High-density mapping of pulmonary veins and left atrium during ibutilide administration in a canine model of sustained atrial fibrillation

Chung-Chuan Chou, Shengmei Zhou, Alex Y. Tan, Hideki Hayashi, Motoki Nihei, and Peng-Sheng Chen
Division of Cardiology, Department of Medicine, Cedars-Sinai Medical Center and the David Geffen School of Medicine, University of California, Los Angeles, California

Submitted 20 May 2005; accepted in final form 26 July 2005

Chou, Chung-Chuan, Shengmei Zhou, Alex Y. Tan, Hideki Hayashi, Motoki Nihei, and Peng-Sheng Chen. High-density mapping of pulmonary veins and left atrium during ibutilide administration in a canine model of sustained atrial fibrillation. Am J Physiol Heart Circ Physiol 289: H2704–H2713, 2005. First published July 29, 2005; doi:10.1152/ajpheart.00537.2005.—Ibutilide can prolong refractory period and terminate reentry. Whether ibutilide has the same effects on pulmonary vein (PV) focal discharge (FD) is unclear. We induced sustained atrial fibrillation (AF) in seven dogs by rapid left atrial (LA) pacing for 74 ± 46 days. Ibutilide was repeatedly infused until it terminated AF (0.02 ± 0.01 mg/kg) or when a cumulative dose was reached (0.04 mg/kg). High-resolution computerized epicardial mapping was performed. We found intermittent FD at the PVs and reentry at the PV-LA junction during AF. Ibutilide increased the cycle length of consecutive reentry from 97 ± 13 to 112 ± 18 ms and increased FD from 96 ± 7 to 113 ± 9 ms. In four dogs with both FD and reentry at the PVs, the incidence of reentry decreased from 3.5 ± 1.9/s at baseline to 2.2 ± 1.8/s after ibutilide administration. However, the incidence of FD remained unchanged. The conducted wave fronts between PV and LA were significantly reduced by ibutilide (10.4 ± 2.0/s vs. 8.0 ± 1.6/s). The ibutilide dose needed to terminate AF correlated negatively with the baseline effective refractory period of PV and LA. We conclude that ibutilide reduces reentrant wave fronts but not PV FD in a canine model of pacing-induced sustained AF. These findings suggest that the PV FD during AF is due to nonreentrant mechanisms. High doses of ibutilide may completely terminate all reentrant activity, converting AF to PV tachycardia before the resumption of sinus rhythm.

MATERIALS AND METHODS

The research protocol was approved by the Institutional Animal Care and Use Committees and conforms to the American Heart Association Guidelines. Seven female mongrel dogs (22–27 kg) were used in the study.

Baseline studies. Under isoflurane anesthesia, the chest was opened via left thoracotomy. Screw-in bipolar pacing leads were inserted into the left atrial appendage (LAA) and left superior pulmonary vein (LSPV). After eight baseline beats at the pacing cycle lengths (CL) of 400, 300, and 250 ms, an extrastimulus at twice diastolic threshold current and 5-ms pulse width was introduced at 10-ms step decremental and then 2-ms step incremental coupling intervals to determine the ERP. ERP was defined as the longest coupling interval that failed to result in atrial or PV capture at each of these pacing rates.

Chronic atrial pacing-induced sustained AF. After baseline ERP tests, one pacing lead was left in the LAA and connected to a Medtronic Irel III neurostimulator for chronic pacing at 20 Hz for 5 s alternating with a 2-s rest period. The pacemaker was turned off periodically to evaluate the rhythm at least on weekly intervals. If AF was induced and persisted for >6 h, we considered that the dogs developed sustained AF. We then continued to pace the dogs until the time of the second surgery. We have used pacing-induced AF in previous studies (5, 14, 17). In all dogs, AF termination occurred only after electrical defibrillation, radio frequency ablation, or drug infusion. We have not observed spontaneous AF termination in this model.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
**Computerized mapping study.** During the second surgery, the chest was opened via median thoracotomy under isoflurane anesthesia. We performed high-density computerized mapping studies using a 1,792-channel computerized mapping system (Unemap; Uniservices) (5). Four patches, each with 448 bipolar electrodes with 1-mm interelectrode distance covering a 15 × 27-mm area, were used to map the LAA and LA posterior wall (LAPW), which included the ligament of Marshall (LOM), right PVs (RPVs), and superior vena cava (SVC) simultaneously. Figure 1 shows a schematic of plaque electrode coverage. The anterior PV-LA junction can be identified by a fold on the epicardium (8). A photograph of the plaque electrode was previously published in Fig. 1A of Ref. 18. Six pairs of bipolar hook electrodes were inserted into the LSPV, left inferior PV, LAPW, LAA, right atrial appendage, and SVC. The Irel pacemaker was turned off, and ibutilide (0.025 mg/ml) was infused intravenously at the rate of 0.001 mg·kg⁻¹·min⁻¹ with continuous monitoring of rhythm. Activation data during AF were collected by the mapping system at 2- to 4-min intervals. Drug infusion was discontinued when AF converted or when a cumulative dose of 0.04 mg/kg was reached. Dogs were observed for additional 30 min after finishing the fourth infusion of ibutilide if AF persisted. If dogs failed to achieve chemocconversion, electrical cardioversion 10–25 J was performed through epicardial patches with an attempt to terminate AF.

Postconversion PV ERP and atrial ERP were determined immediately after AF conversion. After ERP measurements, burst LA pacing for 3 s at a CL of 50 ms was applied three times to test whether AF could be reinduced and sustained for >3 min. Computerized mapping was also performed for the reinduced AF episodes.

**Data analyses.** Computerized mapping data were analyzed according to methods described previously (11). FD (18) was defined by activation arising from within the mapped region and propagating away from that site in all directions, or originating from the distal (with respect to LA) site of the PV and propagating toward the LA. The overall incidence of FD was calculated as the average total number of FD in 8 s for one Unemap recording. A reentrant wave front was defined as a wave front that completes a circular pathway and reentries near its site of origin. The number of reentry circuits per 8 s was also determined. The CL of consecutive (≥3 beats) FD and reentrant wave fronts were calculated at baseline and during ibutilide infusion. The dominant frequency (DF) at a given site was defined as the highest power of frequency spectrum (12). The highest DF in each mapped region is the maximum DF for that region. The postdrug DF remained unchanged (4.1 ± 0.9/s at baseline and 4.2 ± 0.9/s after ibutilide administration, P = not significant).

**RESULTS**

Sustained AF was induced in all seven dogs after a total of 74 ± 46 days of pacing. Ibutilide defibrillated five of seven dogs with the cumulative dose of 0.02 ± 0.01 mg/kg and failed to terminate in the other two dogs with 0.04 mg/kg ibutilide (Table 1). Electrical cardioversion was needed to convert AF in these two dogs. There was no clinical evidence of heart failure in any of the dogs studied. Two dogs (dog 1, dog 5) developed torsade de pointes ventricular tachycardia during post-AF ERP measurements. The postdrug QTc intervals were 490 and 413 ms in these two dogs. In comparison, the postdrug QTc intervals for the other five dogs were 399 ± 19 ms (range: 371–414 ms).

**Effects of ibutilide on PV activities during AF.** As previously reported (5), FD and reentrant wave fronts were observed in PVs during baseline AF. Frequent PVFD was found in all seven dogs, and consecutive FD was found in four dogs. Consecutive reentry loops were found in four dogs. Ibutilide did not suppress the overall incidence of FD (4.5 ± 1.7/s vs. 4.4 ± 1.5/s before and after ibutilide infusion, respectively; n = 7, P = 0.43). However, the CL of consecutive FD was significantly prolonged by ibutilide (96 ± 7 vs. 113 ± 9 ms before and after ibutilide, respectively; n = 4, P = 0.02).

Ibutilide significantly prolonged the CL of reentry in PV (97 ± 13 vs. 112 ± 18 ms before and after ibutilide, respectively; n = 4, P = 0.03) and in LAA (84 ± 10 vs. 107 ± 10 ms before and after ibutilide, respectively; n = 7, P = 0.0001). The relative importance of FD increased after ibutilide administration. In four dogs with consecutive FD and reentrant episodes for analyses, the incidence of reentry reduced from 3.5 ± 1.9/s at baseline to 2.2 ± 1.8/s after ibutilide administration (P = 0.01252, paired t-test). However, the incidence of RD remained unchanged (4.1 ± 1.1/s at baseline and 4.2 ± 0.9/s after ibutilide administration, P = not significant).

Figure 2 shows an example of ibutilide effects on right superior pulmonary vein (RSPV) in a chemoconverted dog (dog 5). Figure 2A shows the activation snapshots of RSPV during baseline AF, showing three consecutive FDs (6,081,
6,203, and 6,316 ms). The FD wave fronts met lines of functional conduction block (dotted lines) followed by the formation of complete reentry loops (6,409 to 6,595 ms). The wave fronts from the LA also encountered a functional line of block, followed by the formation of reentry. The mean CL of consecutive FD and reentry were 105 ± 7 and 108 ± 5 ms in this episode, respectively. Figure 2B shows the PV activation pattern after 0.02 mg/kg ibutilide administration from the same dog in A. There were FDs (6,344 and 6,581 ms) and reentrant wave fronts (6,035 to 6,296 ms), but at slower rates. Also note that the functional lines of block were not fixed between the upper and lower RSPV branches. The mean CL of consecutive FD and reentry were lengthened to 128 ± 7 and 135 ± 7 ms, respectively.

The interplay between PV and LA was also suppressed significantly by ibutilide. The average rates of conducted wave fronts between PV and LA before and after ibutilide were 10.4 ± 2.0/s and 8.0 ± 1.6/s, respectively (*n = 7, P < 0.001).

### Table 1. Dose response of mean maximum DF of 4 mapped regions during intravenous ibutilide infusion

<table>
<thead>
<tr>
<th>Ibutilide Dose, mg/kg</th>
<th>Dog 1</th>
<th>Dog 2</th>
<th>Dog 3</th>
<th>Dog 4</th>
<th>Dog 5</th>
<th>Dog 6</th>
<th>Dog 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>13.0±1.0</td>
<td>11.1±1.6</td>
<td>12.6±1.6</td>
<td>11.5±1.6</td>
<td>10.0±1.3</td>
<td>10.5±0.7</td>
<td>9.1±1.6</td>
</tr>
<tr>
<td>0.01</td>
<td>11.9±1.8</td>
<td>10.9±2.1</td>
<td>11.5±2.7</td>
<td>10.5±1.5</td>
<td>9.0±0.8</td>
<td>9.1±0.9</td>
<td>7.5±1.4</td>
</tr>
<tr>
<td>0.02</td>
<td>12.0±1.0</td>
<td>10.3±1.8</td>
<td>9.9±2.1</td>
<td>9.7±1.0</td>
<td>8.6±0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.03</td>
<td>11.6±1.8</td>
<td>9.8±1.8</td>
<td>9.6±2.5*</td>
<td>9.3±1.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.04</td>
<td>10.9±1.2†</td>
<td>9.6±2.0†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dominant frequency (DF) values are presented as means ± SD. *Cumulative ibutilide dose was 0.032 mg/kg. †Ibutilide did not convert atrial fibrillation at 0.04 mg/kg in these 2 dogs.

6.203, and 6,316 ms). The FD wave fronts met lines of functional conduction block (dotted lines) followed by the formation of complete reentry loops (6,409 to 6,595 ms). The wave fronts from the LA also encountered a functional line of block, followed by the formation of reentry. The mean CL of consecutive FD and reentry were 105 ± 7 and 108 ± 5 ms in this episode, respectively. Figure 2B shows the PV activation pattern after 0.02 mg/kg ibutilide administration from the same dog in A. There were FDs (6,344 and 6,581 ms) and reentrant wave fronts (6,035 to 6,296 ms), but at slower rates. Also note that the functional lines of block were not fixed between the upper and lower RSPV branches. The mean CL of consecutive FD and reentry were lengthened to 128 ± 7 and 135 ± 7 ms, respectively.

The interplay between PV and LA was also suppressed significantly by ibutilide. The average rates of conducted wave fronts between PV and LA before and after ibutilide were 10.4 ± 2.0/s and 8.0 ± 1.6/s, respectively (*n = 7, P < 0.001).

### Table 1. Dose response of mean maximum DF of 4 mapped regions during intravenous ibutilide infusion

<table>
<thead>
<tr>
<th>Ibutilide Dose, mg/kg</th>
<th>Dog 1</th>
<th>Dog 2</th>
<th>Dog 3</th>
<th>Dog 4</th>
<th>Dog 5</th>
<th>Dog 6</th>
<th>Dog 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>13.0±1.0</td>
<td>11.1±1.6</td>
<td>12.6±1.6</td>
<td>11.5±1.6</td>
<td>10.0±1.3</td>
<td>10.5±0.7</td>
<td>9.1±1.6</td>
</tr>
<tr>
<td>0.01</td>
<td>11.9±1.8</td>
<td>10.9±2.1</td>
<td>11.5±2.7</td>
<td>10.5±1.5</td>
<td>9.0±0.8</td>
<td>9.1±0.9</td>
<td>7.5±1.4</td>
</tr>
<tr>
<td>0.02</td>
<td>12.0±1.0</td>
<td>10.3±1.8</td>
<td>9.9±2.1</td>
<td>9.7±1.0</td>
<td>8.6±0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.03</td>
<td>11.6±1.8</td>
<td>9.8±1.8</td>
<td>9.6±2.5*</td>
<td>9.3±1.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.04</td>
<td>10.9±1.2†</td>
<td>9.6±2.0†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dominant frequency (DF) values are presented as means ± SD. *Cumulative ibutilide dose was 0.032 mg/kg. †Ibutilide did not convert atrial fibrillation at 0.04 mg/kg in these 2 dogs.

6.203, and 6,316 ms). The FD wave fronts met lines of functional conduction block (dotted lines) followed by the formation of complete reentry loops (6,409 to 6,595 ms). The wave fronts from the LA also encountered a functional line of block, followed by the formation of reentry. The mean CL of consecutive FD and reentry were 105 ± 7 and 108 ± 5 ms in this episode, respectively. Figure 2B shows the PV activation pattern after 0.02 mg/kg ibutilide administration from the same dog in A. There were FDs (6,344 and 6,581 ms) and reentrant wave fronts (6,035 to 6,296 ms), but at slower rates. Also note that the functional lines of block were not fixed between the upper and lower RSPV branches. The mean CL of consecutive FD and reentry were lengthened to 128 ± 7 and 135 ± 7 ms, respectively.

The interplay between PV and LA was also suppressed significantly by ibutilide. The average rates of conducted wave fronts between PV and LA before and after ibutilide were 10.4 ± 2.0/s and 8.0 ± 1.6/s, respectively (*n = 7, P < 0.001).
There were 7.6 ± 1.6/s wave fronts in the LA during baseline AF. Among them, 5.5 ± 1.4/s propagated to the PV. After ibutilide, the numbers of total wave fronts and wave fronts that propagated to PV were 7.0 ± 1.5/s and 4.5 ± 1.0/s, respectively. The average rate of propagating wave fronts from PV into LA was 5.0 ± 2.3/s (total: 6.5 ± 2.3/s); after ibutilide, it was 3.5 ± 1.7/s (total: 5.6 ± 1.8/s). There were more wave fronts in the LA at baseline (7.6 ± 1.6/s) than can be accounted for by the propagation from RPV to LA (6.5 ± 2.3/s). The balance of these two numbers was due to the wave fronts that were generated by wave breaks in the LA and/or originated from the other unmapped PVs. The percentages of wave fronts that successfully propagated between RSPV and LA after ibutilide infusion were also decreased (from PV to LA: 74 ± 13% before drug, 60 ± 15% after drug, n = 7, P = 0.009; from LA to PV: 72 ± 9% before drug, 65 ± 10% after drug, n = 7, P = 0.056).

Terminal atrial tachycardia. Figure 3A shows snapshots of terminal AT that converted to sinus rhythm. It occurred 3 min after the second dose of ibutilide infusion in the same dog as shown in Fig. 2. The mean CL of the terminal AT was 164 ± 31 ms, which was longer than the consecutive FD before the second dose of ibutilide. As the rate of FD slowed down, there were competing LA wave fronts that impeded the propagation of AT in RSPV to the LA (snapshots 3,805 to 4,547 ms). When sinus resumed, RSPV was passively activated (last 3 snapshots). Organized P waves (arrowheads) are shown on the surface ECG tracing during this terminal AT. Figure 3, B and C, shows the isochronal maps during RSPV AT and during sinus rhythm, respectively. The red color represents the earliest activation. Note that there were crowded isochronal lines at the RSPV-LA junction during RSPV AT and sinus rhythm, suggesting slow propagation at this region.

Resistance of PV to ibutilide during AF. In two dogs, ibutilide at the accumulated dose of 0.04 mg/kg with a total observation time of 100 min from the start of ibutilide infusion failed to terminate AF. Figure 4 shows an example of PV activation during ibutilide-resistant baseline AF (dog 1). In Fig. 4A, two successive FDs (arrowheads) occurred in the proximal lower branch of RSPV. These FDs were followed by a complete reentry loop. The LA wave front sometimes propagated to RSPV and then formed a “figure eight” reentry (snapshots 3,607 to 3,656 ms) at the PV-LA junction. This reentry was followed by seven consecutive FDs (arrowheads, snapshots 3,832 to 4,302 ms). Except for the first two FDs, there were wave fronts coming from the LA that collided with FD (snapshots 4,006 and 4,090 ms) and formed reentrant wave fronts (snapshots 4,224 to 4,302 ms). Thereafter, figure eight reen-
Fig. 4. Patterns of activation during baseline AF in an ibutilide-resistant dog (dog 1). 

A: snapshots of FD and reentrant activation patterns within the RSPV at baseline AF (see text). B: the 3 main activation patterns in the RSPV. C: actual bipolar recordings according to sites indicated in B: sites a–k, sites along the reentry shown in B, middle; site g, FD in the RSPV. Red arrows indicate wave front propagation. Asterisks above tracing g indicate the earliest activation site during FD. Oblique red lines below tracing g indicate conduction block between sites g and h. Horizontal red lines above tracing a indicate conduction block from the RSPV to the LA. The numbers below tracing g represent the time in ms that site g activated, with the beginning of data acquisition being time 0.
trant wave fronts formed again to activate the FD site. These FDs contributed to the LA electrical activity (snapshots 4,333 to 4,409 ms). Figure 4B shows the three main activation patterns during which RSPV contributed to the AF activation. Figure 4C shows the local bipolar electrograms along the reentrant wave fronts (sites a–k) and FD site (site g) corresponding to the sites labeled in B. The electrogram at site g shows the earliest activation during FD (asterisks) and intermittent double potentials during reentry (red arrows). Site f shows persistent double potentials, representing the slow conduction between sites h and f that facilitated the reentry formation. In this episode, the mean CL of consecutive FD and reentry were 79.5 ± 7.9 and 79 ± 4.5 ms, respectively.

Figure 5 shows the PV activation after the fourth dose of ibutilide infusion in the same dog as in Fig. 4. In Fig. 5A, two successive reentrant wave fronts were followed by eight consecutive FDs originated from the lower branch of RSPV. The wave fronts then propagated to the LA (snapshots 1,011 to 1,178 ms) and contributed to the LA activations. The functional line of conduction block occurred at the lower branch of PV-LA junction (dotted line, snapshot 1,757 ms). However, the conduction block did not develop into complete reentry until the line of block moved rightward (snapshot 2,233 ms). Snapshots at 2,351 and 2,453 ms show two FDs that failed to propagate to LA because of the collision with LA wave fronts. Figure 5B shows the three main activation patterns during which RSPV contributed to the AF activation. Compared with Fig. 4B, no more figure eight reentry activation pattern occurred within RSPV after ibutilide infusion. Figure 5C shows the local bipolar electrograms along the reentrant pathways (sites a–l) corresponding to the sites labeled in B. The activation rate was slower, but the activation sequences were still complicated because of the slow conduction, conduction block, and multidirectional conduction of propagating wave fronts, as demonstrated in A. Site h shows the earliest activation electrogram during FD (asterisks). Sites g, i, and l show fragmented potentials during the period of reentry, representing the slow conduction at these sites that facilitated the reentry formation. After 0.04 mg/kg ibutilide infusion, the mean CL of consecutive FD and reentry were lengthened to 99.3 ± 9.8 and 94 ± 11.6 ms, respectively.

Table 2 shows the comparison between ibutilide-resistant and ibutilide-converted groups. The ibutilide-resistant dogs have shorter CL of baseline consecutive FD, reentry, postdrug consecutive FD, and reentry. Also, there were higher percentages of propagating wave fronts at baseline and after ibutilide infusion at both directions in ibutilide-resistant dogs.

**Correlation between ERP and drug dosage needed for chemoconversion.** The baseline (first surgery) PV ERP correlated negatively with the dose of ibutilide needed for AF conversion in the second surgery (r = -0.089, P < 0.001). In chemoconverted dogs (n = 5), the PV ERP observed during the first surgery, before induction of AF, was 110 ± 15 ms, and it was 90 ± 16 ms after ibutilide terminated AF during the second surgery. In the ibutilide-resistant group (n = 2), the baseline PV ERP (80 ± 5 ms) and post-electrical defibrillation PV ERP (84 ± 5 ms) were shorter than in the converted group. The baseline LAA ERP also correlated negatively with the dose of ibutilide needed for AF conversion (r = -0.92, P < 0.001). In chemoconverted dogs (n = 5), the baseline and postconversion LAA ERP were 92 ± 18 and 76 ± 11 ms, respectively. For the dogs refractory to ibutilide (n = 2), the baseline LAA ERP (58 ± 10 ms) and post-electrical defibrillation LAA ERP (68 ± 6 ms) were shorter than for the converted dogs.

**Correlation between DF and drug dosage needed for conversion.** As shown in Fig. 6A (dog 4), the highest DF occurred near the PV-LA junctions during baseline AF, especially the left PV-LA junction (12.0 ± 1.3 Hz). The mean maximum DFs were 11.6 ± 1.6, 11.7 ± 1.4, and 9.2 ± 1.6 Hz for RPV, LAPW, and SVC-RA mapped areas, respectively (n = 7). Table 1 shows the dose response of the mean maximum DF of four mapped regions during intravenous ibutilide infusion in seven dogs. Ibutilide reduced these DFs in a dose-dependent pattern. There was significant correlation between the mean maximum DF of baseline AF and the accumulated ibutilide dosage required for AF conversion (n = 7, r = 0.8, P < 0.001). In the meantime, the percentage of the decrement of mean maximum DF after the first dose of ibutilide also correlated negatively with the ibutilide dosage needed for AF conversion (n = 7, r = 0.92, P < 0.001). These data suggest that ibutilide more effectively slowed the AF activation in chemoconverted dogs than in nonchemoconverted dogs.

Figure 6B shows electrograms and DF analyses recorded from the computerized mapping plaque at LAA, demonstrating the dose-dependent effects on DF during ibutilide infusion. Figure 6, C and D, shows an example of the ibutilide effects on AF electrograms recorded by bipolar hook electrodes at baseline AF and after 0.03 mg/kg ibutilide infusion, respectively. All six recordings in Fig. 6D show slower and simpler electrograms than the baseline, and AF was first converted to a terminal AT before sinus rhythm resumed. The earliest activation of the terminal AT was from LSPV (arrow). In dog 5 (as shown in Figs. 2 and 3), the transitional AT occurred at a shorter CL than the terminal AT (143 ± 6.8 ms, 0.01 mg/kg ibutilide vs. 164.1 ± 31.4 ms, 0.02 mg/kg ibutilide) in which the earliest site was mapped at the FD site in RSPV. In the other three chemoconverted dogs, AF termination was preceded by atrial flutter in two dogs or directly converted to sinus in one dog.

**Susceptibility of AF after conversion.** We tested the susceptibility of AF by burst pacing after AF conversion. AF could be reinduced in all seven dogs. Among them, three were >20 min, including two ibutilide-resistant dogs, and the other four dogs had a mean AF duration of 14 ± 4 min (range: 10–19 min; median: 14 min).

**DISCUSSION**

This study has the following major findings. 1) Ibutilide prolongs the CL of consecutive FD in PVs, the reentrant wave fronts in PV-LA junctions, and in LAA during AF but does not suppress the overall incidence of FD from PVs. 2) Ibutilide reduces the interpaly between LA and PV wave fronts. 3) Ibutilide-induced termination of AF is preceded by PV AT or atrial flutter. 4) Inherent PV and LA ERP and the baseline maximum DF of AF are important in determining the antifibrillatory efficacy of ibutilide. These data suggest that suppressing the PV electrical activities and the interpaly between PV and LA play important roles in the antifibrillatory efficacy of ibutilide and that PV tachycardia is more resistant to ibutilide than the AF wave fronts in the LA. The failure for
Fig. 5. Patterns of activation during postdrug AF in an ibutilide-resistant dog (dog 1). A: snapshots of FD and reentrant activation patterns within the RSPV during AF after 0.04 mg/kg ibutilide infusion (see text). B: the 3 main active activation patterns in the RSPV. C: actual bipolar recordings according to sites indicated in B: sites a–l, sites along the reentry shown in B, middle; site h, FD in the RSPV. Asterisks above tracing h indicate the earliest activation site during FD. Horizontal red lines indicate conduction block. The numbers below tracing h represent the time in ms that site h activated.
ibutilide to reduce the incidence of FD suggests that the PV FD during AF is due to nonreentrant mechanisms. By suppressing the reentrant wave fronts in LA and PV, ibutilide may convert AF to PV tachycardia before the resumption of sinus rhythm.

**Effects of ibutilide on atrial electrical activations during AF.** As a class III antiarrhythmic drug, ibutilide might have exerted its anti-AF actions by prolonging the atrial action potential duration and ERP without significant effects on resting membrane potential, the upstroke of the action potential, and conduction velocity and devoid of interactions with the autonomic nervous system (9). It was reported that baseline atrial CL and monophasic action potential duration are electrophysiological determinants of ibutilide efficacy for termination of AF (15). Whereas ibutilide’s effects on reentrant wave fronts in the atria

### Table 2. Comparison of ibutilide-resistant and ibutilide-converted groups

<table>
<thead>
<tr>
<th></th>
<th>Ibutilide-Resistant Group</th>
<th>Ibutilide-Converted Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CL of consecutive FD, ms</td>
<td>86.9 ± 10.3 ms (n = 2)</td>
<td>105.6 ± 0.6 ms (n = 2)</td>
</tr>
<tr>
<td>Baseline CL of consecutive reentry, ms</td>
<td>86.5 ± 10.6 ms (n = 2)</td>
<td>106.5 ± 2.1 ms (n = 2)</td>
</tr>
<tr>
<td>Postdrug CL of consecutive FD, ms</td>
<td>104.2 ± 9.0 ms (n = 2)</td>
<td>120.4 ± 10.8 ms (n = 2)</td>
</tr>
<tr>
<td>Postdrug CL of consecutive reentry, ms</td>
<td>99.0 ± 7.1 ms (n = 2)</td>
<td>124.5 ± 14.8 ms (n = 2)</td>
</tr>
<tr>
<td>Baseline incidence of wave fronts propagating from PV to LA</td>
<td>7.0/s (91%) (n = 2)</td>
<td>4.1/s (69%) (n = 5)</td>
</tr>
<tr>
<td>Baseline incidence of wave fronts propagating from LA to PV</td>
<td>5.9/s (74%) (n = 2)</td>
<td>5.3/s (71%) (n = 5)</td>
</tr>
<tr>
<td>Postdrug incidence of wave fronts propagating from PV to LA</td>
<td>5.0/s (73%) (n = 2)</td>
<td>2.8/s (55%) (n = 5)</td>
</tr>
<tr>
<td>Postdrug incidence of wave fronts propagating from LA to PV</td>
<td>4.8/s (73%) (n = 2)</td>
<td>4.4/s (62%) (n = 5)</td>
</tr>
</tbody>
</table>

Values for cycle length (CL) are means ± SD; n = no. of dogs per group. Values for wave front propagation are means, with nos. in parentheses representing the percentage of propagating wave fronts. FD, focal discharge; PV, pulmonary veins; LA, left atrium.

*Fig. 6. Response of dominant frequency (DF) to ibutilide. A: DF map of 4 plaques during baseline AF (dog 4). Red color indicates the highest DF. B: dose-dependent effects of ibutilide on DF in electrograms recorded using bipolar hook electrodes. C and D: actual activations recorded at baseline and during ibutilide infusion, respectively. Note that ibutilide converted AF to AT before termination. Red arrow in D indicates the earliest activation at the LSPV during terminal AT.*

AJP-Heart Circ Physiol • VOL 289 • DECEMBER 2005 • www.ajpheart.org
have been studied (2), little information is available on ibutilide’s effects in reentrant wave fronts in the PVs. In this study we used high-density mapping to determine and visualize the functional reentrant wave fronts in PV and at the PV-LA junction. Our results show that ibutilide also has significant effects on reentrant wave fronts in these structures. Because PV and PV-LA junction have the highest DF during AF in this model, these results suggest that ibutilide’s effects on reentry in PV and PV-LA junction might play important roles in its antifibrillatory action.

Focal discharge within PVs are resistant to ibutilide. Class III antiarrhythmic agents, such as ibutilide, are designed to prolong ERP and suppress reentry, not triggered activity. If the FD is due to microreentry, then ibutilide should be able to suppress it. We found that the opposite is true. These findings support the hypothesis that nonreentrant mechanisms underlie the PV FD in this canine model (16). Others have already demonstrated that the isolated PV cells are capable of developing afterdepolarizations in vitro (1). Because of the rapid rate of activation, AF creates a condition of calcium overload, which may facilitate triggered activity and FD in the PV (4). Although ibutilide does not appear to directly suppress FD in the PVs, it might have indirectly helped them to spontaneously terminate. We have shown in this study that ibutilide suppressed reentrant excitations and lengthened the AF CL. It also reduced the PV-LA interaction by allowing fewer wave fronts to invade the PV from the LA. These changes resulted in prolonged CL and probably reduced intracellular Ca$^{2+}$ accumulation in the PVs. Therefore, even though ibutilide did not directly suppress PV FD, it might have facilitated the eventual termination of the FD by suppressing reentrant activity in the LA.

Comparison with Na$^+$ channel blockers. Our group reported previously (5) that procainamide terminates AF by suppressing PD in the PVs in addition to reducing the conduction velocity and the interaction between the wave fronts in the LA and PV. Ibutilide does not suppress the Na$^+$ channel; however, it also reduces the interaction between PV and LA via the prolongation of ERP. Although these antiarrhythmic drugs block different ion channels, they all reduce the interaction between the PV and LA. “Pharmacological PV isolation” (10) might be a common mode of action of these anti-AF drugs.

Clinical implications. This is the first in vivo study using high-resolution mapping to describe the actions of ibutilide on the PVs. We have demonstrated that even after AF completely terminated in the atria, PV FD could continue to serve as a source of AT. Because the fast, repetitive, rapid activities within the PV may still cause wave break in the atria to maintain AF, successful pharmacological treatment of sustained AF may require not only the reduction of reentrant excitation but also the suppression of PV FD. Understanding the interaction between FD and reentry may lead to a clearer direction of drug development in the future.

Limitations. We did not map the entire circumference of the RSPV. Therefore, if there were reentrant wave fronts that circulated around the entire RSPV orifice, they would have been missed by our mapping techniques. Furthermore, if there is significantly faster conduction in the PV endocardium than in the PV epicardium, the reentrant wave front might have propagated from the edge of the mapped region, broken through in the center, and then spread in all directions manifesting as FD. Because a large, anatomically based reentry may have an excitable gap that cannot be closed by ERP prolongation, this reentrant mechanism (hence, the FD) would appear to be insensitive to ibutilide infusion. However, PV muscle sleeve is usually no more than 2 mm thick (4). There is not much separation between endocardial and epicardial layers. We propose that this alternative mechanism is unlikely to explain all episodes of FD. Therefore, this limitation does not invalidate the conclusions of the study.

ACKNOWLEDGMENTS

We thank Avile McCullen, Lei Lin, and Elaine Lebowitz for assistance. We thank Dr. Xiaohong Zhou and Medtronic, Inc., for donating the Irel pacemakers used in the study.

GRANTS

This study was supported by a fellowship grant from the Chang Gung Memorial Hospital, Taipei, Taiwan (to C.-C. Chou), a Pauline and Harold Price Endowment (to P.-S. Chen), and in part by National Heart, Lung, and Blood Institute Grants R01-HL-71140, P50-HL-52319, R01-HL-66389, and R01-HL-78932.

REFERENCES


