Response to Flecainide Infusion Predicts Long-Term Success of Hybrid Pharmacologic and Ablation Therapy in Patients With Atrial Fibrillation

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OBJECTIVES
We tested the hypothesis that the response to flecainide infusion can identify patients with atrial fibrillation (AF) in whom the hybrid pharmacologic and ablation therapy reduces the recurrences of AF.

BACKGROUND
Infusion of class IC anti-arrhythmic drugs may promote transformation of AF into atrial flutter. Catheter ablation of atrial flutter has been demonstrated to be highly effective in preventing recurrences of atrial flutter.

METHODS
Seventy-one consecutive patients with paroxysmal or chronic AF, in whom flecainide infusion (2 mg/kg body weight, intravenously) determined the transformation of AF into common atrial flutter (positive response), were randomized to receive one of the following treatments: oral pharmacologic treatment with flecainide (group A, n = 23); the hybrid treatment (catheter ablation of the inferior vena cava-tricuspid annulus isthmus, plus oral flecainide) (group B, n = 24); or catheter ablation of the isthmus only (group C, n = 24). Thirty-seven patients with a negative response to flecainide, who chose to be submitted to the hybrid treatment, were selected as the control group (group D).

RESULTS
During a mean follow-up period of 24 ± 7.2 months, the recurrences of AF and atrial flutter in group B (42%) were significantly lower than those in group A (78%, p < 0.001), group C (92%, p < 0.001) and group D (92%, p < 0.001).

CONCLUSIONS
The creation of a complete bi-directional conduction block at the inferior vena cava-tricuspid annulus isthmus, plus flecainide administration, reduces the recurrences of both AF and atrial flutter in patients with class IC atrial flutter. Moreover, the early response to flecainide is safe and reliable in identifying patients who may benefit from this therapy. (J Am Coll Cardiol 2000;37:1639–44) © 2001 by the American College of Cardiology
The atrial flutter, achievement of bi-directional isthmus compartmentalization, was selected as the control group. All patients were followed up for at least 15 months (mean 24 ± 7.2), with a clinical examination and ECG recording scheduled every month. Patients were instructed to obtain an ECG record in case of symptomatic palpitation. During the follow-up, patients received no other anti-arrhythmic drug except flecainide, nor drugs affecting the atrioventricular node conduction (digoxin, beta-blockers and calcium channel blockers), so that the patient’s capacity to recognize arrhythmia recurrences would not be diminished.

The study was approved by the Ethics Committee of our institutions, and all patients gave their informed consent to participate in the study.

Definitions. Typical atrial flutter was defined as atrial flutter exhibiting a counterclockwise or clockwise activation around the tricuspid annulus, with a proximal to distal coronary sinus depolarization, as well as concealed entrainment demonstrated at annular pacing sites within the tricuspid valve-eustachian ridge isthmus, with a post-pacing interval similar to the flutter cycle length (6,7). Atypical atrial flutter was defined as all other flutters in which participation of the isthmus in the circuit was excluded by the aforementioned criteria.

Electrophysiologic study and radiofrequency ablation. All patients underwent electrophysiologic study and catheter ablation in a single session, while in the fasting state, after discontinuation of all anti-arrhythmic therapies for at least five half-lives. Two decapolar electrode catheters or a halo catheter with 20 electrodes were placed around the tricuspid annulus to assess the activation sequence in the lateral wall; two quadripolar electrode catheters were placed in the coronary sinus, with the proximal electrode pair located at the ostium, and in the His bundle area, respectively. A 7F, thermistor, quadripolar electrode catheter (EP Technology, Mountain View, California), with an 8- or 10-mm deflectable tip, was used to stimulate and ablate. All patients were in stable AF at the time of the flecainide test. Once completed, the patients who had flecainide infusion were observed for at least 20 min, during which time they had no further drug infusion. If AF was converted into stable, common atrial flutter, the patients underwent radiofrequency catheter ablation. The method of ablation was anatomic: a line of sequential overlapping lesions was given during pullback of the ablation catheter from the tricuspid valve annulus toward the inferior vena cava-eustachian ridge. Radiofrequency energy was delivered by a generator (EPT 1000XP, EP Technology) to achieve a tip-tissue interface temperature of 65°C and an output of up to 150 W. Successful ablation was defined as interruption of the atrial flutter, achievement of bi-directional isthmus conduction block and no induction of persistent, common atrial flutter (8). Complete isthmus block was defined by the co-existence of a counterclockwise conduction to the point of block, followed by the delayed arrival of septal activation up to the line of block from the opposite direction, during low lateral right atrium pacing, and a similar activation pattern in the opposite direction, during proximal coronary sinus pacing (9,10).

Statistical analysis. Continuous variables are expressed as the mean ± SD and were compared using the two-tailed Student t test or the exact Fisher test for proportional comparisons. Analysis of variance, with Bonferroni and Tukey post hoc multiple comparison tests, was performed to make comparisons among multiple groups. For categorical data, Bonferroni correction was applied. The Cox proportional hazards model was used to assess the relationship between explanatory variables and event-free survival times. The log-rank test was used to compare the Kaplan-Meier event-free survival curves in the four groups.

RESULTS

Patients characteristics. Table 1 summarizes the clinical characteristics of the patients with positive and negative test responses. The incidence of at least one episode of documented atrial flutter occurring before the flecainide test was significantly higher in the group with a positive test response than in the group with a negative test response (39% vs. 15%, p < 0.001). As shown in Table 2, there was no significant difference in any of the clinical characteristics between the three study groups and the control group, excluding, once again, the incidence of pre-test atrial flutter, which was significantly lower in group D than in group A (p < 0.05). Among the 108 patients of groups A, B, C and D, 49 (7 in group A, 6 in group B, 7 in group C and 29 in group D) received anti-coagulation therapy with warfarin, whereas the remaining 59 patients received anti-aggregant therapy with acetylsalicylic acid, indobufene or ticlopidine. During the follow-up, one patient in group D had a nonfatal stroke.

Flecainide test response and ablation catheter outcome. During flecainide infusion, sinus rhythm was restored in four patients, all with paroxysmal AF, and they were included in the group with a negative test response; two other patients in whom sinus rhythm restoration was preceded by a stable period (5 and 12 min, respectively) of typical atrial flutter were enrolled in the group with a positive test response. In the group with a positive test response, 1:1 atrioventricular conduction was observed in 9 (12.6%) of 71 patients, resulting in hemodynamic detriment in one of them, which required atrial overdrive pacing to convert the atrial flutter into sinus rhythm; in four other patients (5.6%), a transient bundle branch block was observed, one of whom had first-degree atrioventricular block after restoration of sinus rhythm. Among the patients who showed 1:1 atrioventricular conduction during the flecainide
Figure 1. Surface intracardiac electrograms recorded before (A) and after (B) flecainide infusion, showing the transformation of atrial fibrillation into typical atrial flutter. I, III and V1 = electrocardiographic leads; CS = coronary sinus; HIS = His bundle; -d = distal; -p = proximal; T = tricuspid annulus, with T12 located at the low lateral atrium and T1516 at the high inter-atrial septum.
test, three were randomized into group A, four into group B and four into group C. During the follow-up, only one patient in group A experienced atrial flutter with 1:1 atrioventricular conduction, with a mean atrial flutter cycle of 420 ms, with no hemodynamic compromise. The mean atrial flutter cycle was 238 ± 33 ms; surface ECG monitoring and intracardiac mapping revealed that 64 (90%) of 71 patients had counterclockwise typical atrial flutter, and 7 (10%) of 71 patients had clockwise typical atrial flutter. In the group with a negative test response, a transient bundle branch block was observed in 12 patients (3.6%); in 29 other patients (8.7%), transient (n = 16) or persistent (n = 13) atypical atrial flutter was observed. Among this latter group, two patients showed a phase of 1:1 atrioventricular conduction.

A complete bi-directional isthmus conduction block was obtained in all patients in groups B, C and D, with a mean number of 7.8 ± 4.5 pulses of radiofrequency energy; in two patients, a second procedure was required to achieve a complete isthmus block. The mean procedure time was 32 ± 6 min, with a mean X-ray time of 17 ± 5 min. No major complications were observed during and after the isthmus ablation. During the follow-up, four patients (one in group A, one in group B and two in the control group) were excluded because of pharmacologic side effects: one patient had central nervous system adverse reactions, with blurred vision and headache; one patient showed a first-degree atrioventricular block; and two patients had effort dyspnea due to hemodynamic compromise.

**Recurrents of AF.** Atrial fibrillation- and atrial flutter-free survival curves are shown in Figure 2. Log-rank test comparisons resulted in a significant difference between the curves of group B and those of groups A, C and D (chi-square 9.6, p < 0.002; chi-square 21.1, p < 0.001; and chi-square 18.2, p < 0.001, respectively). No significant differences were found between the curves of groups A, C and D. All patients in groups A, B, C and D had AF recurrences, except for one patient in group A who experienced atrial flutter recurrence. After the first arrhythmia recurrence, 17 of 18 patients in group A underwent isthmus ablation; all patients in group C began long-term oral pharmacologic treatment with 200 mg of flecainide; and 9 of 10 patients in group B required electrical cardioversion to restore sinus rhythm.

Age, gender, left atrial diameter, left ventricle ejection fraction, paroxysmal or chronic AF, the presence of heart disease, a history of atrial flutter and therapeutic modalities (group A, B, C or D) were considered as explanatory variables in the Cox proportional hazards model. Only the therapeutic modalities variable was retained in the final model after stepwise selection, and, in particular, the coding for only group B reached statistical significance, confirming

### Table 1. Clinical Characteristics of the Patients With Positive and Negative Test Responses

<table>
<thead>
<tr>
<th></th>
<th>Positive Test Response (n = 71)</th>
<th>Negative Test Response (n = 333)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.3 ± 13</td>
<td>54.4 ± 13</td>
<td>0.53</td>
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<tr>
<td>Gender (M/F)</td>
<td>47/24</td>
<td>207/126</td>
<td>0.52</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>52.5 ± 8.6</td>
<td>53.7 ± 7.4</td>
<td>0.26</td>
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<tr>
<td>LA diameter (mm)</td>
<td>41.3 ± 4.7</td>
<td>42.2 ± 4.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Clinical arrhythmia (PAF/CAF)</td>
<td>49/22</td>
<td>239/94</td>
<td>0.65</td>
</tr>
<tr>
<td>Heart disease</td>
<td>43 (60.5%)</td>
<td>242 (72.7%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (38%)</td>
<td>147 (44.2%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Valvular</td>
<td>10 (14.1%)</td>
<td>66 (19.8%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Ischemic</td>
<td>6 (8.4%)</td>
<td>29 (8.7%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Pre-test AFL</td>
<td>28 (39.4%)</td>
<td>49 (14.7%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD or number (%) of patients.

AFL = atrial flutter; CAF = chronic atrial fibrillation; F = female; LA = left atrium; LVEF = left ventricular ejection fraction; M = male; PAF = paroxysmal atrial fibrillation.

### Table 2. Clinical Characteristics of the Four Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 23)</th>
<th>Group B (n = 24)</th>
<th>Group C (n = 24)</th>
<th>Group D (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 ± 12</td>
<td>53 ± 13</td>
<td>52 ± 14</td>
<td>54 ± 14</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>17/6</td>
<td>16/8</td>
<td>14/10</td>
<td>25/11</td>
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<tr>
<td>LVEF (%)</td>
<td>52 ± 9</td>
<td>52 ± 9</td>
<td>53 ± 9</td>
<td>54 ± 6</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>41 ± 4</td>
<td>41 ± 5</td>
<td>41 ± 5</td>
<td>43 ± 5</td>
</tr>
<tr>
<td>Clinical arrhythmia (PAF/CAF)</td>
<td>16/7</td>
<td>16/8</td>
<td>17/7</td>
<td>21/16</td>
</tr>
<tr>
<td>Heart disease</td>
<td>14 (60.8%)</td>
<td>14 (58.3%)</td>
<td>15 (62.5%)</td>
<td>30 (81%)</td>
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<tr>
<td>Hypertension</td>
<td>9 (39.1%)</td>
<td>9 (37.5%)</td>
<td>9 (37.5%)</td>
<td>16 (43.2%)</td>
</tr>
<tr>
<td>Valvular</td>
<td>3 (13%)</td>
<td>4 (16.7%)</td>
<td>3 (12.5%)</td>
<td>9 (24.3%)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>2 (8.7%)</td>
<td>1 (4.1%)</td>
<td>3 (12.5%)</td>
<td>5 (13.5%)</td>
</tr>
<tr>
<td>Pre-test AFL</td>
<td>10 (43.5%)</td>
<td>9 (37.5%)</td>
<td>9 (37.5%)</td>
<td>4 (10.8%)</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD or number (%) of patients.

Abbreviations as in Table 1.
that the event-free survival curve of patients with a positive response to flecainide administration and the hybrid therapy was different from the curves of all of the other groups. Considering only the patients receiving the hybrid therapy, after 15 months of follow-up, 58% of the patients with a positive flecainide test were free of AF and atrial flutter recurrence, whereas only 8% of the patients with a negative test did not experience a new episode of AF or atrial flutter.

**DISCUSSION**

To our knowledge, this is the first study to demonstrate, in a prospective, randomized fashion, the efficacy of the hybrid therapy, inferior vena cava-tricuspid annulus ablation, plus anti-arrhythmic drug administration, in the treatment of class IC atrial flutter. Moreover, validation of the flecainide infusion test, as a predictor of long-term success, might facilitate the selection of patients who are candidates for this approach.

**Conversion of AF into atrial flutter.** Atrial fibrillation and atrial flutter are re-entrant atrial arrhythmias involving multiple re-entrant wave fronts in the case of AF and a single macro-re-entrant wave front in the case of atrial flutter. In the canine model (11), the spontaneous transformation of AF into atrial flutter was related to the development of a line of functional block, of critical length, along the right free wall; the occurrence of this phenomenon was enhanced by the administration of class I anti-arrhythmic drugs. In humans, a brief period of irregular atrial activity in one or more intracardiac leads was observed in most of the study patients with inducible atrial flutter during programmed atrial stimulation (12). In patients after open heart surgery, Waldo and Cooper (13) reported the presence of a transitional rhythm, usually AF, preceding the spontaneous onset of atrial flutter. Recently, a mapping study (1), performed with multi-electrode recordings, stressed the role of excitability of the narrow isthmus between the inferior vena cava and the tricuspid annulus as crucial for the organization of AF into atrial flutter. Class I anti-arrhythmic drugs may predispose to the development of atrial flutter by depressing conduction velocity to a greater extent than they prolong the atrial refractory period, resulting in a decrease in the atrial wavelength. In our study, early infusion of flecainide promoted the transformation of AF into atrial flutter in 17.5% of patients, a value slightly superior to that (11% to 12.8%) of patients with AF developing atrial flutter during oral therapy with class IC anti-arrhythmic drugs (5,14). The difference might be due to the pharmacokinetics of the intravenous infusion and the dosage used, which, in our study, was adjusted to the patients’ weight. Moreover, 77 (19%) of 404 patients had at least one documented pre-test episode of typical atrial flutter. In our study, this variable was the only clinical characteristic that predicted the response to flecainide (positive in 36.4% of patients with pre-test atrial flutter vs. 13.1% of patients without pre-test atrial flutter; p < 0.001).

**Effects of combined ablation and drug therapy on AF recurrences.** The conversion of AF into atrial flutter by anti-arrhythmic drugs, as well as the observation of atrial flutter in patients with untreated AF, with periodic transition from one arrhythmia to the other, suggesting a causative relationship between AF and atrial flutter, led some investigators (3–5,14–16) to propose the hybrid pharmacologic and ablation therapy for the treatment of patients with AF developing atrial flutter during anti-arrhythmic drug therapy. In these small, noncontrolled series, the long-term success rate of the hybrid therapy ranged widely from 36.8% to 93%. In our study of patients with a positive response to flecainide, the hybrid therapy was significantly superior to the anti-arrhythmic drug therapy and the ablation therapy alone, in reducing the recurrences of both AF and atrial flutter (58.3% vs. 21.7% vs. 8.3% of patients were symptom free in the three respective groups). For the first time, we report that the efficacy of the hybrid therapy was confined to patients with a positive test (only 8.1% of patients with a negative response were symptom-free at late follow-up), leading to the conclusion that the response to flecainide infusion is reliable in detecting patients who could benefit from the hybrid therapy.

**Study limitations.** The study has several potential limitations: 1) the efficacy of the therapy was assessed on the basis of the patients’ symptoms; however, brief episodes of atrial arrhythmias may be asymptomatic. 2) The results of this study might be of limited clinical value in countries in which the intravenous form of flecainide is not available. However, these results should impel the introduction of this modality of drug administration. Naturally, it should be investigated whether similar results can be achieved with other class IC anti-arrhythmic drugs, like propafenone. 3) Although a positive flecainide test was a significant predictor of the long-term success of the hybrid therapy, the test was far from being an accurate predictor (42% of patients with a positive flecainide test had recurrent arrhythmias during the hybrid therapy). It is obvious that the response to a single intravenous dose of flecainide may not reflect what happens during long-term oral therapy. However, the safety and reliability of the test, as well as isthmus ablation, should...
encourage this approach, instead of performing isthmus ablation alone, in patients with stable atrial flutter during long-term oral flecainide therapy.

**Clinical implications.** The results of our study suggest that the hybrid therapy is effective in preventing both AF and atrial flutter recurrences in ~60% of patients with class IC atrial flutter. Moreover, the response to flecainide infusion is safe and reliable in identifying patients who may benefit from this therapy. The routine use of the flecainide test in the electrophysiology laboratory, to study patients with AF, might widen the percentage of patients who are candidates for the hybrid therapy.

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**REFERENCES**