Electrophysiological Response of the Right Atrium to Ibutilide During Typical Atrial Flutter

Jie Cheng, MD, PhD; Kathryn Glatter, MD; Yanfei Yang, MD; Shulong Zhang, MD; Randall Lee, MD; Melvin M. Scheinman, MD

Background—The efficacy of ibutilide in conversion of atrial fibrillation and flutter (AFL) has been demonstrated. However, its electrophysiological effects on human atria have not been fully studied.

Methods and Results—Twelve patients with typical AFL were studied. Electrograms were recorded from the anterolateral right atrium, His bundle position, and coronary sinus. During AFL, we measured the conduction time, CTi, through the isthmus between the tricuspid annulus and eustachian ridge and the conduction time, CTni, through the remainder of the right atrium. Resetting response curves and atrial effective refractory periods were determined with single extrastimuli delivered in the tricuspid annulus–eustachian ridge isthmus. After infusion of ibutilide (2 mg over 15 minutes), AFL cycle length (CL) increased from 260±30 to 295±39 ms (P<0.0003) because of an increase in either CTi, CTni, or both. Effective refractory periods increased from 149±16 to 208±26 ms (P<0.001). AFL CL variability increased, with a rightward shift of the resetting response curves and loss of full excitability. In 8 patients, AFL was terminated by atrial overdrive pacing after ibutilide at CLs equal to or longer than those that were not effective at baseline, which was caused by orthodromic block in the tricuspid annulus–eustachian ridge isthmus or was associated with development of transient rapid rhythms around newly formed sites of intra-atrial conduction block.

Conclusions—Ibutilide causes prolongation of AFL CL and increased CL variability by abolishment of a fully excitable gap. Ibutilide may facilitate pace termination of AFL by development of new short-lived reentry around functional blocks. (Circulation. 2002;106:814-819.)

Key Words: atrial flutter ■ electrophysiology ■ antiarrhythmic agents

Clinical trials have demonstrated the efficacy of ibutilide, a class III antiarrhythmic agent, in conversion of atrial fibrillation and flutter.1–3 Ibutilide selectively blocks the rapid-activating delayed potassium rectifying current, Ikr, and may enhance a slow inward sodium current during the plateau phase of the action potential.4–6 Recent data have shown that ibutilide increases atrial effective refractory periods (AERPs) and leads to significant variability in cycle length (CL) of typical atrial flutter (AFL) before termination.7,8 In addition, others have noted that atrial overdrive pacing (AODP) is more effective in terminating AFL after ibutilide infusion.9 The purpose of the present study was to define the mechanisms of AFL CL variation and AODP-induced AFL termination with ibutilide.

Methods

Patient Selection

Twelve consecutive patients with AFL were studied between September 1996 and March 1997. Eleven were males, and the average age was 65.8±13.7 years (range 35 to 79 years). Three had no structural heart disease; 3 had coronary artery disease; 2 had hypertension; 4 had moderately decreased left ventricular ejection fraction; and 1 had moderate mitral regurgitation. All had normal thyroid function tests. None had clinical evidence of myocardial ischemia. None were taking antiarrhythmic medications or digitals. β-Antagonists or calcium channel blockers were discontinued at least 3 half-lives before the study. These patients were included in our previous report on AFL acceleration by programmed electrical stimulation.10

Electrophysiological Testing

Patients were admitted to the electrophysiology laboratory in a postabsorptive and unsedated state. Venous access was obtained with 7F and 8F sheaths in the right internal jugular and femoral veins. A 20-pole catheter was placed in a counterclockwise orientation against the tricuspid annulus with its distal tip at the lateral entrance point to the isthmus between the tricuspid annulus and the eustachian ridge (TA-ER isthmus) and its proximal electrode at the high interatrial septum, as shown in Figure 1. Atrial activation at the anterior septum and coronary sinus was also recorded. A 4-mm-tip radiofrequency ablation catheter was placed within the TA-ER isthmus. Pulse oximetry and vital signs were monitored throughout the study.

The 12-lead surface ECGs and intracardiac signals were recorded with a computerized multichannel data acquisition system (CardioLab by Prucka Engineering Inc). Intracardiac signals were filtered with low and high cutoff frequencies of 30 and 500 Hz, respectively.
Ibutilide Effects During Typical Atrial Flutter

Cheng et al

Figure 1. Electrode positioning and conduction times. Outermost circle represents tricuspid annulus (TA) in left anterior oblique (LAO) projection. SVC indicates superior vena cava; CS os, coronary sinus os; CT, cristae terminalis; TA 1 to TA 10, recording sites along 20-pole catheter placed anterior to CT; and RF catheter, radiofrequency ablation catheter. Isthmus conduction time (CTi) is defined as difference in local activation recorded from TA1 and CS os. Conduction time through remainder of AFL circuit in right atrium (CTni) is derived by subtracting CTi from AFL CL.

Determination of AERP and Resetting Response Curve

Single atrial extrastimuli (AES) at twice the diastolic pacing threshold with a 2-ms pulse width were delivered in the TA-ER isthmus. The coupling interval of the AES was progressively decreased at 5- to 10-ms decrements to scan the entire AFL cycle. The AERP in the TA-ER isthmus was defined as the longest AES coupling interval that failed to result in local atrial depolarization. The excitable gap was determined as the range of coupling intervals that advanced local activation in the TA-ER isthmus and reset AFL.

The resetting response curve (RRC) was derived by plotting the return cycle in response to an AES against the coupling interval of the AES during AFL. Because of the pacing artifact in the TA-ER isthmus signals and variable latency in local capture, we chose to use corresponding atrial electrograms from the closest recording site in the orthodromic direction. For example, local atrial electrograms from the coronary sinus os were used to measure the coupling interval of the test cycle and the return cycle during counterclockwise AFL (Figures 2A and 2B). Likewise, atrial electrograms from recording site TA1 were used in clockwise AFL (Figure 1). We defined the test cycle as the interval between the last atrial electrogram in response to the pacing stimulation and the advanced atrial electrogram in response to the pacing stimulation and the return cycle as the CL of the immediately following cycle. Resetting is defined as sequential advancement of local atrial electrograms in all recording sites within the AFL circuit in response to the test stimulation without change in the overall activation sequence. To compare baseline RRCs with those after ibutilide, we normalized the return cycle and the test cycle by expressing them as percentages of the prevailing AFL CL (Figure 2). We defined the flat portion of the RRC as the portion of the curve where the return cycle did not exceed 5 ms over the AFL CL (Figure 2C). Because of the significant CL variability after ibutilide, average AFL CL over 5 consecutive beats was used as the prevailing AFL CL.

Termination of AFL by AODP in the TA-ER Isthmus

AODP was performed at baseline and after ibutilide. The pacing CL was selected to be 20 to 70 ms below the AFL CL at baseline, except in patient 7, in whom aggressive AODP at a CL of 100 ms was used. After ibutilide infusion, AODP CL was initially selected to be 20 to 50 ms below the prolonged AFL CL and then progressively decreased until it reached the minimum pacing CL used at baseline or the AFL was terminated.

After the study protocol, patients underwent radiofrequency AFL ablation. The Institutional Review Board of the University of California San Francisco Medical Center approved the study protocol. Informed consent was obtained from each patient.

Statistical Analysis

Statistical analyses were performed with commercial software (Excel 4.0, Microsoft Corp). Variables are reported as mean ± SD. Comparison between means was performed with 2-tailed t test. A probability value of <0.05 was considered statistically significant.

Results

Eleven patients had counterclockwise AFL with negative flutter waves in the inferior surface ECG leads. Clockwise AFL was induced in 1 patient with paroxysmal AFL with predominantly positive flutter waves in the inferior surface ECG leads. During baseline study, AFL was terminated in 3 patients after a transient episode of double-wave reentry. In 2 of them, AFL could not be reinduced, and ibutilide was not given. Ibutilide increased the corrected QT interval, determined by Bazett formula, from 428 ± 40 to 498 ± 45 ms (P < 0.001). No patient had adverse effects such as torsade de pointes. In 2 patients, spontaneous AFL termination was observed with ibutilide infusion. AFL terminated with block in the TA-ER isthmus in 1 patient. In the other, a premature atrial depolarization or breakdown of the lateral boundary occurred in the lower right atrium that had an activation sequence similar to lower-loop reentry pattern.

Effects of Ibutilide on AFL CL and Intra-Atrial Conduction Times

In 10 patients who received ibutilide, AFL CL increased significantly from 260 ± 29 to 295 ± 39 ms (P < 0.0003) after ibutilide infusion (Table). As shown in the Table, the prolongation of AFL CL was primarily due to slower TA-ER
isthmus conduction in 3 patients (patients 6, 9, and 11), slower conduction in the nonisthmus right atrium in 6 patients (patients 2, 3, 5, 7, 10, and 12), and significantly slowed conduction in both the TA-ER isthmus and the nonisthmus right atrium in 1 (patient 1). Ibutilide increased the maximum difference in AFL CL from 7.6/11006 3.3 to 14.3/11006 4.9 ms (P/11005 0.005), increased the standard deviation in AFL CL from 3.1/11006 1.4 to 5.5/11006 2.0 ms (P/11005 0.02), and increased the coefficient of variation from 1.25/11006 0.70% to 1.86/11006 0.68% (P/11005 0.034).

Effects of Ibutilide on Atrial Refractoriness
AERP increased from 149/11006 16 to 208/11006 26 ms after ibutilide (P/11005 0.001). The excitable gap decreased from 101/11006 36 to 71/11006 27 ms (P/11005 0.003). The percentage of the AFL CL occupied by the excitable gap dropped from 39.5/11006 10.2% to 25.0/11006 8.0% (P/11005 0.001).

RRCs were constructed in 8 patients at baseline and after ibutilide. At baseline, the RRC consisted of a flat portion on the right side that represented a fully excitable gap, followed by an upward slope that represented the relative refractory period, as the test cycle approached the AERP (Figures 2A and 2C). Ibutilide shifted the RRCs rightward, with complete loss of the flat portion, which indicated the loss of a fully excitable gap (Figures 2B and 2C). Therefore, the AFL circuit was operating in its range of relative refractoriness after ibutilide infusion. The slope of the RRC was approximated by linear regression in 6 patients. In these patients, the slope became much steeper (from −0.76/11006 0.05 to −0.97/11006 0.08, P/11005 0.001). In the remaining 2 patients, the slope was not calculated because the RRC was shifted so markedly rightward that it contained fewer than 4 data points after ibutilide infusion.

Atrial Overdrive Termination of AFL After Ibutilide
We assessed the effects of AODP in 8 patients in whom AFL persisted after ibutilide infusion. AFL was not terminated with driving CL 20 to 70 ms below the AFL CL at baseline. As shown in Figure 3, AODP at a comparable or even longer CL successfully terminated AFL (AODP CL 227/11006 26 at baseline versus 240/11006 32 after ibutilide infusion, P/11005 0.06). AODP after ibutilide infusion may terminate AFL by orthodromic block of the paced impulse with antidromic collision (Figure 4A). In 7 (87%) of the 8 patients, however, AFL termination by AODP after ibutilide occurred without such orthodromic block. Instead, there was formation of new functional conduction block as evidenced by development of double potentials (Figure 4B). Thereafter, new nonsustained faster rhythms were induced (Figures 3 and 4).
Mechanism of CL Variability and Conduction Slowing During AFL in Response to Ibutilide

One of our major findings was the complete loss of a fully excitable gap in the AFL circuit after ibutilide (Figure 2). Our data are consistent with previous reports on the effects of ibutilide.7,8 However, we have further demonstrated that the right atrium operates in its range of relative refractoriness during AFL after ibutilide infusion. The right atrial conduction time became prolonged as the incoming flutter wave front encroached on the relative refractory tail of the preceding flutter wave front. Guo et al7 speculated that ibutilide-induced changes in action potential duration (APD) and atrial refractory period "may be the primary driving force producing oscillations of cycle length." Recent data indicated that increased APD variation in the right atrium, measured by monophasic action potential, coincided with increased CL variability and shortened diastolic interval.12 Given these findings and the present data, elimination of the fully excitable gap is the most likely cause for such beat-to-beat change in atrial refractoriness and CL variability, as well as APD alternation.

We have shown that the prolongation of AFL CL may result from slower conduction in either the TA-ER isthmus, the nonisthmus right atrium, or both, which indicates the effects of ibutilide are not limited to the TA-ER isthmus. Tai et al8 demonstrated that ibutilide did not decrease atrial conduction velocity in the TA-ER isthmus until the pacing CL was shortened to the range of AFL. This finding further supports our hypothesis that the prolonged conduction time and increased AFL CL are indirect effects of ibutilide that result from encroachment of the atrial relative refractory period. However, they did not find a statistically significant decrease in conduction velocity in the right atrial free wall with ibutilide, which suggests the effects of ibutilide may be limited to or more dominant in the TA-ER isthmus.8 Their data only showed a trend toward decreased conduction velocity in the right atrial free wall at a pacing CL that was comparable to the AFL CL after ibutilide infusion. Several factors may help to explain the difference between the present data and the findings by Tai et al.8 First, the dose of ibutilide in the present study was higher than that used by Tai et al8 (2 mg versus 0.02 mg/kg), so the effects of ibutilide may have become more apparent. Second, accurate measurement of conduction velocity is difficult if the 20-pole catheter in the right atrium is not placed in a direction exactly parallel to the direction of the activation wave front. In the present study, we minimized the impact of catheter orientation by measuring conduction time instead of conduction velocity. Because the catheter orientation is reasonably parallel to the direction of propagation in the TA-ER isthmus, it is not surprising to see more comparable results in isthmus conduction between the

### Ibutilide-Induced Changes in AFL Cycle Length and Right Atrial Conduction Times

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>BCL</th>
<th>ICL</th>
<th>BCTi</th>
<th>ICTi</th>
<th>BCTni</th>
<th>ICTni</th>
<th>ΔCTi/ΔCL, %</th>
<th>ΔCTni/ΔCT, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>232.8</td>
<td>283.3</td>
<td>91.8</td>
<td>116.3</td>
<td>141.0</td>
<td>167.0</td>
<td>48.5</td>
<td>51.5</td>
</tr>
<tr>
<td>2</td>
<td>281.2</td>
<td>356.4</td>
<td>101.4</td>
<td>110.2</td>
<td>179.8</td>
<td>246.2</td>
<td>11.7</td>
<td>88.3</td>
</tr>
<tr>
<td>3</td>
<td>262.1</td>
<td>283.3</td>
<td>66.5</td>
<td>65.5</td>
<td>195.6</td>
<td>217.8</td>
<td>-4.7</td>
<td>104.7</td>
</tr>
<tr>
<td>4</td>
<td>271.2</td>
<td>NA</td>
<td>70.8</td>
<td>NA</td>
<td>200.4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>233.0</td>
<td>254.0</td>
<td>81.0</td>
<td>87.0</td>
<td>152.0</td>
<td>167.0</td>
<td>28.6</td>
<td>71.4</td>
</tr>
<tr>
<td>6</td>
<td>277.4</td>
<td>300.6</td>
<td>113.2</td>
<td>136.2</td>
<td>164.2</td>
<td>164.4</td>
<td>99.1</td>
<td>0.9</td>
</tr>
<tr>
<td>7</td>
<td>303.8</td>
<td>327.5</td>
<td>64.8</td>
<td>66.5</td>
<td>239.0</td>
<td>261.0</td>
<td>7.17</td>
<td>92.8</td>
</tr>
<tr>
<td>8</td>
<td>242.1</td>
<td>NA</td>
<td>102.7</td>
<td>NA</td>
<td>139.4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>297.0</td>
<td>336.0</td>
<td>89.0</td>
<td>117.0</td>
<td>208.0</td>
<td>219.0</td>
<td>71.8</td>
<td>28.2</td>
</tr>
<tr>
<td>10</td>
<td>231.3</td>
<td>251.6</td>
<td>109.8</td>
<td>110.7</td>
<td>121.5</td>
<td>140.9</td>
<td>4.43</td>
<td>95.6</td>
</tr>
<tr>
<td>11</td>
<td>270.0</td>
<td>315.0</td>
<td>149.0</td>
<td>192.0</td>
<td>121.0</td>
<td>123.0</td>
<td>95.6</td>
<td>4.44</td>
</tr>
<tr>
<td>12</td>
<td>218.6</td>
<td>237.0</td>
<td>76.2</td>
<td>79.8</td>
<td>142.4</td>
<td>157.2</td>
<td>19.6</td>
<td>80.4</td>
</tr>
<tr>
<td>Mean</td>
<td>260.0</td>
<td>294.5</td>
<td>93.0</td>
<td>108.1</td>
<td>167.0</td>
<td>186.4</td>
<td>38.2</td>
<td>61.8</td>
</tr>
<tr>
<td>SD</td>
<td>28.0</td>
<td>39.6</td>
<td>24.2</td>
<td>37.7</td>
<td>34.0</td>
<td>46.4</td>
<td>38.5</td>
<td>38.5</td>
</tr>
</tbody>
</table>

All intervals are expressed in ms.

BCL and ICL indicate AFL CL before and after ibutilide; BCTi and ICTi, TA-ER isthmus conduction time before and after ibutilide; BCTni and ICTni, nonisthmus conduction time before and after ibutilide; ΔCTi/ΔCL, ratio of changes in TA-ER conduction time and AFL CL due to ibutilide; ΔCTni/ΔCT, ratio of changes in nonisthmus conduction time and AFL CL due to ibutilide.

In patients 4 and 8, AFL was terminated by AODP at baseline.

### Discussion

Mechanism of CL Variability and Conduction Slowing During AFL in Response to Ibutilide

One of our major findings was the complete loss of a fully excitable gap in the AFL circuit after ibutilide (Figure 2). Our data are consistent with previous reports on the effects of ibutilide.7,8 However, we have further demonstrated that the right atrium operates in its range of relative refractoriness during AFL after ibutilide infusion. The right atrial conduction time became prolonged as the incoming flutter wave front encroached on the relative refractory tail of the preceding flutter wave front. Guo et al7 speculated that ibutilide-induced changes in action potential duration (APD) and atrial refractory period “may be the primary driving force producing oscillations of cycle length.” Recent data indicated that increased APD variation in the right atrium, measured by monophasic action potential, coincided with increased CL variability and shortened diastolic interval.12 Given these findings and the present data, elimination of the fully excitable gap is the most likely cause for such beat-to-beat change in atrial refractoriness and CL variability, as well as APD alternation.

We have shown that the prolongation of AFL CL may result from slower conduction in either the TA-ER isthmus, the nonisthmus right atrium, or both, which indicates the effects of ibutilide are not limited to the TA-ER isthmus. Tai et al8 demonstrated that ibutilide did not decrease atrial conduction velocity in the TA-ER isthmus until the pacing CL was shortened to the range of AFL. This finding further supports our hypothesis that the prolonged conduction time and increased AFL CL are indirect effects of ibutilide that result from encroachment of the atrial relative refractory period. However, they did not find a statistically significant decrease in conduction velocity in the right atrial free wall with ibutilide, which suggests the effects of ibutilide may be limited to or more dominant in the TA-ER isthmus.8 Their data only showed a trend toward decreased conduction velocity in the right atrial free wall at a pacing CL that was comparable to the AFL CL after ibutilide infusion. Several factors may help to explain the difference between the present data and the findings by Tai et al.8 First, the dose of ibutilide in the present study was higher than that used by Tai et al8 (2 mg versus 0.02 mg/kg), so the effects of ibutilide may have become more apparent. Second, accurate measurement of conduction velocity is difficult if the 20-pole catheter in the right atrium is not placed in a direction exactly parallel to the direction of the activation wave front. In the present study, we minimized the impact of catheter orientation by measuring conduction time instead of conduction velocity. Because the catheter orientation is reasonably parallel to the direction of propagation in the TA-ER isthmus, it is not surprising to see more comparable results in isthmus conduction between the

---

**Figure 3.** Ibutilide facilitates AODP termination of AFL. Same pacing CL (190 ms) failed to terminate AFL at baseline but succeeded after ibutilide infusion in the same patient. Note that AFL did not terminate immediately after pacing train. Instead, a more rapid transient new rhythm was induced. CS indicates coronary sinus; TA, tricuspid annulus.
present study and that by Tai et al.8 Tai et al.8 showed that ibutilide increased the AERP by a similar magnitude in the TA-ER isthmus and the other parts of the right atrium, which supports the notion that ibutilide effects in the right atrium are generalized.

We assessed conduction times in the TA-ER isthmus and the remainder of the right atrium simultaneously. Conduction in one segment of the AFL circuit affects conduction in the subsequent segment in a reciprocal fashion because the right atrium operates in a state of relative refractoriness during AFL after ibutilide. Any slowing in the septum or right atrial free wall may lessen or even mask the effect of ibutilide on conduction velocity in the TA-ER isthmus and vice versa. This may explain the different effects of ibutilide on right atrial conduction times among individual patients (Table).

Mechanisms of AFL Termination by AODP After Ibutilide Infusion
AODP termination of AFL is a well-recognized phenomenon.13,14 It may result in orthodromic block and antidromic collision with the tachycardia wave front, leading to annihilation of the reentrant tachycardia (Figure 4A). However, the present data suggest an additional mechanism that may be operative in the setting of increased refractoriness. As described previously,9 AODP often does not result in a clean termination of AFL. Rather, there were rapid transitional atrial rhythms before reversion to sinus rhythm. With increased atrial refractoriness after ibutilide infusion, rapid AODP may favor the formation of arcs of functional blocks, as suggested by the development of double potentials15 (Figure 4B). Such newly formed functional blocks may serve as the substrate for 1 or more reentrant circuits and lead to more rapid reentrant rhythms that supplant the slower macroreentrant AFL. These new rapid rhythms then became quickly extinguished, probably because of the prolongation of AERP by ibutilide that exceeded the conduction time around the arcs of functional block. However, the present data do not provide conclusive evidence to exclude other focal mechanisms, such as triggered activity, for these new rapid rhythms, in part because of the limited recording sites.

Study Limitations
We did not measure conduction velocity. We chose to measure conduction times to avoid the pitfalls one might face measuring conduction velocity with the standard catheter technique. It is reasonable to assume that with ibutilide infusion, the actual length of the AFL circuit pathway does not change significantly.

The repeat stimulation protocol was performed only 10 to 20 minutes after infusion of ibutilide, leading to a lower spontaneous conversion rate from AFL to sinus rhythm. A short study period did not allow us to quantify the temporal trend of changes in atrial electrophysiological properties in response to ibutilide. A steady state of ibutilide plasma level was not maintained during the present study. However, one would expect little change in plasma level over the 10-minute period during which we measured electrophysiological parameters.

We did not derive the resetting curve from the TA-ER isthmus because of technical difficulties. However, the coronary sinus os and lower lateral right atrium are considered part of the AFL circuit. Furthermore, we cannot comment on the effects of pacing at sites other than the TA-ER isthmus.

Conclusions
Consistent with its cellular electrophysiological effects, ibutilide prolongs AFL CL indirectly by eliminating the fully
excitable gap in the AFL reentrant circuit that also accounts for the associated CL variability. In addition, the facilitative effect of ibutilide on AODP termination of AFL may be best explained by the formation of functional blocks that may lead to new rapid but unstable, short-lived circus movement(s) of excitation in the atria.

References
Electrophysiological Response of the Right Atrium to Ibutilide During Typical Atrial Flutter

Jie Cheng, Kathryn Glatter, Yanfei Yang, Shulong Zhang, Randall Lee and Melvin M. Scheinman

_Circulation._ 2002;106:814-819; originally published online July 22, 2002; doi: 10.1161/01.CIR.0000025635.38200.75

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 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/106/7/814

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/