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Pharmacologic Alterations in Human Type I Atrial Flutter Cycle Length and Monophasic Action Potential Duration

Evidence of a Fully Excitable Gap in the Reentrant Circuit

BRUCE S. STAMBLER, MD, FACC, MARK A. WOOD, MD,*
KENNETH A. ELLENBOGEN, MD, FACC*

West Roxbury, Massachusetts and Richmond, Virginia

Objectives. **This study compared the effect of changes in action potential duration versus conduction velocity on atrial flutter cycle length to determine whether there is a fully or partially excitable gap in atrial flutter.**

Background. **In an excitable gap reentrant circuit, cycle length is proportional to conduction velocity. Action potential duration is not a direct determinant of cycle length when the gap is fully excitable.**

Methods. **Right atrial monophasic action potentials were recorded from 41 patients during type I atrial flutter before and during pharmacologic interventions.**

Results. **Adenosine (17 ± 3 mg [mean ± SD]) shortened ($p < 0.001$) action potential duration but did not change cycle length. Edrophonium (10 mg) had no significant effect on action potential duration or cycle length. Isoproterenol (0.03 μg/kg body weight per min) shortened ($p < 0.05$) and procainamide (15 mg/kg, then 2 mg/min) prolonged ($p < 0.001$) action potential duration and cycle length. Alterations in cycle length were not correlated with changes in action potential duration. Procainamide's prolongation of action potential duration was reversed by adenosine without affecting cycle length. Procainamide's prolongation of action potential duration and cycle length was partially reversed by isoproterenol. Adenosine's and isoproterenol's shortening of action potential duration and isoproterenol's shortening of cycle length were enhanced by procainamide.**

Conclusions. **Atrial flutter cycle length is determined primarily by conduction velocity and does not depend directly on action potential duration. Atrial flutter has a fully excitable gap, and procainamide does not convert the gap from full to partial excitability. Adenosine and isoproterenol interact with procainamide such that their effects are enhanced and procainamide's effects are diminished.**

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Most evidence suggests that the mechanism of type I atrial flutter in humans involves a macroreentrant circuit around an anatomically or anisotropically defined obstacle with either a partially or fully excitable gap (1–8). The tachycardia cycle length of an excitable gap reentrant circuit is directly proportional to conduction velocity. Action potential duration and refractoriness are direct determinants of cycle length only if the excitable gap is partially rather than fully excitable. In a reentrant circuit in which the wavefront circulates through partially refractory tissue, shortening of action potential duration will increase the excitable gap, accelerate conduction velocity and decrease the flutter cycle length. In contrast, in a reentrant circuit in which there is full recovery of excitability by the end of the gap, shortening of action potential duration will not lead to a change in conduction velocity or tachycardia cycle length. Thus, the effect on the atrial flutter cycle length of changes in action potential duration compared to alterations in conduction velocity will depend on which mechanism of reentry better describes human atrial flutter.

The objectives of this study were to use pharmacologic interventions in humans with atrial flutter 1) to evaluate the relative importance of changes in action potential duration compared to alterations in conduction velocity on atrial flutter cycle length by investigating the effects of adenosine, edrophonium, isoproterenol and procainamide on atrial flutter cycle length and monophasic action potential duration; 2) to determine, based on these pharmacologic interventions, whether the excitable gap in the atrial flutter reentrant circuit is fully or partially excitable, and 3) to examine whether the response to adenosine, edrophonium or isoproterenol is altered by procainamide.

Methods

Study patients. The study cohort included 41 patients referred for cardioversion of sustained type I atrial flutter. Type I atrial flutter was diagnosed according to standard

From the Department of Cardiology, West Roxbury Veterans Affairs Medical Center, Harvard Medical School, West Roxbury, Massachusetts; and *Department of Cardiology, Medical College of Virginia and the McGuire Veterans Affairs Medical Center, Richmond, Virginia.

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Address for correspondence: Dr. Bruce S. Stambler, West Roxbury Veterans Affairs Medical Center, Cardiology (111A), 1400 VFW Parkway, West Roxbury, Massachusetts 02132.

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electrocardiographic (ECG) criteria (7,8). Patients with atrial rates of 200 to 240 beats/min were included, provided that the ECG contained the characteristic sawtooth appearance in the inferior leads, and patients with type II atrial flutter defined as an atrial rate greater than 339 beats/min were excluded (8).

Forty men and one woman (mean [±SD] age 69 ± 9 years, range 51 to 82) were studied. The mean duration of atrial flutter was 42 ± 86 days (range 2 to 365), and 23 patients (56%) had at least one previous episode of atrial flutter. The underlying heart disease was coronary artery disease in 20, congestive heart failure in 16, hypertension in 15, valvular heart disease in 5, conduction system disease in 5 and heart transplantation in 2. No patient was in the immediate period after cardiac surgery. By echocardiography, the mean left atrial size and left ventricular ejection fraction were 4.5 ± 0.8 cm and 38 ± 15%, respectively. Class I and III antiarrhythmic drugs were discontinued at least five half-lives before the study; no patient was receiving theophylline or dipyridamole or was previously treated with amiodarone. Other cardioactive drugs were continued, and at the time of the study 20 patients were receiving digoxin, 19 calcium channel blocking agents, 18 angiotensin-converting enzyme inhibitors and 7 beta-adrenergic blocking agents. All patients were in hemodynamically stable condition and tolerated drug infusions without adverse effects.

Electrophysiologic study. The study was approved by the Committee on the Conduct of Human Research of the Virginia Commonwealth University, and patients were studied in the fasting state after written informed consent had been obtained. A steerable catheter with a pair of silver/silver chloride electrodes at the distal tip, and a pair of platinum ring electrodes located adjacent to the tip was used for recording atrial monophasic action potentials and bipolar electrograms, respectively (EP Technologies). This catheter was inserted through the femoral vein to the right atrium in a position where a stable monophasic action potential recording was obtained, usually in the lateral right atrium or atrial appendage. Monophasic action potential signals obtained with a direct current–coupled preamplifier, bipolar intraatrial electrograms filtered at 30–500 Hz and three or more ECG leads filtered at 0.05 to 100 Hz were recorded at paper speeds of 100–200 mm/s.

Drug studies. After baseline recordings were obtained, drug studies were instituted in the following order: 1) in 29 patients, isoproterenol (0.03 μg/kg body weight per min) was infused intravenously for 5 min, 2) in 32 patients, edrophonium (10 mg) was given as an intravenous bolus over 1 min; 3) in 34 patients, adenosine was administered as a rapid bolus (mean dose 17 ± 3 mg, range 6 to 18) 5 min after edrophonium; 4) in 20 patients, procainamide was given intravenously as a loading infusion of 15 mg/kg (mean dose 1,148 ± 190) at a rate not exceeding 50 mg/min, followed by a maintenance infusion of 2 mg/min; 5) 5 min after the procainamide loading infusion, isoproterenol (n = 18), edrophonium (n = 14) and adenosine (n = 15) were again administered as outlined in steps 1 to 3. A blood sample was obtained 5 min after the loading infusion of procainamide was completed for measurement of procainamide and N-acetylprocainamide plasma concentrations (11.0 ± 3.6 and 1.4 ± 0.6 μg/ml, respectively).

Data analysis. The atrial flutter cycle length and monophasic action potential duration were determined from an average of at least 10 cycles at baseline and during each pharmacologic intervention (for isoproterenol 5 min after initiation of the infusion, for edrophonium 2 to 3 min after the bolus, for adenosine during atrioventricular block, for procainamide 5 min after the loading infusion). The monophasic action potential duration was measured from the action potential upstroke to the point at which repolarization was 90% complete. If repolarization was not complete before the next action potential, the baseline was defined by the points of intersection of the action potential upstroke with the preceding action potential and the repolarization phase with the next upstroke.

A Student two-tailed *t* test for paired data or a repeated measures analysis of variance was used where appropriate. When significant F values were demonstrated, the Student-Newmann-Keuls multiple comparisons test was used to determine significance of individual comparisons. Linear regression analysis was used to examine the relationships between changes in atrial flutter cycle length and monophasic action potential duration. A value of $p < 0.05$ was considered statistically significant, and data are reported as mean value ± 1 SD.

Results

Characteristics of atrial flutter. At baseline before pharmacologic intervention, the atrial flutter cycle lengths ranged from 189 to 299 ms (mean 234 ± 31), and monophasic action potential durations recorded from the right atrium during atrial flutter ranged from 114 to 226 ms (mean 169 ± 26). Most action potential recordings during atrial flutter demonstrated a distinct diastolic resting membrane potential separating each action potential (Fig. 1A,B). A few episodes of atrial flutter, however, particularly at shorter atrial cycle lengths (less than 210 ms), demonstrated an apparent absence of electric diastole (Fig. 1C).

Effects of adenosine, edrophonium and isoproterenol. The effects of adenosine on atrial flutter were rapid in onset, occurring within 10 to 15 s, persisted for only 20 to 30 s and were fully reversible (Fig. 2). Examples of the effect of adenosine on atrial flutter activity are shown in Figure 3. In 34 patients, adenosine shortened ($p < 0.001$) atrial monophasic action potential duration by 17 ± 16 ms but did not significantly change atrial flutter cycle length (Table 1). No patient developed atrial fibrillation in response to adenosine.

Edrophonium decreased atrial action potential duration in 21 patients and increased atrial cycle length in 24 patients; however, among all 32 patients who received edrophonium, these changes were not statistically significant (Table 1).

In 29 patients, isoproterenol reversibly shortened ($p < 0.05$) atrial monophasic action potential duration by 10 ± 9 ms and decreased ($p < 0.05$) atrial flutter cycle length by 7 ± 4 ms

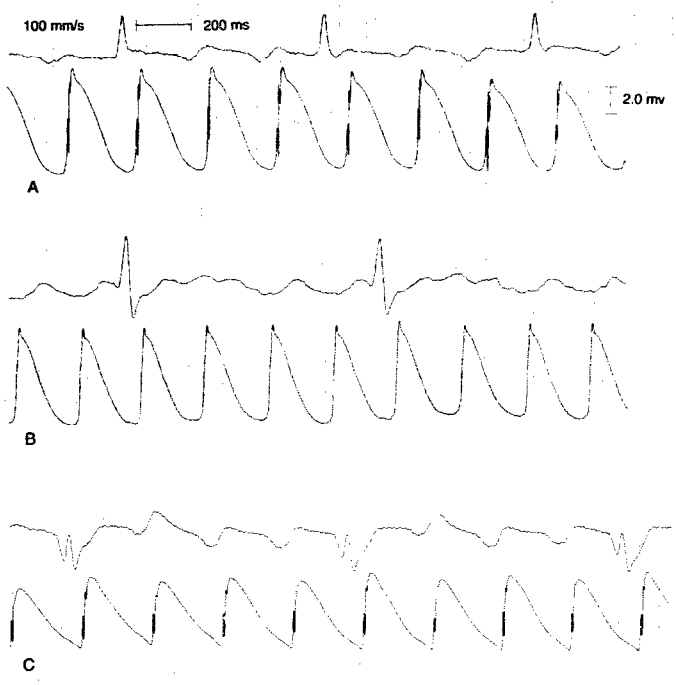


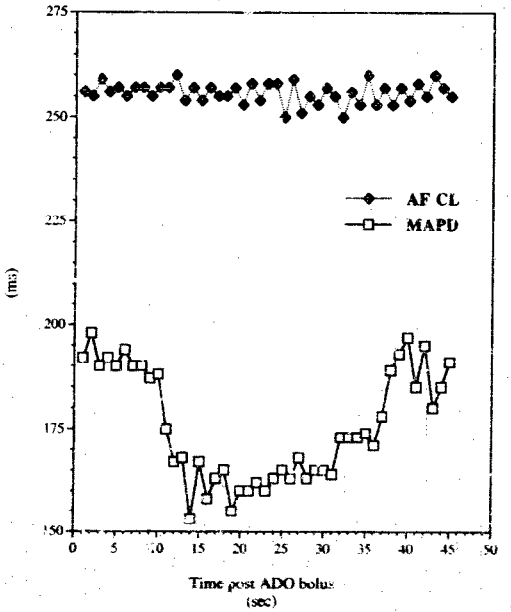
Figure 1. Surface electrocardiographic (lead aVF) and monophasic action potential recordings from the right atrium during episodes of atrial flutter from three patients. The atrial flutter cycle lengths in A, B and C are 260, 235 and 206 ms, respectively.

(Table 1). Although the mean changes in action potential duration and cycle length were not significantly different from each other, the decrease in cycle length was not significantly correlated ($r = -0.01$, $p = 0.591$) by linear regression analysis with the decrease in action potential duration.

Effects of procainamide. In 20 patients, procainamide prolonged ($p < 0.001$) action potential duration by 40 ± 18 ms and flutter cycle length by 61 ± 20 ms (Table 1). The increase in action potential duration induced by procainamide was significantly less ($p < 0.01$) than the increase in cycle length. The increase in cycle length was not significantly correlated ($r = 0.15$, $p = 0.529$) with the change in action potential duration. No patient converted to sinus rhythm in response to procainamide.

Reversal of procainamide's effects by adenosine and isoproterenol. In 15 patients, adenosine was given as an intravenous bolus in the presence of procainamide. An example of the effect on atrial flutter activity of adenosine administered in the presence of procainamide is shown in Figure 4. Adenosine given during procainamide significantly shortened ($p < 0.001$) atrial monophasic action potential duration by 40 ± 24 ms but did not significantly change atrial flutter cycle length (Table 2). In 12 patients, adenosine fully reversed, and in 3 patients adenosine partially reversed, the procainamide-induced prolongation of action potential duration. In the 15 patients studied, the combination of procainamide and adenosine

Figure 2. Time course of atrial flutter cycle length (AF CL) and monophasic action potential duration (MAPD) changes after 18 mg of adenosine (ADO).



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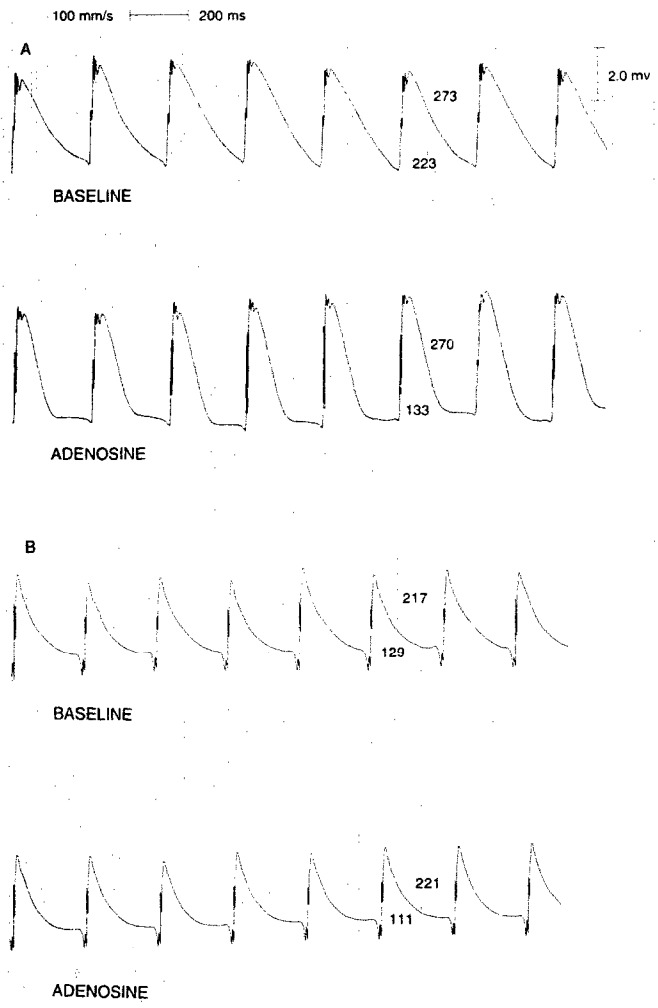

Figure 3. Monophasic action potential recordings during atrial flutter from two patients at baseline and during adenosine. The atrial cycle lengths and action potential durations are above and below the tracings, respectively. Adenosine shortened the action potential duration without significantly altering the atrial cycle length.

significantly shortened ($p < 0.05$) action potential duration and prolonged ($p < 0.001$) cycle length compared to baseline before both agents (Table 2, Fig. 5).

Isoproterenol administered to 18 patients in the presence of procainamide significantly shortened ($p < 0.05$) atrial flutter cycle length by 20 ± 7 ms and monophasic action potential duration by 25 ± 15 ms (Table 2). Isoproterenol did not completely reverse the procainamide-induced increases in cycle length and action potential duration (Fig. 6). Although the increases in cycle length and action potential duration induced by procainamide were significantly smaller during isoproterenol, the atrial cycle length and action potential duration were significantly increased by procainamide both before and during isoproterenol (Table 2).

Table 1. Atrial Monophasic Action Potential Duration and Atrial Flutter Cycle Length at Baseline and During Adenosine, Edrophonium, Isoproterenol and Procainamide

	Monophasic Action Potential Duration (ms [mean ± SD])	Atrial Flutter Cycle Length (ms [mean ± SD])
Baseline	166 ± 22	236 ± 27
Adenosine (n = 34)	149 ± 26*	236 ± 29
Baseline	168 ± 26	233 ± 29
Edrophonium (n = 32)	165 ± 22	237 ± 28
Baseline	167 ± 23	237 ± 32
Isoproterenol (n = 29)	157 ± 23†	231 ± 31†
Baseline	171 ± 23	241 ± 33
Procainamide (n = 20)	211 ± 28*	302 ± 48*

*$p < 0.001$ versus baseline. †$p < 0.05$ versus baseline.

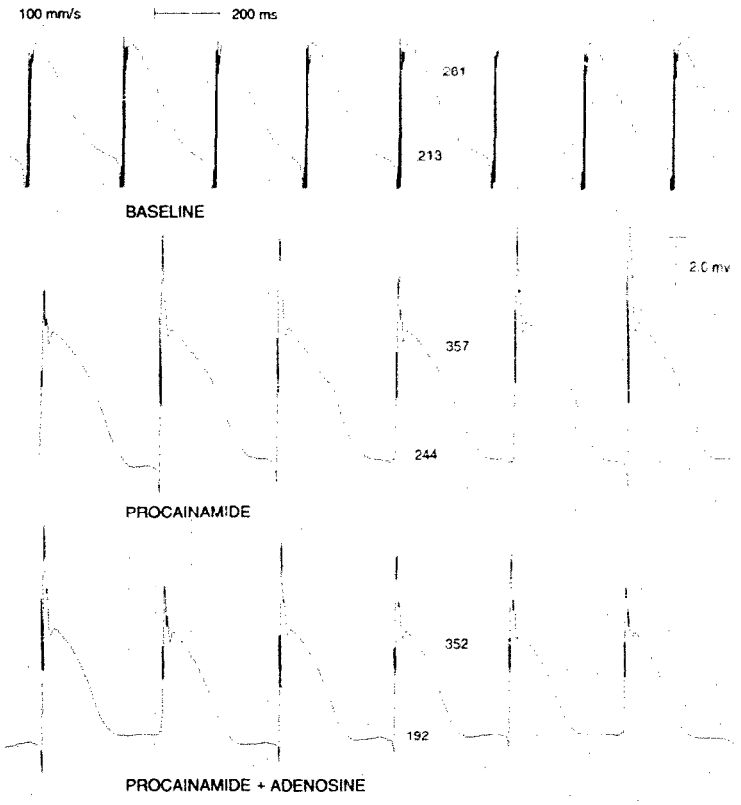

Figure 4. Monophasic action potentials during atrial flutter at baseline, during procainamide and during adenosine in the presence of procainamide. The atrial cycle lengths and action potential durations are above and below the tracings, respectively. Adenosine reversed the procainamide-induced increase in action potential duration (−52 ms) without significantly altering the increase in cycle length (−5 ms).

Potentiation of effects of adenosine and isoproterenol by procainamide. In 15 patients, adenosine induced a significantly greater ($p < 0.001$) decrease in monophasic action potential duration in the presence of procainamide than at baseline in the absence of the antiarrhythmic drug (40 ± 24 vs. 19 ± 18 ms) (Fig. 5). This effect of adenosine during procainamide remained significant even when the decrease was normalized for the preadenosine action potential duration (21 ± 13% vs. 12 ± 11%, $p < 0.01$).

In 18 patients, isoproterenol induced significantly greater ($p < 0.001$) decreases in atrial flutter cycle length (20 ± 7 vs. 7 ± 4 ms) and monophasic action potential duration (25 ± 15 vs. 8 ± 6 ms) during procainamide than at baseline (Fig. 6). This effect of isoproterenol during procainamide remained significant even when these decreases were normalized for the preisoproterenol cycle length (7 ± 2% vs. 3 ± 1%, $p < 0.05$) and action potential duration (12 ± 6% vs. 5 ± 4%, $p < 0.001$). The decrease in cycle length induced by isoproterenol in the presence of procainamide was significantly correlated ($r = 0.79$, $p < 0.001$) with the increase in cycle length induced by procainamide (Fig. 7) rather than with the changes in action potential duration induced by isoproterenol or procainamide.

Table 2. Atrial Monophasic Action Potential Duration and Atrial Flutter Cycle Length at Baseline, During Adenosine and Isoproterenol Alone and in Combination with Procainamide

	Monophasic Action Potential Duration (ms [mean ± SD])	Atrial Flutter Cycle Length (ms [mean ± SD])
Baseline	173 ± 24	240 ± 31
Adenosine	152 ± 32*	240 ± 33
Procainamide	197 ± 33†	283 ± 41†
Procainamide + adenosine (n = 15)	156 ± 40*‡	279 ± 42†
Baseline	167 ± 22	239 ± 34
Isoproterenol	156 ± 26*	232 ± 32*
Procainamide	208 ± 29†	300 ± 50†
Procainamide + isoproterenol (n = 18)	183 ± 24*‡	280 ± 45†§

*$p < 0.05$ versus baseline. †$p < 0.001$ versus baseline. ‡$p < 0.001$ versus procainamide. §$p < 0.01$ versus procainamide.

Discussion

The findings in this study of type I atrial flutter were the following: 1) Adenosine shortened atrial flutter monophasic action potential duration but did not change atrial flutter cycle

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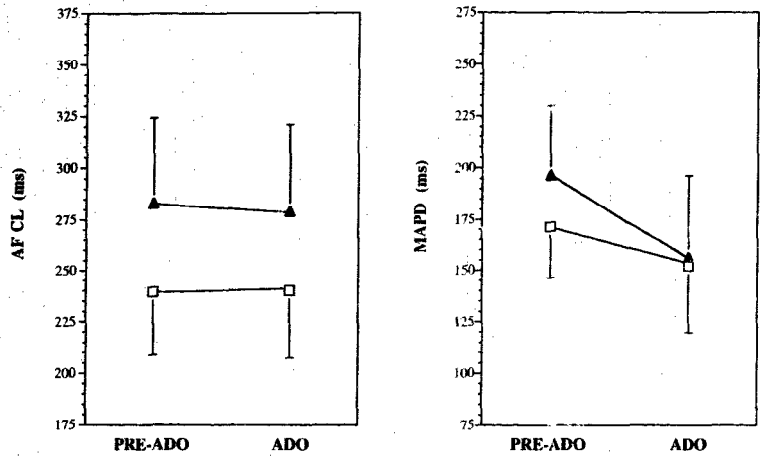

Figure 5. Changes in atrial flutter cycle length (AF CL) and monophasic action potential duration (MAPD) induced by adenosine (ADO) before **(squares)** and during **(triangles)** procainamide.

length, edrophonium did not significantly change either action potential duration or cycle length, isoproterenol shortened both action potential duration and cycle length and procainamide prolonged both action potential duration and cycle length. 2) The changes in flutter cycle length induced by isoproterenol and procainamide were not correlated with changes in atrial action potential duration. 3) Adenosine completely reversed the procainamide-induced prolongation of action potential duration but had no significant effect on the procainamide-induced increase in cycle length, and isoproterenol partially reversed the procainamide-induced prolongation of action potential duration and cycle length. 4) Isoproterenol's shortening of action potential duration and cycle length and adenosine's shortening of action potential duration were potentiated by procainamide. 5) The enhanced shortening of cycle length by isoproterenol in the presence of procainamide was related to a reversal of the procainamide-induced prolongation of cycle length.

Methodologic considerations. The objective of this investigation was to evaluate in patients with atrial flutter the relative importance of changes in action potential duration compared to alterations in conduction velocity on the atrial flutter cycle length. The effects of adenosine, edrophonium and isoproterenol, alone and in combination with procainamide, were studied. It was hypothesized that these agents would have differential effects on atrial refractoriness and conduction velocity, and this would be reflected in alterations in monophasic action potential duration and flutter cycle length. It was further postulated that in human atrial flutter, if there is full recovery of excitability by the end of the excitable gap, then flutter cycle length would be affected by agents that alter conduction velocity and would not be directly affected by

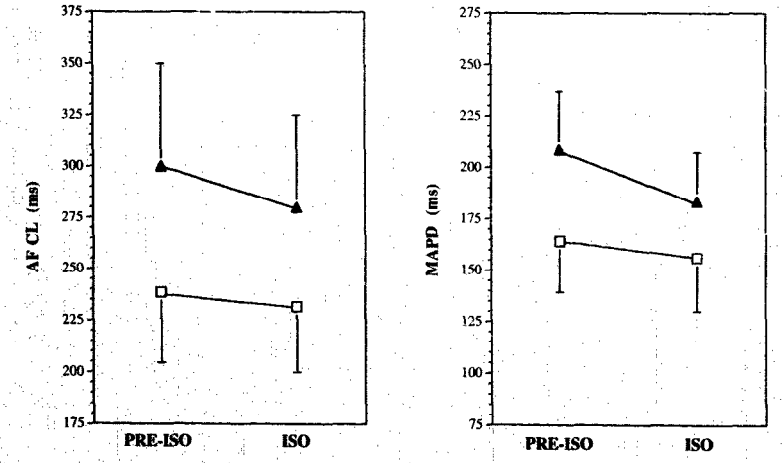

Figure 6. Changes in atrial flutter cycle length (AF CL) and monophasic action potential duration (MAPD) induced by isoproterenol (ISO) before **(squares)** and during **(triangles)** procainamide.

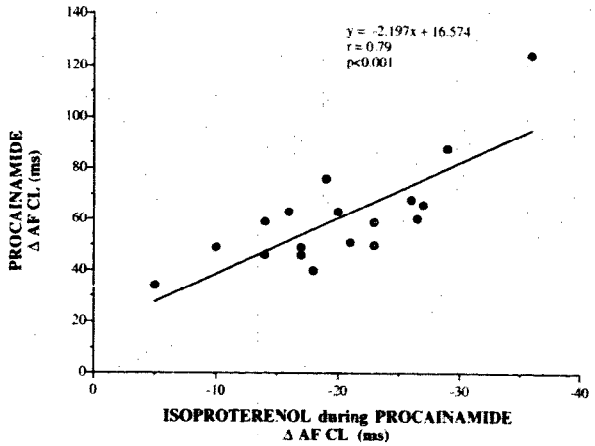

Figure 7. Correlation between the decrease in atrial flutter cycle length (AF CL) induced by isoproterenol during procainamide and the increase in atrial flutter cycle length induced by procainamide alone.

changes in action potential duration or refractory period. On the other hand, if there is incomplete or partial recovery of excitability during the gap, then atrial flutter cycle length would be affected by changes in either action potential duration or conduction velocity. In a partially excitable reentrant circuit, an increase in action potential duration or a slowing of conduction velocity would prolong cycle length, whereas a decrease in action potential duration or an acceleration of conduction velocity would shorten cycle length. Although previous investigations have used pharmacologic agents to characterize the properties of the reentrant circuit in animal models of atrial flutter, this is the first investigation to utilize this approach systematically in human atrial flutter (9–11).

Effects of adenosine. Adenosine hyperpolarizes resting membrane potential and shortens atrial action potential duration by activation of a specific outward potassium current but does not alter intraatrial conduction velocity (12–14). During atrial pacing in humans, adenosine shortens atrial monophasic action potential duration and refractoriness. Several studies have reported in small series of patients that adenosine given during atrial flutter does not change atrial cycle length (15,16). The present study confirmed these findings in a large group of patients with atrial flutter and demonstrated that the lack of change in atrial cycle length was associated with a marked shortening in atrial action potential duration.

Effects of isoproterenol. Isoproterenol presumably decreased atrial action potential duration by stimulating outward potassium currents (17). The decrease in action potential duration may also be related to changes in cycle length because action potential duration is cycle-length dependent (18). In normal myocardial fibers, catecholamines have minimal effects on conduction velocity; however, in abnormal, partially depolarized tissue, isoproterenol speeds conduction by promoting hyperpolarization and improving cell to cell coupling (19,20). In canine models, using either chronic right atrial enlargement or an acute intercaval crush injury, isoproterenol decreases atrial flutter cycle length (9,21). In the present study in human atrial flutter, the decreased atrial flutter cycle length in response to isoproterenol was most likely related to an increase in conduction velocity rather than a decrease in action potential duration or refractoriness.

Effects of edrophonium. Vagal stimulation with edrophonium, a cholinesterase inhibitor, did not produce a statistically significant change in action potential duration or cycle length. In most patients, however, edrophonium shortened action potential duration and prolonged atrial flutter cycle length by 3 to 4 ms. In atrial fibers, cholinergic agonists increase potassium conductance, which shortens atrial action potential duration and effective refractory period (22,23). Vagal stimulation accelerates the cycle length of tachycardia by 6 to 27 ms in leading circle reentry and in anatomic obstacle models (9–11).

Effects of procainamide. The procainamide-induced prolongation of action potential duration was likely secondary to blockade of delayed rectifier potassium current and also to the increase in atrial cycle length (24,25). Atrial action potential duration and the effects of class I antiarrhythmic drugs are highly dependent on cycle length (18,25). The increase in atrial flutter cycle length induced by procainamide was significantly greater than, and was not correlated with, the increase in action potential duration. This suggests that the increase in atrial flutter cycle length induced by procainamide was not related to the increase in action potential duration and was likely caused by a slowing of conduction velocity. Procainamide causes dose- and use-dependent block of fast sodium channels, which decreases conduction velocity in regions exhibiting either normal or slowed conduction (24–26). In animal models, class IA antiarrhythmic drugs prolong refractory period, slow conduction velocity and increase flutter cycle length by 30% to 60% (27–31). The findings in the present report are consistent with the conclusions of these studies that the drug-induced prolongation of atrial flutter cycle length correlates with changes in atrial conduction velocity rather than in refractory period.

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Reversal of effects of procainamide and potentiation of effects of adenosine and isoproterenol. The mechanism of the enhanced effects of adenosine to shorten the atrial action potential duration during procainamide may be related to an alteration in resting membrane potential. It has been reported that the magnitude of adenosine-induced hyperpolarization in atrial myocardium depends on the resting membrane potential before adenosine; the more depolarized the tissue, the larger the hyperpolarization (13).

In ventricular tachycardia, the shortening of tachycardia cycle length by isoproterenol is greater in the presence than absence of procainamide, and this enhanced effect correlates with a greater change in conduction velocity than in refractoriness (32). The present study demonstrates a similar finding in atrial flutter, although the magnitude of the decrease in cycle length was less. The enhanced shortening of flutter cycle length induced by isoproterenol in the presence of procainamide was correlated with the increase in cycle length induced by procainamide alone. Thus, the mechanism of the potentiation of isoproterenol's effects by procainamide was likely related to the slowing of conduction velocity and depression of fast inward sodium current induced by procainamide. Alternatively, the weak anticholinergic properties of procainamide may have caused a withdrawal of the normal inhibitory effect of background parasympathetic tone on the response to sympathetic stimulation (i.e., accentuated antagonism) (33). Finally, catecholamines improve cell to cell coupling, and isoproterenol may have reversed the effects of procainamide on gap junctions or on anisotropic conduction (20,26).

Pharmacologic evidence for mechanism of type I atrial flutter. Atrial flutter models in animals and studies in humans have demonstrated that flutter is caused by a reentrant mechanism (1–11). Depending on the model, the circuit has no excitable gap (leading circle reentry), a partially excitable gap (Y-shaped atrial incision and atrial enlargement models) or a fully excitable gap (sterile pericarditis and atrial crush injury models) (9–11,34–36). Some human studies suggest that the gap is fully excitable, whereas others indicate that it is only partially excitable (4,37–40). On the basis of variations in flutter cycle lengths attributed to the QRS complex, Lammers et al. (39) and Ravelli et al. (40) recently suggested that type I and type II flutter result from partially excitable gap and leading circle reentry, respectively.

The pharmacologic data from the present study support the concept that in human type I atrial flutter there is full recovery of excitability during the gap. The finding that adenosine significantly shortened atrial action potential duration but did not alter cycle length is central to this conclusion. If in atrial flutter there is no or a partially excitable gap, then adenosine would have shortened the cycle length because the wavefront would be accelerated as it progagated through less refractory tissue. The data on isoproterenol and procainamide further support this conclusion. Although these agents had combined effects on action potential duration and cycle length, the changes in cycle length induced by isoproterenol and procainamide were not related to changes in action potential duration. Isoproterenol shortened cycle length by speeding conduction, and procainamide prolonged cycle length by slowing conduction rather than by altering action potential duration. Thus, the cycle length in human type I atrial flutter is determined primarily by conduction velocity rather than by action potential duration or refractoriness.

The present study also suggests that procainamide did not convert the fully excitable gap into one that is partially excitable. Procainamide increased the flutter cycle length by a significantly greater amount than it prolonged the action potential duration. Adenosine given during procainamide did not alter flutter cycle length, whereas isoproterenol shortened cycle length. Previous animal studies likewise suggest that during procainamide there is a persistent gap of full excitability within the reentrant circuit and that procainamide prolongs the cycle length by a direct effect to slow conduction of the wavefront of excitation (30,31).

Study limitations. The atrial monophasic action potentials were recorded from presumably normal tissue to monitor drug-induced changes in atrial flutter and were likely not obtained directly from the atrial flutter circuit. The findings regarding action potential duration are valid only if these measurements were representative of the drugs' effects on the flutter circuit, particularly the local excitable gap and conduction velocity in the area of slow conduction. Conduction velocity and the circuit's path length were not measured directly, and the latter was assumed to remain constant during interventions. The drugs may have affected areas of functional block and thus altered the path length; however, small changes in path length probably would not alter the current findings or conclusions significantly.

Conclusions. The findings of this study of pharmacologic interventions in human type I atrial flutter suggest that the atrial flutter cycle length is determined primarily by conduction velocity and does not depend directly on action potential duration. These results are also consistent with the concept that the atrial flutter reentrant circuit has a fully excitable gap in which the wavefront of excitation does not impinge on refractory tissue. Procainamide prolongs the atrial flutter cycle length by slowing conduction independent of changes in action potential duration and does not convert the excitable gap from full to partial excitability. Adenosine and isoproterenol interact with procainamide such that their effects are enhanced and the effects of procainamide are diminished.

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