Electropharmacologic Effects of Class I and Class III Antiarrhythmia Drugs on Typical Atrial Flutter
Insights Into the Mechanism of Termination

Ching-Tai Tai, MD; Shih-Ann Chen, MD; An-Ning Feng, MD; Wen-Chung Yu, MD; Yi-Jen Chen, MD; Mau-Song Chang, MD

Background—Acute effects of class I and class III antiarrhythmia drugs on the reentrant circuit of typical atrial flutter are not fully studied. Furthermore, the critical electrophysiologic determinants of flutter termination by antiarrhythmia drugs are not clear.

Methods and Results—The study population consisted of 36 patients (mean age, 53 ± 17 years) with clinically documented typical atrial flutter. A 20-pole “halo” catheter was positioned around the tricuspid annulus. Incremental pacing was performed to measure the conduction velocity along the isthmus and lateral wall, and extrastimulation was performed to evaluate atrial refractory period in the baseline state and after intravenous infusion of ibutilide, propafenone, and amiodarone. Efficacy of these drugs in conversion of typical atrial flutter and patterns of termination were also determined. Ibutilide significantly increased the atrial refractory period and decreased conduction velocity in the isthmus at short pacing cycle length. It terminated atrial flutter in 8 (67%) of 12 patients after prolongation of flutter cycle length due to increase (86 ± 19%) of conduction time in the isthmus. Propafenone predominantly decreased conduction velocity with use dependency and significantly increased atrial refractory period, but it only converted atrial flutter in 4 (33%) of 12 patients. Amiodarone had fewer effects on atrial refractory period and conduction velocity than did ibutilide and propafenone, and it terminated atrial flutter in only 4 (33%) of 12 patients. Termination of typical atrial flutter was due to failure of wave front propagation through the isthmus, which occurred with cycle length oscillation, abruptly without variability of cycle length, or after premature activation of the reentrant circuit.

Conclusions—Ibutilide, with a unique increase in atrial refractoriness, was more effective in conversion of atrial flutter than were propafenone and amiodarone. (Circulation. 1998;97:1935-1945.)

Key Words: atrial flutter ■ antiarrhythmia agents ■ drugs

Previous mapping studies in patients with typical atrial flutter have demonstrated a macroreentrant circuit localized to the right atrium with a partially or fully excitable gap.1–8 It was controversial as to whether elimination of the excitable gap through prolongation of the refractory period,9–11 or depression of the conduction to a critical point beyond which propagation of conduction would become impossible,12,13 was responsible for experimental canine atrial flutter termination. In the Sicilian Gambit, conduction and excitability are considered vulnerable parameters, and sodium channel–blocking agents are chosen for treatment of typical atrial flutter.14 However, there are clinical evidences that new class III antiarrhythmia drugs such as ibutilide or dofetilide may be more effective than the class I and old class III antiarrhythmia drugs for conversion of typical atrial flutter to sinus rhythm.15–17 In addition, the critical electrophysiologic determinants of antiarrhythmia drug efficacy in typical atrial flutter are not fully delineated. Therefore, in this study we will investigate the electropharmacologic effects and acute termination mechanisms of ibutilide (new class III) compared with propafenone (class IC) and amiodarone (old class III) in patients with typical atrial flutter.

Methods

Patient Characteristics
Thirty-six patients with clinically documented paroxysmal typical atrial flutter were included. There were 22 men and 14 women, with a mean age 53 ± 17 years (range, 22 to 78). All patients were refractory to or intolerant of a mean of 3 ± 1 (range, 2 to 5) antiarrhythmia drugs before referral. Eight patients had associated cardiovascular diseases including hypertension (4 patients), coronary heart disease (3 patients), and mitral valve prolapse (1 patient).

Catheter Positions
Each patient gave informed consent. As described previously, all antiarrhythmia drugs were discontinued for at least five half-lives...
before entering the study. A programmed digital stimulator (DTU-210 or 215, Bloom Associates Ltd) was used to deliver electrical impulses of 2.0 ms in duration at twice diastolic threshold. The study protocol included (1) incremental pacing from the low right atrium and ostium of the coronary sinus at pacing cycle lengths of 500, 400, 300, and 250 ms to measure the activation time in the low right atrial isthmus and lateral wall; (2) burst atrial pacing from the above sites at progressively shorter cycle lengths until 2:1 atrial capture to induce atrial flutter; (3) single extrastimulus testing with 400-ms drive cycle length that was performed at the above pacing sites, septal wall, and right atrial isthmus to determine the atrial effective refractory periods.

Intracardiac bipolar electrograms were displayed simultaneously with ECG leads V1, II, III, and aVF on a multichannel oscilloscopic recorder (CardioLab System, Prucka Engineering, Inc) and were recorded on paper at a speed of 100 or 200 mm/s. The filter was set from 30 to 500 Hz. The onset of activation electrograms was measured when the first rapid deflection crosses the baseline with an angle $>45$ degrees. In the left anterior oblique (LAO) view, the electrode pairs located in the medial sites of the right atrium–inferior vena cava junction were considered located within the isthmus; those located in the lateral sites of the right atrium–inferior vena cava junction were considered located within the lateral wall. Therefore the relevant conduction velocity could be calculated by measuring the respective activation time and distance between two end-dipoles within the isthmus and lateral wall. The method for measuring activation time during atrial flutter was the same as that during atrial pacing. In Fig 1B, the H1 electrode pair is located at the ostium of the coronary sinus, H2 to H5 electrode pairs are located within the low right atrial isthmus, and H6 to H10 electrode pairs are located within the lateral free wall. Conduction velocity in the low right atrial isthmus was measured from the septal portion to the lateral portion (H1 to H5) and from the lateral portion to the septal portion (H5 to H1) during pacing from the coronary sinus ostium and low lateral right atrium (near the H6 electrode pair), respectively. Conduction velocity in the lateral wall (H6 to H10) was only measured during pacing from the low right atrium (near the H6 electrode pair) because activation of the lateral free wall during pacing from the coronary sinus ostium represents bidirectional conduction through the interatrial septum and low right atrial isthmus with collision of wave fronts in the mid-lateral free wall.

**Pharmacologic Study**

The study population was divided into three groups. There were 12 patients in each group. After baseline study, sustained typical atrial flutter was induced. Group 1 patients received intravenous infusion of ibutilide, 0.02 mg/kg over 10 minutes; group 2 patients received intravenous infusion of propafenone, 2 mg/kg over 10 minutes followed by 0.4 mg/min; and group 3 patients received intravenous infusion of amiodarone, 10 mg/kg over 10 minutes followed by 30 mg/h. Efficacy of antiarrhythmia drugs for conversion of atrial flutter was determined after the beginning of administration, and patterns of termination were evaluated. If atrial flutter was not converted at 15 minutes after completion of the drug-loading infusion, incremental atrial pacing was performed carefully to terminate it without inducing atrial fibrillation. The electrophysiologic study protocol and measurement were repeated immediately after spontaneous or drug-inducing terminated atrial flutter to observe the pharmacologic effects on the atrial conduction velocity and effective refractory period.

**Definitions**

The low right atrial isthmus was defined as a path formed by the orifice of the inferior vena cava, eustachian valve/ridge, coronary sinus ostium, and tricuspid annulus. Counterclockwise (typical) atrial flutter was defined as an atrial flutter with a similar flutter cycle length and reverse activation sequence of the counterclockwise...
Conduction Velocity at Different Pacing Cycle Lengths in the Three Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Ithutilde</th>
<th>Propafenone</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCL 500 ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isthmus (CCW)</td>
<td>0.64±0.10</td>
<td>0.64±0.10</td>
<td>0.74±0.11</td>
<td>0.72±0.10</td>
</tr>
<tr>
<td>Isthmus (CW)</td>
<td>0.65±0.10</td>
<td>0.65±0.10</td>
<td>0.76±0.07</td>
<td>0.74±0.07</td>
</tr>
<tr>
<td>Free wall</td>
<td>0.97±0.18</td>
<td>0.97±0.18</td>
<td>1.14±0.24</td>
<td>1.01±0.09</td>
</tr>
<tr>
<td>Isthmus (CCW)</td>
<td>0.62±0.09</td>
<td>0.62±0.09</td>
<td>0.72±0.10</td>
<td>0.71±0.12</td>
</tr>
<tr>
<td>Isthmus (CW)</td>
<td>0.63±0.10</td>
<td>0.59±0.21</td>
<td>0.74±0.08</td>
<td>0.73±0.09</td>
</tr>
<tr>
<td>Free wall</td>
<td>0.97±0.18</td>
<td>0.97±0.18</td>
<td>1.14±0.24</td>
<td>1.01±0.09</td>
</tr>
<tr>
<td>Isthmus (CCW)</td>
<td>0.60±0.10</td>
<td>0.58±0.11</td>
<td>0.69±0.10</td>
<td>0.67±0.13</td>
</tr>
<tr>
<td>Isthmus (CW)</td>
<td>0.56±0.20</td>
<td>0.53±0.20</td>
<td>0.71±0.06</td>
<td>0.70±0.09</td>
</tr>
<tr>
<td>Free wall</td>
<td>0.96±0.18</td>
<td>0.95±0.19</td>
<td>1.13±0.25</td>
<td>1.01±0.09</td>
</tr>
<tr>
<td>Isthmus (CCW)</td>
<td>0.57±0.10</td>
<td>0.51±0.12</td>
<td>0.63±0.08</td>
<td>0.64±0.13</td>
</tr>
<tr>
<td>Isthmus (CW)</td>
<td>0.54±0.19</td>
<td>0.49±0.18</td>
<td>0.66±0.07</td>
<td>0.67±0.09</td>
</tr>
<tr>
<td>Free wall</td>
<td>0.96±0.18</td>
<td>0.93±0.17</td>
<td>1.10±0.26</td>
<td>0.98±0.12</td>
</tr>
</tbody>
</table>

CCW indicates counterclockwise activation during pacing from the low lateral right atrium; CW, clockwise activation during pacing from the coronary sinus ostium; and PCL, pacing cycle length.

Data are expressed as mean±SD (m/s).
*P<.05, 500 ms vs other PCL.

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Ithutilde</th>
<th>Propafenone</th>
<th>Amiodarone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCL 400 ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isthmus (CCW)</td>
<td>0.62±0.09</td>
<td>0.62±0.09</td>
<td>0.72±0.10</td>
<td>0.71±0.12</td>
<td>.180</td>
</tr>
<tr>
<td>Isthmus (CW)</td>
<td>0.63±0.10</td>
<td>0.59±0.21</td>
<td>0.74±0.08</td>
<td>0.73±0.09</td>
<td>1.000</td>
</tr>
<tr>
<td>Free wall</td>
<td>0.97±0.18</td>
<td>0.97±0.18</td>
<td>1.14±0.24</td>
<td>1.01±0.09</td>
<td>.002</td>
</tr>
<tr>
<td>Isthmus (CCW)</td>
<td>0.60±0.10</td>
<td>0.58±0.11</td>
<td>0.69±0.10</td>
<td>0.67±0.13</td>
<td>.068</td>
</tr>
<tr>
<td>Isthmus (CW)</td>
<td>0.56±0.20</td>
<td>0.53±0.20</td>
<td>0.71±0.06</td>
<td>0.70±0.09</td>
<td>.180</td>
</tr>
<tr>
<td>Free wall</td>
<td>0.96±0.18</td>
<td>0.95±0.19</td>
<td>1.13±0.25</td>
<td>1.01±0.09</td>
<td>.109</td>
</tr>
<tr>
<td>Isthmus (CCW)</td>
<td>0.57±0.10</td>
<td>0.51±0.12</td>
<td>0.63±0.08</td>
<td>0.64±0.13</td>
<td>.043</td>
</tr>
<tr>
<td>Isthmus (CW)</td>
<td>0.54±0.19</td>
<td>0.49±0.18</td>
<td>0.66±0.07</td>
<td>0.67±0.09</td>
<td>.043</td>
</tr>
<tr>
<td>Free wall</td>
<td>0.96±0.18</td>
<td>0.93±0.17</td>
<td>1.10±0.26</td>
<td>0.98±0.12</td>
<td>.068</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Ithutilde</th>
<th>Propafenone</th>
<th>Amiodarone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCL 300 ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isthmus (CCW)</td>
<td>0.60±0.10</td>
<td>0.58±0.11</td>
<td>0.69±0.10</td>
<td>0.60±0.12</td>
<td>.109</td>
</tr>
<tr>
<td>Isthmus (CW)</td>
<td>0.56±0.20</td>
<td>0.53±0.20</td>
<td>0.71±0.06</td>
<td>0.69±0.09</td>
<td>.180</td>
</tr>
<tr>
<td>Free wall</td>
<td>0.96±0.18</td>
<td>0.95±0.19</td>
<td>1.13±0.25</td>
<td>0.94±0.11</td>
<td>.109</td>
</tr>
<tr>
<td>Isthmus (CCW)</td>
<td>0.57±0.10</td>
<td>0.51±0.12</td>
<td>0.63±0.08</td>
<td>0.60±0.12</td>
<td>.043</td>
</tr>
<tr>
<td>Isthmus (CW)</td>
<td>0.54±0.19</td>
<td>0.49±0.18</td>
<td>0.66±0.07</td>
<td>0.65±0.09</td>
<td>.043</td>
</tr>
<tr>
<td>Free wall</td>
<td>0.96±0.18</td>
<td>0.93±0.17</td>
<td>1.10±0.26</td>
<td>0.89±0.12</td>
<td>.068</td>
</tr>
</tbody>
</table>

flatter. Atypical atrial flutter was defined as an atrial flutter other than the counterclockwise and clockwise atrial flutters.

Statistical Analysis
Quantitative values are expressed as mean±SD. The Wilcoxon signed rank test was used for statistical comparison of the conduction velocity and effective refractory periods before and after infusion of antiarrhythmia drugs. Statistical comparison of effective refractory period in the low right atrium, right atrial isthmus, right atrial septal wall, and coronary sinus ostium, and comparison of continuous data among three groups were performed with the use of Kruskal-Wallis one-way ANOVA test. A value of P<.05 was considered to be statistically significant.

Results

Group 1 Patients
Conduction Velocity
Conduction velocity from the septal isthmus to the lateral isthmus during pacing from the coronary sinus ostium and from the lateral isthmus to the septal isthmus during pacing from the low lateral right atrium at 500-, 400-, 300-, and 250-ms drive cycle lengths was significantly lower than that in the lateral wall during pacing from the low lateral right atrium before and after infusion of ibutilide (Table). Ibutilide only decreased conduction velocity in the isthmus at 250-ms pacing cycle length but did not significantly change conduction velocity in the lateral wall at any pacing cycle length (Fig 2A and 2B).

Effective Refractory Period
At baseline study the effective refractory period at the low right atrial isthmus and coronary sinus ostium (215±18 and 213±23 ms) was significantly longer than that at the septal and low right atrium (193±23 and 198±21 ms) (P<.05). Ibutilide significantly prolonged the effective refractory periods to a similar extent in the septal right atrium (251±37 ms, +31±19%), low right atrium (256±24 ms, +30±16%), right atrial isthmus (273±28 ms, +28±20%), and coronary sinus ostium (260±13 ms, +24±12%) (Figs 3 and 4).

Figure 2. Conduction velocity in the right atrial free wall (FW) and low right atrial isthmus (IS) during different pacing cycle lengths in the baseline state and after infusion of ibutilide. A, Results from coronary sinus ostial pacing. B, Results from low right atrial pacing. *P<.05, baseline vs ibutilide; †P<.05, 500 ms vs other pacing cycle lengths.
Termination of Typical Atrial Flutter

Typical (counterclockwise) atrial flutter was induced in all patients, and clockwise atrial flutter was induced in 4 of 12 patients. The baseline cycle length of counterclockwise atrial flutter was 226 ± 22 ms. After ibutilide infusion during counterclockwise atrial flutter, the flutter cycle length was prolonged to 264 ± 22 ms, with termination of atrial flutter in 8 (67%) of 12 patients. Most of the increase in cycle length was due to an increase (86 ± 19%) of activation time in the low right atrial isthmus (Fig 5). Oscillation of flutter cycle length without change of activation sequence resulting in interruption of reentry circuit was found in 4 patients (Fig 6). Two patients had abrupt termination of atrial flutter without cycle length oscillation, and 2 patients had termination after premature activation of the reentrant circuit (Fig 7).

Group 2 Patients

Conduction Velocity

Conduction velocity from the septal isthmus to the lateral isthmus during pacing from the coronary sinus ostium and from the lateral isthmus to the septal isthmus during pacing from the low lateral right atrium at 500-, 400-, 300-, and 250-ms drive cycle lengths was significantly lower than that in the lateral wall during pacing from the low lateral right atrium before and after infusion of propafenone (Table). Propafenone significantly decreased conduction velocity in the isthmus and lateral wall with use-dependent effects (Fig 8A and 8B).

Effective Refractory Period

At baseline study, the effective refractory period at the low right atrial isthmus and coronary sinus ostium (204 ± 17 and 205 ± 22 ms) was significantly longer than that at the septal and low right atrium (184 ± 17 and 193 ± 17 ms) (P < .05). Propafenone significantly prolonged the effective refractory periods to a similar extent in the septal right atrium (229 ± 26 ms, +25 ± 13%), low right atrium (230 ± 27 ms, +19 ± 11%), right atrial isthmus (262 ± 40 ms, +29 ± 18%), and coronary sinus ostium (235 ± 26 ms, +15 ± 12%) (Fig 9).

Termination of Typical Atrial Flutter

Typical (counterclockwise) atrial flutter was induced in all patients, and clockwise atrial flutter was induced in 5 of 12 patients. The baseline cycle length of counterclockwise atrial flutter was 204 ± 18 ms. After propafenone infusion during counterclockwise atrial flutter, the flutter cycle...
length was prolonged to 342±46 ms, with termination of atrial flutter in 4 (33%) of 12 patients. Most of the increase in cycle length was due to an increase (64±13%) of activation time in the low right atrial isthmus (Fig 10). These 4 patients had cycle length oscillation with conduction block in the isthmus resulting in termination of atrial flutter.

Group 3 Patients

Conduction Velocity

Conduction velocity from the septal isthmus to the lateral isthmus during pacing from the coronary sinus ostium and from the lateral isthmus to the septal isthmus during pacing from the low lateral right atrium at 500-, 400-, 300-, and
250-ms drive cycle lengths was significantly lower than that in the lateral wall during pacing from the low lateral right atrium before and after infusion of amiodarone (Table). Amiodarone significantly decreased conduction velocity in the isthmus at 250-ms pacing cycle length but did not significantly change conduction velocity in the lateral wall at any pacing cycle length (Fig 11, A and B).

**Effective Refractory Period**

At baseline study, the effective refractory period at the low right atrial isthmus and coronary sinus ostium (210±17 and 213±16 ms) was significantly longer than that at the septal and low right atrium (185±17 and 194±22 ms) (P<.05). Amiodarone significantly prolonged the effective refractory periods to a similar extent in the septal right atrium (218±21 ms, +18±11%), low right atrium (223±19 ms, +16±10%),

![Figure 7](image7.png)

**Figure 7.** Another case of typical atrial flutter terminated by intravenous infusion of ibutilide. Premature eccentric activation of the reentrant circuit at H6 electrode pair (*) during the last two beats of atrial flutter results in failure of wave front propagation between H5 and H4 electrode pairs in the isthmus. HIS PX indicates proximal His bundle area; CS OS, coronary sinus ostium; and HAL, halo.

![Figure 8](image8.png)

**Figure 8.** Conduction velocity in the right atrial free wall (FW) and low right atrial isthmus (IS) during different pacing cycle lengths in the baseline state and after infusion of propafenone. A, Results from coronary sinus ostial pacing. B, Results from low right atrial pacing. *P<.05, baseline vs propafenone; †P<.05, 500 ms vs other pacing cycle lengths.

![Figure 9](image9.png)

**Figure 9.** Effective refractory periods (ERP) of the low right atrial isthmus (IST), right atrial septum (SEP), right posterolateral atrium (RPL), and coronary sinus ostium (CSO) in the baseline state (open columns) in group 2 patients. Infusion of propafenone significantly increased the atrial ERP (dashed columns). *P<.05.
right atrial isthmus (237±19 ms, +13±9%), and coronary sinus ostium (234±18 ms, +10±7%) (Fig 12).

Termination of Typical Atrial Flutter
Typical (counterclockwise) atrial flutter was induced in all patients, and clockwise atrial flutter was induced in 4 of 12 patients. The baseline cycle length of counterclockwise atrial flutter was 217±14 ms. After amiodarone infusion during counterclockwise atrial flutter, the flutter cycle length was slightly prolonged to 233±17 ms, with termination of atrial flutter in 4 (33%) of 12 patients. All of the increase in cycle length was due to an increase of activation time in the low right atrial isthmus. One patient had abrupt termination of atrial flutter caused by conduction block in the isthmus without cycle length oscillation (Fig 13) and 3 patients had termination after premature activation of the reentrant circuit.

Comparisons Among Groups 1, 2, and 3
Propafenone decreased conduction velocity in the isthmus and lateral wall to a greater extent than did ibutilide and amiodarone at all pacing cycle lengths (Fig 14). Ibutilide and propafenone increased atrial effective refractory period to a greater extent than did amiodarone (Fig 15). Ibutilide was more effective in termination of typical atrial flutter than propafenone and amiodarone (67% versus 33% versus 33%, \( P<.05 \)).

Discussion

Major Findings
In addition to a lower conduction velocity, the low atrial isthmus had a longer effective refractory period than did the septal and free walls in the right atrium. Ibutilide significantly increased atrial effective refractory period and prolonged the flutter cycle length. Propafenone markedly prolonged the flutter cycle length due to a predominant increase of activation time in the low right atrial isthmus. Amiodarone had the least effects on the atrial flutter circuit although it mildly increased atrial effective refractory period. Ibutilide was more effective than was propafenone and amiodarone in converting typical atrial flutter, which occurred with cycle length oscillation, abruptly without variability of flutter cycle length, or after premature activation of the reentrant circuit.

Electropharmacologic Effects of Ibutilide, Propafenone, and Amiodarone
Ibutilide fumarate is a novel class III antiarrhythmia drug that prolongs the action potential duration and effective refractory periods in both the atria and ventricles.\(^{20-22}\) Its cellular electrophysiologic mechanisms involve increasing a slow inward plateau sodium current and inhibiting the outward repolarizing potassium current.\(^{23,24}\) In contrast to class I antiarrhythmia drugs, it does not appear to significantly decrease conduction velocity.\(^{20}\) In conscious dogs with Y-shaped right atrial incisions, Buchanan et al\(^{25}\) reported that oral ibutilide could increase atrial effective refractory period and prevent reinduction of experimental atrial flutter. In a subsequent study, they demonstrated that intravenous ibutilide increased the flutter cycle length before termination of atrial flutter in 8 of 8 dogs, and it was more effective in converting and in preventing reinitiation of atrial flutter than sematilide, lidocaine, and encainide.\(^{21}\) Recently, they compared ibutilide and \( d, l \)-sotalol in an intravenous crossover
study by using the canine atrial sterile pericarditis model; the results showed that ibutilide converted atrial flutter in dogs in which sotalol was not successful, and it had a lower incidence of reinduced arrhythmia compared with sotalol after termination of atrial flutter. In the present study, intravenous ibutilide significantly increased atrial effective refractory period in patients with clinical atrial flutter by 24% to 31%. In contrast, ibutilide only decreased conduction velocity in the isthmus (with a longer effective refractory period) at 250-ms pacing cycle length without slowing conduction in the free wall at any pacing cycle length. Although we did not record atrial monophasic action potentials, the significant slowing of conduction velocity in the isthmus may be due to impingement of paced beats on the relative refractory period of the preceding beat, thus reducing upstroke velocity of the action potential and indirectly reducing conduction velocity. Thus prolongation of atrial flutter cycle length after ibutilide infusion was due to a predominant increase of activation time in the right atrial isthmus.

Propafenone is a class IC antiarrhythmia drug that has weak β-adrenergic antagonist properties. Recently, Duan et al found that propafenone blocked the transient outward, delayed rectifier and inward rectifier potassium currents in rabbit atrial myocytes. In the canine Y-shaped incision model, Spinelli and Hoffman reported that propafenone terminated atrial flutter in 6 of 6 dogs; termination was preceded by marked increases in the flutter cycle length as a result of marked slowing of conduction velocity and less prolongation of atrial refractory period. In the present study, propafenone produced use-dependent decrease of conduction velocity in the isthmus and free wall and increased atrial refractory period by 15% to 29%. It markedly prolonged the flutter cycle length due to a predominant increase of activation time in the low right atrial isthmus.

The primary effects of intravenous amiodarone include depression of sinus rhythm and AV node conduction by blocking β-adrenergic receptors and calcium channels, slowing intraventricular conduction by blocking sodium channels, and slight prolongation of atrial and ventricular refractory period by inhibiting potassium channels. Platou and Refsum reported that intravenous amiodarone could convert rapid pacing-induced atrial flutter to sinus rhythm by increasing atrial refractoriness in 5 of 5 dogs. In the present study, amiodarone prolonged atrial refractory period to a lesser extent (10% to 18%) than did ibutilide and propafenone. Furthermore, it only decreased isthmus conduction velocity at 250-ms pacing cycle length with borderline significance and did not significantly change conduction velocity in the free wall at any pacing cycle length. Thus the cycle length of typical atrial flutter was only slightly prolonged.

Possible Mechanisms of Termination of Typical Atrial Flutter by Antiarrhythmia Drugs

Recent entrainment mapping studies of human typical atrial flutter have demonstrated that this arrhythmia is an anatomically based reentrant circuit in the right atrium. Furthermore, our previous and current studies have demonstrated slow conduction properties in the low right atrial isthmus during atrial pacing and typical atrial flutter. In contrast, Kinder et al reported that decremental conduction is not characteristic of activation through the isthmus when activation is assessed parallel and adjacent to the tricuspid annulus. The different findings may be explained by the fact that Kinder et al did not map multiple points between the coronary sinus ostium and inferolateral tricuspid annulus sites, but it was demonstrated in our previous study that more medial
sites of the isthmus near the coronary sinus ostium have more conduction delay. An important feature of an anatomically defined, ordered reentrant circuit is that there exists a gap of either partially or completely excitable tissue between the crest of the circulating reentrant impulse and the relative refractory “tail.” Therefore antiarrhythmia drugs theoretically can interrupt typical atrial flutter by abolishing the excitable gap through prolongation of the atrial refractory period or slowing of isthmus conduction to a critical point beyond which propagation of the circulating impulse becomes impossible. This study showed that termination of typical atrial flutter by ibutilide, propafenone, and amiodarone was due to failure of wave front propagation through the low right atrial isthmus, which occurred with cycle length oscillation, abruptly without variability of cycle length, or after premature activation of the reentrant circuit.

In the present study, conversion of atrial flutter by ibutilide was characterized mainly by increased cycle length variability. Guo et al have suggested that ibutilide may induce transient beat-to-beat changes in action potential duration and atrial refractoriness and produce unstable oscillations in the reentrant circuit. Presumably during these oscillating cycles of reentry, tissues are excited, depolarized, and begin to repolarize but recover to different levels of full excitability. Finally, oscillations between two consecutive cycle lengths are such that the
arriving reentrant impulse collides with longer refractory isthmus tissues that have not recovered, and block occurs.\textsuperscript{36–38} In the absence of complete elimination of the excitable gap,\textsuperscript{39} a possible explanation for abrupt termination of atrial flutter without cycle length variability by ibutilide and amiodarone would be a reduced safety factor for conduction resulting from decreased atrial excitability or encroachment of the reentrant wave front on the relative refractory period of sites with markedly prolonged refractoriness, as suggested by Cha et al\textsuperscript{27} and Restivo et al.\textsuperscript{40} Termination of atrial flutter after premature activation of the reentrant circuit by ibutilide and amiodarone requires either failure of the lateral boundaries of the reentrant circuit with subsequent penetration by a secondary activation wave front or a reflected impulse generated within the circle path (return reexcitation).\textsuperscript{12,27,41} This most likely occurs as a result of slowing conduction in the reentrant circuit to a greater extent than surrounding tissues, allowing the eccentric wave front to penetrate the reentrant circuit or returning wave front to reactivate the circle path prematurely.\textsuperscript{27} Failure of wave front propagation after premature activation of the reentrant circuit may then result from local elimination of the excitable gap, due to marked transient shortening of the tachycardia cycle length below the local effective refractory period.\textsuperscript{27}

Spinelli and Hoffman\textsuperscript{12} and Derakhchan et al\textsuperscript{42} have demonstrated that the excitable gap of the experimental canine atrial flutter was not significantly changed by propafenone. This finding is due to marked slowing of conduction velocity that neutralizes an increase of the refractory period and exposes a similar or more excitable gap of the reentrant circuit. Therefore, Spinelli and Hoffman\textsuperscript{12} and Inoue et al\textsuperscript{11} suggested that propafenone or other class I antiarrhythmia drugs terminated atrial flutter primarily by depressing conduction to a critical point beyond which wave front propagation becomes impossible. In the present study, termination of typical atrial flutter by propafenone was preceded by prolongation and oscillation of flutter cycle length with long-short cycle length at sites proximal to the site of eventual block in the right atrial isthmus.

Study Limitations

Several aspects of the methodology used in this study may limit our conclusions about the termination mechanism of atrial flutter by antiarrhythmia drugs. First, it is a major problem to measure conduction time in human study. However, we used the halo catheter to map multiple sites around the tricuspid annulus so that the measured activation time should be close to the real conduction time from which conduction velocity is derived. Second, determination of the excitable gap and refractory period during atrial flutter was not performed because programmed stimulation might itself terminate atrial flutter, and the stimulation site relative to the reentrant circuit might affect the measurement of the excitable gap and refractory period. Third, there might be insufficient mapping resolution, and measurement of the local electrophysiologic properties was not performed at the time of tachycardia termination, at which time the effects of the antiarrhythmia drugs were likely different. Thus the exact mechanism of termination remains to be investigated. Fourth, the postdrug electrophysiologic study was not performed at the same time in all patients, so that differences in serum drug level might have contributed to variation in measurement of refractory period and conduction velocity. Finally, we were not certain that the halo and coronary sinus catheters were directly in the path of the atrial flutter circuit; thus assumptions regarding conduction time and velocity are less certain.

Conclusions

Ibutilide, with its unique cellular electrophysiologic effects, increases atrial refractory period so much that it can decrease conduction velocity in the isthmus at short pacing cycle length by encroachment of the relative refractory period. Propafenone, a sodium channel–blocking agent, predominantly depressed conduction velocity in the isthmus and free wall with use dependency and significantly increased atrial refractoriness. Amiodarone had fewer effects on atrial refractory period and conduction velocity than did ibutilide and propafenone. Ibutilide was more effective in conversion of typical atrial flutter than was propafenone and amiodarone. Termination of typical atrial flutter was due to failure of wave front propagation through the low right atrial isthmus, which occurred with cycle length oscillation, abruptly without variability of cycle length, or after premature activation of the reentrant circuit by an eccentric wave front.

Acknowledgments

This study was supported in part by grants from the National Science Council (NSC 85–2331-B-075–071, 85–2331-B-010–047, 85–2331-B-010–048, 86–2314-B-010–048, 86–2314-B-075–034, 86–2314-B-075–097) and Tzou’s Foundation (VGHYM-S4–30, VGHYM-S4–31), Taipei, Taiwan, ROC.

References

11. Inoue H, Yamasita T, Noraka A, Sugimoto T. Effects of antiarrhythmia drugs on canine atrial flutter due to reentry: role of prolongation of
Electropharmacologic Effects of Class I and Class III Antiarrhythmia Drugs on Typical Atrial Flutter: Insights Into the Mechanism of Termination
Ching-Tai Tai, Shih-Ann Chen, An-Ning Feng, Wen-Chung Yu, Yi-Jen Chen and Mau-Song Chang

_Circulation_. 1998;97:1935-1945
doi: 10.1161/01.CIR.97.19.1935

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/97/19/1935

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/