Pharmacologic conversion and suppression of experimental canine atrial flutter: differing effects of d-sotalol, quinidine, and lidocaine and significance of changes in refactororiness and conduction

GREGORY K. FELD, M.D., NAGAMMAL VENKATESH, M.D., AND BRAMAH N. SINGH, M.D., PH.D.

ABSTRACT The electrophysiologic determinants of conversion and the prevention of atrial flutter are poorly defined. This issue was therefore investigated by evaluating the effects of the new class III antiarrhythmic drug d-sotalol and the class I antiarrhythmic drugs quinidine and lidocaine. Atrial flutter was reproducibly induced in the open-chest anesthetized dog with intercaval crush and rapid atrial pacing. In this preparation, intravenous d-sotalol restored sinus rhythm in 14 of 15 (93%) dogs, whereas quinidine converted nine of 15 (60%) and lidocaine two of 10 (20%). d-Sotalol prevented reinduction in eight (53%), whereas quinidine was effective in four (27%) and lidocaine in none (0%). In the atria, d-sotalol induced significant increases in effective refractory period (+32%; p < .01), functional refractory period (+30%; p < .01), conduction time at an atrial paced cycle length of 150 msec (+9%; p < .05), and atrial flutter cycle length (+8%; p < .01). Quinidine increased effective refractory period (+40%; p < .01), functional refractory period (+27%; p < .01), conduction time at sinus cycle length (+13%; p < .01), conduction time at an atrial paced cycle length of 150 msec (+18%; p < .01), and atrial flutter cycle length (+31%; p < .01). Lidocaine decreased functional refractory period (−6%; p < .05) while lengthening the atrial flutter cycle length (+13%; p < .05). A correlation was noted between conversion of atrial flutter and the degree of drug-induced changes in atrial refractoriness; for the combined data, the effective refractory period increased +38% vs +11% and the functional refractory period increased +28% vs +5% in converters compared with nonconverters (p < .01 in all cases). A similar correlation was observed for reinducibility of atrial flutter; for the combined data, the effective refractory period increased +48% vs +18% and the functional refractory period increased +41% vs +10% in those not reinducible compared to those reinducible (p < .01 in all cases). A negative correlation was observed for increases in conduction time and atrial flutter cycle length. Thus the data indicate that prolongation of atrial refractoriness was the crucial determinant of conversion and prevention of reinduction of atrial flutter in our preparation and that this was more effectively accomplished by d-sotalol than by quinidine.

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sotalol,11–14 and those of the class I drugs quinidine and lidocaine15–18 in dogs with atrial flutter involving reentry around an anatomic obstacle to conduction.5–7,10 The objectives of the study were twofold. The first was to determine whether the selective prolongation of atrial refractoriness, as exemplified by sotalol, or depression of conduction velocity with or without prolongation of refractoriness, as exemplified by quinidine and lidocaine, was the crucial determinant for the conversion or prevention of reinduction of atrial flutter. The second was to determine whether the effectiveness of drug action could be correlated with the degree of prolongation of refractoriness or conduction.

Methods

Forty-five mongrel dogs weighing 15 to 30 kg were studied in the postabsorptive state after sedation with 0.05 mg/kg sc morphine sulfate and general anesthesia with 30 mg/kg iv sodium pentobarbital. Additional doses of 1 to 2 mg/kg pentobarbital were administered during the study as needed to suppress the eye-blink reflex. The dogs were endotracheally intubated and ventilated with room air to maintain arterial pH at 7.35 to 7.45. Arterial and venous cannulas were inserted in the right femoral artery and vein by direct cutdown. The dogs were then paralyzed with 0.03 mg/kg iv succinyl choline. A left thoracotomy was performed and the heart was exposed by construction of a pericardial sack. Four sets of bipolar epicardial electrodes with a 1 cm interelectrode distance were then attached, two each, to the bases of the right and left atrial appendages. One bipolar electrode from each atrium was used for sensing atrial electrograms, and the other for pacing. The atrial electrograms, single-lead (II) surface electrocardiogram, and arterial pressure were recorded on an Electronics for Medicine VRG (Honeywell, White Plains, NY) strip-chart recorder. Atrial pacing was performed with a Medtronic 5325 programmable stimulator.

Measurement of electrophysiologic variables. Electrophysiologic measurements were obtained, including QRS and QT intervals during sinus rhythm, and right-to-left atrial conduction time during sinus rhythm and at the atrial paced rate of 400 beats/min (cycle length 150 msec), during control and after placebo and drug studies. Right and left atrial refractory periods were measured with the S1S2 extrastimulus technique scanning atrial diastole after an S1S1 (8 beat) pacing sequence at a cycle length approximately 10% to 20% shorter than the sinus cycle length. The S1S2 cycle length during placebo and drug studies was the same as that used during control. The S1 and S2 stimulus strength was twice the diastolic threshold for atrial capture.

Production of atrial flutter. A crush injury was performed with a 1 cm right-angle surgical clamp at the junction of the inferior vena cava and the right atrium near the interatrial septum, in a posteroanterior approach with respect to the heart; in several instances a second or third crush was required, usually several millimeters cephalad to the first. Sustained atrial flutter was induced reproducibly in 40 dogs after crush injury by rapid atrial pacing (right atrium) at a cycle length of 150, 120, 100, or 75 msec at 5, 10, or 15 mA current for 15 sec. During atrial flutter, recordings were obtained to determine atrial flutter cycle length, RR intervals, and arterial pressure.

Experimental protocol. Upon induction of atrial flutter, a period of 10 min was allowed in each case to ensure that the arrhythmia was sustained. A placebo study was performed before the drug study with 10 ml of normal saline infused over 15 min in 15 dogs later to receive d-sotalol and five of 15 dogs later to receive quinidine. A placebo study was not performed in the remaining dogs. One of the three study drugs was then administered in the following doses: 10 mg/kg quinidine (Eli Lilly, Indianapolis) or 2 mg/kg d-sotalol (Bristol-Meyers, Evansville, IN) over 15 min intravenously in 15 dogs each, or 1.5 mg/kg lidocaine (Astra, Worcester, MA) intravenously over 2 min followed by a 0.03 mg/kg/min constant infusion in 10 dogs. At 1 min intervals during infusion of placebo or drug and for 15 min after completion of the infusion (after the loading infusion and while on the maintenance infusion in the case of lidocaine), recordings were obtained to determine atrial flutter cycle length, RR intervals, and arterial pressure. At 15 min after the completion of the placebo or drug infusion, if the atrial flutter had not converted it was converted to sinus rhythm by rapid atrial pacing. A blood sample was obtained in the case of the drug studies at this time for determination of serum sotalol concentrations (assayed by Dr. R. Kannan at Wadsworth VA Hospital Cardiovascular Research Laboratory using high-pressure liquid chromatography) and lidocaine and quinidine levels (American-Bioscience Laboratories, Van Nuys, CA). After restoration of sinus rhythm the arterial pressure was recorded and electrophysiologic measurements were obtained in a manner identical to that used during the control period. Attempts were then made to reinduce atrial flutter by means of the entire rapid atrial pacing protocol used during the control phase, as described above. If atrial flutter was reinduced, recordings were obtained and it was defined to be sustained if lasting greater than 30 sec.

Definitions of terms. Corrected QT interval (QTc) was calculated by the Bazett formula: QTc = QT/square root RR interval.19 The right-to-left atrial conduction time was measured during sinus rhythm and rapid atrial pacing from the onset of the right atrial electrogram (initial steep deflection) to the onset of the left atrial electrogram (average of 5 beats). The atrial effective refractory period was defined as the longest S1S2 paced interval not capturing the atrium, while the atrial functional refractory period was defined as the shortest A1A2 interval observed during premature stimulation, measured in the ipsilateral atrial sensing lead adjacent to the pacing lead. The atrial flutter cycle length was defined as the maximum observed, averaging 10 beats, during control just before infusion of placebo or drug and at 1 min intervals during and after the infusion. In those dogs that converted to sinus rhythm, the maximum flutter cycle length was measured during the 1 min recording just before conversion or earlier.

Statistical analysis. The data are presented as means ± SD. Comparison for statistical significance of the differences between means for control and those after placebo or drug administration was performed with Student’s t test (two-tailed) for paired data or unpaired data as appropriate. Conversion and suppression frequencies of atrial flutter were assessed for statistically significant differences with Fisher’s exact test for individual drugs compared with placebo and between drugs with a Pearson chi-square analysis of the data in a three-by-two table. The data presented on refractory periods and conduction times represent the right atrial pacing measurements only, since the left atrial measurements did not yield significantly different results.

Results

Characteristics of the canine atrial flutter. In 40 of 45 dogs (89%), sustained atrial flutter was reproducibly inducible after atrial intercalated crush and rapid atrial pacing. The mean atrial flutter cycle length was 138 ± 20 msec (range 110 to 220). The ventricular response
conversion of atrial flutter to sinus rhythm by rapid atrial pacing, repeat electrophysiologic and electrocardiographic measurements revealed no significant changes. Atrial flutter of identical morphology and rate was reproducibly inducible after placebo and was sustained for a further 10 min in all dogs tested.

Effects of drugs on electrocardiographic and electrophysiologic variables during sinus rhythm. The mean data demonstrating the effects of d-sotalol, quinidine, and lidocaine in comparison to their respective baseline values are shown in table 1. The QTc (+15%; p < .01) was significantly increased by d-sotalol (table 1). The QRS duration did not change. d-Sotalol significantly increased the atrial effective (+32%; p < .01) and functional (+30%; p < .01) refractory periods. The interatrial conduction time during sinus rhythm was not affected (+1%; p = NS).

Quinidine (table 1) significantly prolonged the QRS duration (+10%; p < .01), QTc (+9%; p < .01), conduction time during sinus rhythm (+15%; p < .01), and atrial effective (+40%; p < .01) and functional refractory periods (+27%; p < .01).

Lidocaine (table 1) produced no change in QRS and QTc intervals, atrial effective refractory period, or conduction time during sinus rhythm, but significantly decreased the atrial functional refractory period (−6%; p < .05).

During rapid atrial pacing at a cycle length of 150 msec, similar to the observed cycle lengths of atrial flutter, a significant increase in conduction time was noted after quinidine (+18%; p < .01), whereas a smaller increase was noted (+9%; p < .05) after d-sotalol. Conduction time during rapid atrial pacing was not measured in the earlier lidocaine studies.

The mean drug levels for the three compounds were as follows: quinidine, 4.4 ± 1.5 µg/ml; sotalol, 2.2 ± 0.7 µg/ml; and lidocaine, 1.6 ± 0.7 µg/ml (table 2).

Effects of drugs on atrial flutter. d-Sotalol produced a small but statistically significant increase (table 1) in the atrial flutter cycle length (+8%; p < .01) with comparable slowing in the ventricular response (+9%; p < .01, minimum RR interval). Acceleration of ventricular response and 1:1 conduction did not occur. Quinidine produced a marked increase in the atrial flutter cycle length (+31%; p < .01) with a decrease (−7%; p = NS) in minimum RR interval (table 1). In seven of 15 dogs, quinidine converted a 2:1 or variable ventricular response to a 1:1 response, thus accelerating the average ventricular rate. Lidocaine produced a significant increase in the atrial flutter cycle length (+13%; p < .05) without a significant change in minimum RR interval (table 1).
**TABLE 1**

Electrocardiographic and electrophysiologic effects of intravenous *d*-sotalol, quinidine, and lidocaine in anesthetized dogs with induced atrial flutter

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 15)</th>
<th>d-Sotalol (n = 15)</th>
<th>Quinidine (n = 15)</th>
<th>Lidocaine (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS</td>
<td>53 ± 9</td>
<td>54 ± 10 (1)</td>
<td>51 ± 8</td>
<td>50 ± 7</td>
</tr>
<tr>
<td>QTc</td>
<td>314 ± 39</td>
<td>360 ± 35 (15)b</td>
<td>323 ± 30</td>
<td>353 ± 35 (9)b</td>
</tr>
<tr>
<td>AERP</td>
<td>125 ± 17</td>
<td>166 ± 20 (32)b</td>
<td>111 ± 25</td>
<td>155 ± 38 (40)b</td>
</tr>
<tr>
<td>AFRP</td>
<td>146 ± 13</td>
<td>189 ± 18 (30)b</td>
<td>148 ± 24</td>
<td>187 ± 53 (27)b</td>
</tr>
<tr>
<td>Ct</td>
<td>25 ± 8</td>
<td>26 ± 9 (1)</td>
<td>27 ± 7</td>
<td>31 ± 6 (13)b</td>
</tr>
<tr>
<td>Ct-150</td>
<td>53 ± 8</td>
<td>57 ± 9 (9)b</td>
<td>51 ± 11</td>
<td>60 ± 12 (18)b</td>
</tr>
<tr>
<td>AFcl</td>
<td>140 ± 11</td>
<td>151 ± 15 (8)b</td>
<td>131 ± 26</td>
<td>171 ± 38 (31)b</td>
</tr>
<tr>
<td>RRmin</td>
<td>259 ± 26</td>
<td>281 ± 35 (9)b</td>
<td>240 ± 45</td>
<td>224 ± 62 (7)</td>
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</tbody>
</table>

The data are presented as the mean ± 1 SD in milliseconds. The values in parentheses represent the percent change of mean values from controls. The drug doses were: *d*-sotalol, 2 mg/kg; quinidine, 10 mg/kg; and lidocaine, 1.5 mg/kg followed by 0.03 mg/kg/min.

AFcl = maximum atrial flutter cycle length; AERP = atrial effective refractory period; AFRP = atrial functional refractory period; Ct = right to left atrial conduction time; Ct-150 = Ct during rapid atrial pacing at a cycle length of 150 msec; ND = not done; RRmin = minimum RR interval.

Significance of the mean differences from controls: *p < .05; **p < .01.

*d*-Sotalol converted atrial flutter to sinus rhythm in 14 of 15 dogs (93%) and prevented reinduction in eight (figure 2). Quinidine converted atrial flutter to sinus rhythm in nine of 15 (60%) and prevented reinduction in four (figure 2). After lidocaine, atrial flutter converted in only two of 10 dogs and it was reinducible in all 10 (figure 2). The frequency of conversion of atrial flutter to sinus rhythm was statistically significant (p < .01) for *d*-sotalol and quinidine compared with placebo, but not for lidocaine (figure 2, A). The frequency of suppression of atrial flutter for *d*-sotalol compared with placebo was also significant (p < .01); for lidocaine and quinidine it was not (figure 2, B). The differences in the frequencies of conversion and suppression of atrial flutter between the three drugs were also statistically significant (p < .01 and p < .02, respectively), *d*-sotalol being the most effective, quinidine intermediate, and lidocaine the least effective (figure 2). There was no significant relationship between serum drug level and response.

In most cases, atrial flutter was converted to sinus rhythm abruptly, after a variable prolongation of the atrial flutter cycle length. In three dogs a brief period of atrial fibrillation (<30 sec) preceded restoration of sinus rhythm. In all cases in which sustained atrial flutter (>30 sec) was reinducible the arrhythmia lasted at least 10 min further.

**Changes in electrophysiologic variables relative to effects on atrial flutter**

*Conversion of atrial flutter.* In the group of dogs in which atrial flutter was converted to sinus rhythm (nine of 15) by quinidine compared with the group in which it was not converted (six of 15), there were larger increments in atrial effective refractory period (+57%...

**TABLE 2**

Effects of quinidine on electrophysiologic variables in relation to conversion of atrial flutter (AF)

<table>
<thead>
<tr>
<th></th>
<th>AF converted (n = 9)</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Quinidine</td>
<td>p value&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>AERP</td>
<td>100 ± 23</td>
<td>157 ± 47 (57)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>.09</td>
</tr>
<tr>
<td>AFRP</td>
<td>144 ± 28</td>
<td>198 ± 65 (37)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>.06</td>
</tr>
<tr>
<td>Ct</td>
<td>29 ± 5</td>
<td>32 ± 4 (12)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NS</td>
</tr>
<tr>
<td>Ct-150</td>
<td>46 ± 10</td>
<td>54 ± 11 (16)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>AFcl</td>
<td>133 ± 32</td>
<td>157 ± 40 (18)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

The data are presented as the mean ± 1 SD in milliseconds. The values in parentheses represent the percent change of means from control.

Abbreviations as in table 1.

<sup>a</sup>Significance of the difference between converters and nonconverters in the mean changes from control.

Significance of mean differences from control: *p < .05; **p < .01.
vs +20%; p = .09) and in functional refractory period (+37% vs +12%; p = .06) in the converters than in the nonconverters, although these differences did not quite reach statistical significance (table 2). In contrast, smaller increments from control were observed in conduction time during sinus rhythm (+12% vs +17%; p = NS) and during rapid atrial pacing (+16% vs +20%; p < .01) and in atrial flutter cycle length (+18% vs +51%; p < .01) in the converters than in the nonconverters (table 2). No difference in quinidine level was noted between converters and nonconverters.

Reinduction of atrial flutter. In the case of d-sotalol, there were significant differences in electrophysiologic variables between the group in which atrial flutter was prevented (eight of 15) and the group in which atrial flutter was reinducible (seven of 15). For example, increments in effective refractory period (+35% vs 29%; p < .05) and functional refractory period (+35% vs +23%; p < .01) were significantly greater in those in which atrial flutter was prevented than in those in which it was reinducible (table 3). By contrast, a smaller increment from control was noted in the atrial flutter cycle length (+7% vs +10%; p = NS) and in conduction time during rapid atrial pacing (+5 vs +13%; p = NS) in those in which atrial flutter was prevented than in those in which it was reinducible; there was no significant change in either group in conduction time during sinus rhythm (table 3). There was no difference in the mean serum sotalol levels between the two groups.

The correlation for quinidine was similar (table 3). In the group of dogs in which the reinduction of atrial flutter was prevented (four of 15) compared with the group in which atrial flutter was reinducible (11 of 15), there were larger increments in atrial effective refractory period (+87% vs +26%; p < .01) and in functional refractory period (+52% vs +17%; p < .01). Again, a smaller increment from control was noted in the conduction time during sinus rhythm (0% vs -

### TABLE 3

**Effects of d-sotalol and quinidine on electrophysiologic variables in relation to reinducibility of atrial flutter (AF)**

<table>
<thead>
<tr>
<th></th>
<th>AF not reinducible</th>
<th>p value^\text{a}</th>
<th>AF reinducible</th>
<th>p value^\text{a}</th>
<th>AF not reinducible</th>
<th>p value^\text{a}</th>
<th>AF reinducible</th>
<th>p value^\text{a}</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 8)</td>
<td>d-Sotalol</td>
<td>Control (n = 7)</td>
<td>d-Sotalol</td>
<td>Control (n = 4)</td>
<td>Quinidine</td>
<td>Control (n = 11)</td>
<td>Quinidine</td>
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<tr>
<td>AERP</td>
<td>133 ± 12</td>
<td>179 ± 15 (35\text{c})</td>
<td>&lt;.05</td>
<td>117 ± 18</td>
<td>151 ± 16 (29\text{c})</td>
<td>.00</td>
<td>116 ± 22</td>
<td>146 ± 15 (26\text{c})</td>
</tr>
<tr>
<td>AFRP</td>
<td>148 ± 14</td>
<td>201 ± 14 (35\text{c})</td>
<td>&lt;.01</td>
<td>143 ± 10</td>
<td>175 ± 12 (23\text{c})</td>
<td>.01</td>
<td>145 ± 16</td>
<td>170 ± 11 (17\text{c})</td>
</tr>
<tr>
<td>Ct</td>
<td>26 ± 7</td>
<td>26 ± 7 (0)</td>
<td>NS</td>
<td>26 ± 9</td>
<td>26 ± 10 (3)</td>
<td>.00</td>
<td>25 ± 6</td>
<td>30 ± 7 (20\text{c})</td>
</tr>
<tr>
<td>Ct-150</td>
<td>53 ± 10</td>
<td>55 ± 8 (5)</td>
<td>NS</td>
<td>53 ± 5</td>
<td>59 ± 8 (13\text{b})</td>
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<tr>
<td>AFcel</td>
<td>145 ± 11</td>
<td>155 ± 16 (7\text{c})</td>
<td>NS</td>
<td>134 ± 7</td>
<td>146 ± 12 (10\text{c})</td>
<td>.00</td>
<td>126 ± 10</td>
<td>172 ± 33 (37\text{c})</td>
</tr>
</tbody>
</table>

The data are presented as the mean ± 1 SD in milliseconds. The values in parentheses represent the percent change in the mean from control. Abbreviations as in table 1.

\^\text{a}Significance of the difference between those not reinducible and those reinducible in the mean changes from control.

Significance of the mean difference from control to drug condition: \text{b}p < .05; \text{c}p < .01.
+ 20%; p = NS), atrial flutter cycle length (+ 18% vs + 37%; p = NS), and conduction time during atrial pacing (+ 14% vs + 20%; p = NS) in those in which atrial flutter was prevented than in those in which it was reinducible (table 3). There was no difference in mean quinidine level between the two groups.

To further examine the relationship between the changes in the various electrophysiologic variables and their effects on atrial flutter, the data from the three drugs were pooled. The mean data are shown in figures 3 and 4. There were significantly larger increments in the effective refractory period (+ 38% vs + 11%; p < 0.01) and in the functional refractory period (+ 28% vs + 5%; p < .01) for those animals that converted to sinus rhythm after the drugs than in those that did not (figure 3). For those in which atrial flutter was prevented, the increments in effective refractory period (+ 48% vs + 18%; p < .01) and in functional refractory period (+ 41% vs + 10%; p < .01) were also greater when compared with those in which atrial flutter remained reinducible after the drugs (figure 4). Conversely, the atrial flutter cycle length was more prolonged in those dogs that did not convert to sinus rhythm (+ 27%) compared with those that did (+ 12%) and in those in which atrial flutter was reinducible (+ 21%) compared with those in which it was not (+ 10%) after the drugs (figures 3 and 4).

**Discussion**

Our data have shown that d-sotalol, quinidine, and lidocaine produced significantly different electrophysiologic effects in a canine preparation of experimental atrial flutter. Consistent with the known electrophysiologic effects of these compounds in vitro, d-sotalol, which has one-fiftieth the β-blocking potency of l-sotalol,13 markedly lengthened the atrial refractory period without altering conduction. Quinidine lengthened the refractory period and prolonged conduction, whereas lidocaine had little effect on conduction but abbreviated refractoriness.11-18, 20 These differences in the electrophysiologic effects permitted the evaluation of the major determinants of conversion of atrial flutter to sinus rhythm and the prevention of its induction by electrical stimulation. Drug efficacy was found to correlate with the lengthening of the atrial refractory period and not the prolongation of conduction or the tachycardia cycle length. Our data may thus have clinical relevance and provide some insight into the mechanism of antiarrhythmic drug action in atrial flutter.

**Mechanism of atrial flutter and basis for pharmacologic conversion.** The anatomic obstacle model of atrial flutter used in this study has been previously reported to behave as a reentrant tachycardia with a measurable excitable gap of an average of 25 to 35 msec or 20% of...
the atrial flutter cycle length. This would imply that a segment (20%) of the reentrant circuit is repolarized ahead of the advancing waveform of electrical activity in the atrium during atrial flutter, thus perpetuating reentry. Furthermore, in an anatomic obstacle model of reentry such as the one used in this study, the tachycardia cycle length has been postulated to be dependent on the length of the tachycardia circuit and to be inversely proportional to the conduction velocity. Thus changes in the refractory period alone should have little effect on the tachycardia cycle length. In contrast, in the leading-circle model of reentry proposed by Allessie et al., changes in refractoriness rather than conduction velocity would affect the tachycardia cycle length, since there is no excitable gap in the circuit and its length is not fixed. These hypotheses were tested directly and confirmed by Allessie et al. in both models in rabbit atrial preparations using tetrodotoxin and carbamyl choline, which selectively depress conduction and shorten refractoriness, respectively.

Thus we postulated that in an anatomic obstacle model of atrial flutter with an excitable gap, the prolongation of the atrial refractory period to a critical degree in the absence of any depression of conduction or slowing of the tachycardia would result in the interruption of reentry, conversion to sinus rhythm, and suppression of reinduction of atrial flutter. Conversely, the depression of conduction should lead to significant slowing of the tachycardia but may not convert it or prevent its reinduction.

Our data are therefore consistent with this hypothesis, since d-sotalol, which selectively prolonged atrial refractoriness with little effect on conduction or tachycardia cycle length, produced conversion of atrial flutter in 93% of the dogs and prevented reinduction in 53%. In contrast, quinidine, which markedly prolonged conduction and tachycardia cycle length but affected the refractoriness to a varying degree, was less effective in this regard because it produced conversion in only 60% and prevented reinduction in only 27%. Lidocaine, having little or no electrophysiologic effects, was neither effective in converting atrial flutter nor in preventing its reinduction. Furthermore, our data demonstrate that when a drug altered both atrial refractoriness and conduction, as in the case of quinidine, the degree of prolongation induced by the drug in the refractory period, and not in the conduction time or tachycardia cycle length, correlated with conversion and prevention of reinduction of atrial flutter. Thus the data emphasize the significance of increases in atrial refractoriness in the conversion of atrial flutter to sinus rhythm and prevention of reinduction in this preparation. It also suggests that a depressant effect on conduction may not be beneficial.

It is also of interest that in those dogs in which atrial flutter converted to sinus rhythm or was not reinducible with either quinidine or d-sotalol, the mean increases in effective and functional refractory periods were greater than the length of the excitable gap of 25 to 35 msec or 20% of the atrial flutter cycle length observed in the same preparation of atrial flutter in previous studies.

**Limitations of the data.** We have correlated the frequency of conversion and suppression of atrial flutter with the effects of pharmacologically induced changes in atrial refractoriness and conduction, measured in areas of normal atrial tissues that are probably not located in the presumed area of reentry. It is therefore possible that the changes in refractoriness and conduction induced by the drugs in the actual area of reentry as compared with those in the remote sites of measurement might have differed. Nonetheless, it is clear that changes were effected in certain electrophysiologic variables in the area of reentry, as evidenced by the slowing of the atrial flutter rate by those drugs that primarily affected conduction, namely quinidine and to a lesser degree lidocaine. Quinidine and lidocaine, as in the case of other class I antiarrhythmic agents, depress conduction more markedly in depolarized fibers such as those that may be involved in the area of intercaval crush in our preparation of atrial flutter. In the case of d-sotalol, such an effect was much less marked than that after quinidine, although a depressant effect on conduction in the area involved in the reentrant circuit cannot be completely excluded because there was a small increase in the tachycardia cycle length. Thus the greater observed incidence of conversion of atrial flutter and the prevention of its reinduction in our preparation appears to be attributable to the prolongation of atrial refractoriness rather than to the slowing of conduction and atrial flutter rate. Therefore it is likely that the effects of the drugs on the tachycardia circuit are similar to those in the normal tissue, although conceivably even greater quantitatively.

Previous studies of canine atrial flutter in a preparation similar to ours have also shown that the reentry may occur entirely within the normal tissue surrounding an anatomic obstacle to conduction. Thus the drug-induced changes observed in this preparation were directionally similar to those that might be predicted to occur in a tachycardia produced by reentry in normal tissue around an anatomic obstacle to conduction.

**Clinical implications of the data.** Although the nature
of canine atrial flutter in this preparation may not be the same as that of its human counterpart, certain similarities have been noted in previous studies, including similar morphologies, the presence of an excitable gap during premature atrial stimulation, and the ability to entrain and convert atrial flutter by overdrive pacing in both man and dog. Previous studies in man have also shown a possible relationship between the atrial monophasic action potential duration, a measure of atrial refractoriness, and the spontaneous initiation and conversion of atrial flutter, with the lengthening of the monophasic action potential recorded by suction electrodes correlating with conversion and stability of sinus rhythm. If the mechanisms of canine atrial flutter in this preparation and those in human atrial flutter were similar, i.e., reentry around an anatomic obstacle to conduction, our data suggest that a drug such as sotalol with class III antiarrhythmic action may be more likely to convert and prevent recurrence of atrial flutter in man than the class Ia antiarrhythmic agents such as quinidine. The efficacy of quinidine and procainamide, currently the drugs most commonly used for conversion and for the long-term prophylaxis of atrial flutter in man, has not been systematically studied. Furthermore, only limited data are available regarding the efficacy of class III antiarrhythmic agents in the short-term conversion and long-term suppression of atrial flutter. Our data suggest that the evaluation of the efficacy of the class III antiarrhythmic drugs such as sotalol or N-acetylprocainamide compared with the class Ia antiarrhythmic drugs such as quinidine or procainamide in the short-term conversion and long-term suppression of atrial flutter in man is warranted. Thus the data may not only be of practical significance but may also provide further insight into the mechanism of atrial flutter.

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G K Feld, N Venkatesh and B N Singh

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