0.001), and CDZ (70±21 vs 42±22 ms, p<0.001) were significantly longer in the patients with RAF than in those without RAF in the baseline study.

Flecainide significantly reduced the RAFZ in the patients
with RAF (43±22 to 13±19 ms, p<0.0001), but had no significant effect on the RAFZ in those without RAF (0±0 to 9±24 ms). Flecainide significantly reduced the FAAZ in the patients with RAF (18±22 to 37±34 ms, p<0.05), whereas it significantly increased the FAAZ in those without RAF. (Right panel) Flecainide significantly reduced the CDZ in those without RAF (42±22 to 49±24 ms) (Fig 4).

Fig 5. Relationship between the effective refractory period of the right atrium (ERP-A) and the percentage change in the ERP-A upon flecainide administration (ΔERP-A). There was a significant negative correlation between the ERP-A in the baseline study and the percentage change in ERP-A upon flecainide administration (n=36, r=0.45, y=−0.53x+139, p<0.01). (□) Patients without repetitive atrial firing (RAF) in control group who had RAF induced after administration of flecainide.

CDZ in those without RAF (42±22 to 49±24 ms) (Fig 4).

ERPA at Baseline and the Changes in the ERP-A and Max.CD After Flecainide Administration

There was a significant negative correlation between the ERP-A in the baseline study and the change in ERP-A after flecainide administration (n=36, r=0.45, p<0.01; Fig 5). There was a significant negative correlation between the
change in the ERP-A and the change in the Max.CD after flecainide administration (n=36, r=0.70, p<0.0001; Fig 6).

**Plasma Drug Concentration Study**

The plasma flecainide concentration was 617±294 (mean±standard deviation) ng/ml immediately before the electrophysiologic studies were performed, and 338±129 ng/ml immediately after, which suggests that the plasma concentration of flecainide in our electrophysiologic study was within the therapeutic range.11 There were no significant differences in the plasma flecainide concentration between the patients with RAF and those without RAF before the electrophysiologic studies (645±310 vs 583±285 ng/ml), nor immediately after the electrophysiologic studies (331±116 vs 307±70 ng/ml).

**Discussion**

There are several limitations to clinical electrophysiological studies of PAF. Investigations based on recordings of local abnormal atrial electrograms occurring during sinus rhythm and abnormal responses elicited by premature atrial stimulation, including RAF, FAA, and intra-atrial CD, have provided information on the electrophysiological properties of the diseased atrium.21,22 However, although these responses do not directly demonstrate the existence of AF, they are closely related to its development and maintenance in predisposed patients.11 Some investigators have reported that RAF is a nonspecific response of atrial muscle, and therefore is not a reliable parameter of a tendency to spontaneous development of AF.21,22,27 Although these findings suggest that flecainide has the potential to prevent the initiation of PAF in patients with RAF and to induce it in those without RAF, our findings indicate that flecainide has the potential to prevent the initiation of PAF in patients with RAF and to induce it in those without RAF.

**Effects of Flecainide on Atrial Refractoriness and Conduction**

There are reports concerning the effects of flecainide on atrial refractoriness and conduction in humans. Pop and Treese reported that flecainide prolonged the ERP-A in patients who had RAF in the baseline study. These findings suggest that flecainide has the potential to prevent the initiation of PAF in patients with RAF and to induce it in those without RAF.

**Effect of Flecainide on Atrial Refractoriness and Conduction**

There are reports concerning the effects of flecainide on atrial refractoriness and conduction in humans. Pop and Treese reported that flecainide prolonged the ERP-A in patients with increased atrial vulnerability and Matsuo et al reported that flecainide prolonged the ERP-A and reduced the Max.CD in patients with PAF.3 However, these reports are of the effects of flecainide on abnormal atrial muscle, and therefore is not a reliable parameter of a tendency to spontaneously develop AF.21,22,27 Although these findings suggest that flecainide has the potential to prevent the initiation of PAF in patients with RAF and to induce it in those without RAF, our findings indicate that flecainide has the potential to prevent the initiation of PAF in patients with RAF and to induce it in those without RAF.

In the present study, we measured several parameters reflecting the electrophysiologic properties of the atrial muscle, including the RAFZ, FAAZ, and CDZ, before and after infusion of flecainide. These zones were reduced by flecainide in the patients with RAF, but were increased in those without RAF. Although further studies are necessary to determine whether these properties can be used to assess antiarrhythmic efficacy and/or pro-arrhythmic potentiality, our findings indicate that flecainide has the potential to prevent the initiation of PAF in patients with RAF and to induce it in those without RAF.

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**Study Limitations**

First, there was not a placebo group. Because all patients received flecainide, the true rates of drug-related suppression of RAf and induction of AF are unclear. Second, RAf or AF in diseased human atria cannot always be explained by reentry and may sometimes be caused by triggered activity. Third, it is known that the atria have significant electrophysiological heterogeneity and that flecainide has anisotropic effects on the wavelengths. By measuring at a single position, it is very difficult to conclusively demonstrate the effects of flecainide on the trigger and substrate of AF. Fourth, the plasma flecainide concentration decreased immediately after the electrophysiologic studies, although it was within the therapeutic range during the study. The prevention of AF.

**Conclusion**

In summary, our study demonstrated that flecainide induced significant prolongation of the ERP-A among the electrophysiological properties of the patients with RAf who had a relatively short ERP-A and long Max.CD in the baseline study. Thus, flecainide may preferentially affect the substrate for RAf or AF, mainly by inducing prolongation of atrial refractoriness and/or by resulting in reduction of the Max.CD. On the other hand, flecainide may worsen the atrial vulnerability of the electrophysiological properties of patients without RAf, mainly by prolonging the conduction delay.

**References**