Mechanism of Interruption of Atrial Flutter by Moricizine
Electrophysiological and Multiplexing Studies in the Canine Sterile Pericarditis Model of Atrial Flutter

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Background  Moricizine is said to have potent effects on cardiac conduction but little or no effect on cardiac refractoriness.

Methods and Results  The effects of moricizine (2 mg/kg IV) on induced atrial flutter were studied 2 to 4 days after the creation of sterile pericarditis in 11 dogs. Ten episodes of stable atrial flutter before and after the administration of moricizine were studied in 9 dogs in the conscious, nonsedated state, and 7 episodes were studied in 6 dogs in the anesthetized, open chest state. In the conscious state, the effects of moricizine on atrial excitability, atrial effective refractory period, and intra-atrial conduction times were studied by recording during overdrive pacing of sinus rhythm from epicardial electrodes placed at selected atrial sites. Moricizine prolonged the atrial flutter cycle length in all the episodes, from a mean of 133±9 to 172±27 milliseconds (P<.001), and then terminated 7 of the 10 episodes. Moricizine increased the atrial threshold of excitability from a mean of 2.3±1.4 to 3.3±2.2 mA (P<.01) and prolonged intra-atrial conduction times (measured from the sulcus terminalis to the posteroinferior left atrium) from a mean of 58±6 to 64±5 milliseconds (P<.005). Prolongation of the atrial effective refractory period from 166±20 to 174±24 milliseconds (P<.05) was observed only at the sulcus terminalis site. In the open chest studies, administration of moricizine prolonged the atrial flutter cycle length from a mean of 150±15 to 216±30 milliseconds (P<.001) and then terminated the atrial flutter in all 7 episodes. As demonstrated by simultaneous multisite mapping from 95 bipolar sites on the right atrial free wall, the atrial flutter cycle length prolongation was either due to further slowing of conduction in an area of slow conduction in the reentrant circuit of the atrial flutter (5 episodes) or further slowing of conduction in an area of slow conduction plus the development of a second area of slow conduction (2 episodes). The change in conduction times in the rest of the reentrant circuit was negligible (10.9±8.7% of the total change). In all 7 episodes, the last circulating reentrant wave front blocked in an area of slow conduction.

Conclusions  Moricizine (1) prolongs the atrial flutter cycle length, primarily by slowing conduction in an area of slow conduction in the reentrant circuit, (2) terminates atrial flutter by causing block of the circulating reentrant wave front in an area of slow conduction of the reentrant circuit, and (3) effectively interrupts otherwise stable atrial flutter in this canine model. The reason for these effects of moricizine are not readily explained by its effects on global atrial conduction times and refractoriness studied during sinus rhythm. Local changes in conduction in an area(s) of slow conduction are responsible for both cycle length prolongation and atrial flutter termination rather than the traditional wavelength concept of head-tail interaction. (Circulation. 1994;89:2860-2869.)

Key Words  ● moricizine ● reentry ● atrial flutter ● pericarditis

Moricizine is a phenothiazine derivative that was developed in the USSR in 1954. Clinical studies have been performed previously to assess the effectiveness of this drug in controlling atrial premature beats,1 ventricular premature beats,1-10 atrioventricular (AV) reentrant tachycardia in patients with Wolff-Parkinson-White syndrome,11 AV nodal reentrant tachycardia,12 automatic atrial ectopic tachycardia,13 non-sustained ventricular tachycardia,3,4,6-8,14 and sustained ventricular tachycardia.14-18 Animal studies of moricizine have been performed to test the effectiveness of this drug in suppressing ventricular arrhythmias after coronary artery occlusion19 and abnormal automaticity induced in isolated canine Purkinje fibers.20-21 However, very little is known about the effects of moricizine on atrial flutter. We are aware of only one report in which moricizine was used successfully to terminate atrial flutter13 and two reports12,22 in which moricizine was found to suppress atrial ectopic tachycardias in children.

Our laboratory has developed a reliable canine sterile pericarditis model of atrial flutter.23 In this model, sustained, stable atrial flutter can be repeatedly induced both in the conscious and in the anesthetized, open chest states. The mechanism of the atrial flutter in this model is circus movement located in the right atrial free wall.24-26 This pericarditis model has been shown to be a suitable model for studying the effects of antiarrhythmic drugs on atrial flutter.27-32 In the present study, moricizine was administered intravenously during sustained atrial flutter in the conscious state to test its effects on atrial flutter and on several atrial electrophysiological properties. Subsequently, moricizine’s effects on the components of the reentrant circuit of atrial flutter were
studied using simultaneous multisite mapping techniques in the anesthetized, open chest state.

Methods

Eleven adult mongrel dogs weighing 18 to 24 kg were studied after the creation of sterile pericarditis. The effects of intravenous moricizine on induced atrial flutter and on selected atrial electrophysiological properties were studied in 9 dogs in the conscious, nonsedated state during 10 episodes of induced atrial flutter. Also, the effects of moricizine on the reentrant circuit were studied using multiplexing techniques to perform simultaneous multisite mapping during 7 episodes of induced atrial flutter in 6 dogs. In sum, 2 dogs were studied only in the open chest state, 5 dogs were studied only in the closed chest state, and 4 dogs were studied in both closed and open chest states. All of the studies were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee, the American Heart Association on Research Animal Use, and the current US Public Health Service Policy on Humane Care and Use of Laboratory Animals.

Creation of the Sterile Pericarditis Atrial Flutter Model

The canine sterile pericarditis model was created as previously described. At the time of the surgery, three pairs of stainless steel wire electrodes coated with FEP polymer except at the tip (O Flexon, Davis and Geck) were sutured on the following atrial sites: the mid-sulcus terminalis of the right atrium, the interatrial band (Bachmann’s bundle), and the posteroinferior aspect of the left atrium near the proximal portion of the coronary sinus. The distal ends of these wire electrodes were brought out through the chest wall and exteriorized posteriorly in the interscapular region for use during subsequent studies. Antibiotics and analgesics were administered, and the dogs were allowed to recover.

Electrophysiological Studies in the Conscious, Nonsedated State

Two to three days after creating sterile pericarditis, we performed electrophysiological studies in 9 dogs in the conscious, nonsedated state using the epicardial wire electrodes placed at the initial surgery. Three surface ECGs (leads I, II, and III) were recorded simultaneously with three bipolar electrogams obtained from the sulcus terminalis, Bachmann’s bundle region, and posteroinferior left atrium. The ECGs were filtered between a band pass of 0.1 and 500 Hz, and the epicardial electrogams were between 30 and 500 Hz. Data were monitored on an oscilloscope and recorded on photographic paper at a speed of 100 mm/s using an Electronics-for-Medicine VR-16 switched-beam oscilloscope recorder. Data were also recorded simultaneously on FM tape using a Honeywell 101 FM tape recorder for subsequent playback and analysis. All pacing studies were performed using a modified Medtronic 5325 programmable stimulator with a pulse width of 1.8 milliseconds.

Measurement of Baseline Atrial Electrophysiological Properties

The following atrial electrophysiological properties were measured during each study.

1) The threshold of excitability was measured at each electrode site (sulcus terminalis, Bachmann’s bundle region, and posteroinferior left atrium) during atrial pacing at a rate of 150 beats per minute, and the mean value of three measured thresholds was used as the threshold value.

2) The atrial effective refractory period at each of the three electrode sites was determined by introducing a premature atrial beat to scan diastole after a train of eight atrial paced beats at rates of 150, 200, and 300 beats per minute. Each premature atrial beat was delivered at twice threshold stimulus strength, and the coupling interval of the premature beat was decremented by 5-millisecond intervals until the effective refractory period was found.

3) Atrial flutter was induced by programmed atrial pacing. After atrial flutter termination, the local electrogram recorded at the posteroinferior left atrial wall was compared before and after drug for each study, so that each dog and each pacing rate served as its own control.

Induction of Atrial Flutter

Induction of atrial flutter was attempted using programmed atrial stimulation or rapid atrial pacing techniques. Both methods were performed using stimuli of at least twice threshold stimulus strength and up to 20 mA (maximal output of the stimulator).

Moricizine Study Protocol

After measuring the baseline electrophysiological properties, we attempted atrial flutter induction using the methods described above. When stable atrial flutter was induced, moricizine (2 mg/kg) was administered intravenously over a 5-minute period, and the drug’s effects on the atrial flutter cycle length were determined. If moricizine failed to terminate the atrial flutter after 10 minutes from the onset of drug administration, the atrial flutter was terminated by overdrive atrial pacing. After atrial flutter termination, the above electrophysiological studies were performed during sinus rhythm to establish the drug’s effects on the above electrophysiological parameters.

If moricizine administration changed the threshold of atrial excitability, to avoid spurious changes in intra-atrial conduction times, the atria were paced using the same control stimulus strength (twice diastolic threshold) used before moricizine administration. If the threshold of the atrial excitability measured after the moricizine administration increased to more than twice that measured before moricizine, the intra-atrial conduction time was measured using just threshold stimuli after drug administration. In one dog, the electrophysiological study was performed on both the second and third postoperative days. The interval between these two studies was longer than five times the elimination half-life of moricizine (mean, 1.86 hours; range, 0.82 to 4.2 hours).

Simultaneous Multisite Mapping Studies in the Open Chest State

In 6 dogs, on the fourth postoperative day, and after first demonstrating that stable atrial flutter could be induced in the conscious state, an open chest study was performed. The dogs were anesthetized with pentobarbital (30 mg/kg IV) and mechanically ventilated using a Harvard respirator. The body temperature of the dog was kept within physiological range throughout the study using a heating pad. The chest was opened through a median sternotomy. The heart was exposed by dissecting the pericardium gently from the adherent epicardium and then suspended in a pericardial cradle. After the gauze strips were removed from both atria, the talcum powder that had become encrusted was carefully peeled off. The pair of stainless steel wire electrodes previously sutured on the sulcus terminalis were removed to permit epicardial placement of the 190-electrode array described in the next section. A new
reference bipolar electrode was sutured on the tip of the right atrial appendage.

Creation of Complete Heart Block

Over the course of the studies, our laboratory began to produce complete heart block to control the ventricular response rate and thereby make still easier the analysis of atrial activation. This was because during induced atrial flutter, 2:1 AV conduction usually occurred, and occasionally 1:1 AV conduction occurred. Therefore, temporal superimposition of ventricular activation with atrial activation could interfere with interpretation of the recorded atrial electrograms. To minimize this, we produced complete AV block in the last two open chest studies by performing radiofrequency ablation of the His bundle using standard electrode catheter techniques before the chest was opened. Thus, an electrode catheter specially designed for delivery of radiofrequency energy (Mansfield 7F steerable Polaris catheter with a 4-mm electrode tip) was advanced through a femoral vein to the His bundle recording position. Using a Radionics RFG-3C RP Lesion Generator System (Radionics Inc), we performed His bundle ablation. Then, with the previously placed ventricular electrodes, ventricular pacing was initiated at a rate of 80 to 100 beats per minute. Ventricular pacing was performed at 60 beats per minute during the data acquisition (simultaneous multisite recording) portions of the studies to decrease further periods of temporal superimposition of atrial and ventricular events. Ventricular pacing was performed using a modified Medtronic 5375 external ventricular inhibited pulse generator (Medtronic, Inc).

Placement of the Electrode Array

An epicardial electrode array containing 190 electrodes (Fig 1) was placed on the right atrial free wall and secured with a Velcro belt. The array was constructed of a sheet of Dacron-reinforced Silastic (Dow Corning), into which fine silver-wire electrodes were embedded and fixed with room temperature vulcanizing silicon rubber adhesive. The interelectrode distance between electrode pairs was 1.5 mm, and the distance between the center of each electrode pair was 4.2 mm diagonally and 6.0 mm perpendicularly. With this electrode array, bipolar electrograms were recorded simultaneously from 95 sites (Fig 2).

Moricizine Study Protocol

After the placement of the electrode array, atrial flutter was induced using the same pacing protocol used during the closed chest studies. The only difference was that pacing from the sulcus terminalis was replaced by pacing from the tip of the right atrial appendage. During atrial flutter immediately before the administration of moricizine, during drug administration, and until the return of sinus rhythm following interruption of atrial flutter by moricizine, electrograms were recorded simultaneously from all 190 unipolar electrodes in the array along with ECG lead II.

Data Acquisition

Data recording and processing were performed using a cardiac mapping system designed at Case Western Reserve University. All signals were individually amplified, filtered between a band width of 1 to 500 Hz, sampled at 1000 Hz, and digitized with a 12-bit analog-to-digital converter. The data were then transferred to a 68020 coprocessor with 4 Mbytes of memory via optoisolators. Data collection and processing were performed using this coprocessor, which is resident in a Sperry IT PC host system (IBM AT compatible). A SGT PEPPER (Number Nine Computer Corp) graphic processor with color monitor was used to display raw and processed data. The system had all processing units (68020, Sperry, SGT PEPPER) designed to operate in parallel. This parallel organization gave the mapping system “real-time” processing capability. For the first four studies, a 4-second circulating buffer was used to permit continuous monitoring of the atrial flutter and to record selected events, including the control period of atrial flutter before moricizine administration and the period just before, during, and immediately after termination of the atrial flutter by moricizine. For the last two studies, data were recorded continuously, as the system was capable of storing and archiving 30 minutes of...
Data Analysis

Analysis of data consisted of selecting activation times and computation of an isochronous map with a maximal resolution of 1 millisecond. Data in their raw unipolar format and processed in a bipolar format (subtracted in software) were available to assist in the selection. Data were filtered in software with a low-cutoff frequency (high-pass filter) of 10 Hz before analysis to avoid baseline drift of the electrograms. A 600-millisecond analysis window was chosen from the stored data. A time reference signal was selected from one of the electrode sites and used to depict zero activation time. The electrograms recorded at each site during the time window were displayed on a graphics screen, and selection of activation time was done manually with a cursor with the aid of the computer, which automatically provided the $-\text{dv/dt}$ from the unipolar signal for any site selected. The moment of activation at each site was taken as the peak of the first rapid deflection in a predominant monophasic recording or as the time of the intrinsic deflection in a predominantly biphasic recording. The activation time at sites at which multiple component electrograms were recorded was assigned to the major deflection (highest amplitude for bipolar electrograms or fastest downstroke for monopolar electrograms). Care was taken first to identify all components that were a result of ventricular activation using the QRS complex in the ECG as a marker. If there were two discrete deflections for one atrial complex in the ECG (ie, a so-called double potential), the activation time at these sites was assigned to the deflection with the highest amplitude for bipolar electrograms or the more rapid deflection for unipolar electrograms.36,37

Because the size of the right atrium differed from dog to dog, anatomic landmarks (vena cavae, right atrial appendage, AV groove) were identified and positioned on the grid (electrode array) by visual inspection. For each atrial beat, activation time at each site was placed on an anatomic grid representing activation at each bipolar recording site, and isochronous lines at 10-millisecond intervals were drawn manually.

Definitions

In this study, slow conduction was defined as a conduction velocity of <0.2 m/s,39 and relatively slow conduction was identified by crowding of isochrons. Atrial flutter was defined as a rapid atrial rhythm (rate, >240 beats per minute) characterized by a constant beat-to-beat cycle length, polarity, morphology, and amplitude of the recorded bipolar electrograms.24,25,39 Stable atrial flutter was defined as atrial flutter lasting at least 10 minutes. It was further defined by the presence of a single, constant reentrant circuit with a constant atrial activation sequence. Atrial flutter with cycle length oscillations was defined by the presence of a single, constant reentrant circuit with a constant activation sequence but with cycle lengths that changed by at least 3 milliseconds per beat.40 Drug-induced termination of atrial flutter was defined as the cessation of atrial flutter and return to sinus rhythm within the 10-minute period from the onset of the drug administration.

Statistical Analysis

All values are given as mean ± 1 SD. Statistical analysis was performed using a Student’s paired $t$ test. $P < .05$ was considered statistically significant.

Results

Studies in the Conscious, Nonsedated State

In all 9 dogs studied, atrial flutter was induced in the conscious, nonsedated state on at least one of the first three postoperative days. A representative example of induced atrial flutter is shown in Fig 2. During the entire period of atrial flutter, the atrial cycle length was remarkably constant, as is typical during episodes of atrial flutter in this model.23-32 The atrial electrogram morphology and the relative atrial activation sequence at the three fixed electrode recording sites were also constant.

Effects of Moricizine on Atrial Flutter

Moricizine (2 mg/kg) was administered intravenously during 10 episodes of sustained, stable atrial flutter in 9 dogs. A representative example is shown in Fig 3 (same episode as Fig 2). Moricizine increased the atrial flutter cycle length from 140 to 165 milliseconds 2 minutes after starting drug administration, to 177 milliseconds after 3 minutes, and to 209 milliseconds after 5 minutes.
Electrophysiological Properties

Effects of Moricizine on Atrial Flutter

Fig 4. Plot of effects of moricizine on the atrial flutter cycle length (AFL-CL) in the closed chest studies. The AFL-CL before drug administration and at the time of maximal change in AFL-CL after drug administration are shown. Open circles indicate that the atrial flutter was not interrupted. Closed squares and vertical bars indicate mean values and standard deviations. Closed circles indicate that moricizine interrupted the atrial flutter (seven episodes [70%]).

and then terminated the atrial flutter 5 minutes 30 seconds after starting its administration.

The results of the effects of moricizine on atrial flutter cycle length for all 10 episodes are shown in Fig 4. Moricizine increased the atrial flutter cycle length in all 10 episodes from a mean baseline value of 133±9 milliseconds to a mean maximal value of 172±27 milliseconds (P<.001). After achieving the maximal increase in the atrial flutter cycle length, moricizine interrupted the atrial flutter in 7 (70%) of the 10 episodes at a mean time of 177±107 seconds (range, 73 to 330 seconds) after its administration.

During administration of moricizine, the ventricular rate in response to atrial flutter increased in 6 of the 10 episodes and decreased in the remaining 4. Although the mean value of the ventricular rate for all episodes increased slightly (180±34 and 202±42 beats per minute before and after moricizine, respectively), it did not reach statistical significance (P=.078).

Effects of Moricizine on Atrial Electrophysiological Properties

Moricizine increased the mean threshold of atrial excitability measured during pacing at 150 beats per minute from 2.3±1.4 mA to 3.3±2.2 mA (P<.01) (Table). Moricizine increased the mean atrial effective refractory period at the sulcus terminalis recording site from 166±20 to 174±24 milliseconds (P<.05) measured during atrial pacing at 150 beats per minute, from 158±24 to 166±25 milliseconds (P<.05) measured at 200 beats per minute, and from 152±20 to 162±20 milliseconds (P<.05) measured at 300 beats per minute. However, moricizine did not change the atrial effective refractory period measured at Bachmann’s bundle or at the posteroinferior left atrium at all three pacing rates studied. Moricizine significantly prolonged the intratrial conduction time from the sulcus terminalis to the posteroinferior left atrium. It increased the intra-atrial conduction time from 58±6 to 64±5 milliseconds (P<.005) during atrial pacing at 150 beats per minute, from 61±7 to 69±9 milliseconds (P<.005) at 300 beats per minute, and from 63±8 to 72±8 milliseconds (P<.001) at 350 beats per minute.

Studies in the Open Chest State

Effects of Moricizine on Atrial Flutter

Moricizine increased the atrial flutter cycle length in all seven episodes studied from a mean baseline value of 150±15 milliseconds to a mean maximal value of 216±30 milliseconds (P<.001). Termination of the atrial flutter as a result of intravenous administration of moricizine occurred in all seven episodes.

Fig 5 shows atrial electrograms recorded from selected sites (see Fig 6 for the location on the right atrial free wall of recording sites a through f and the reference recording site) during a representative example of induced, stable atrial flutter. During the control period of stable atrial flutter, the beat-to-beat atrial cycle length was constant, with a mean beat-to-beat cycle length variability of ±2 milliseconds.

Fig 6 shows the isochronous map of the right atrial free wall during stable atrial flutter at a cycle length of 193 milliseconds in the same representative example before moricizine administration. Note that the reentrant excitation wavefront circulates in a counterclockwise direction around an area of apparent functional block, represented by dashed lines in the center of the reentrant circuit. Before moricizine administration, two
regions of slow conduction were present in the reentrant circuit, as evident by the crowding of isochronous lines. One region corresponds anatomically to the upper portion of the sulcus terminalis, and the other broader region is in the lower portion of the right atrial free wall. Conduction time through this latter region (between electrode sites c and e) was 60 milliseconds, quite long compared with conduction time in the remainder of the reentrant circuit (133 milliseconds). In this episode, as seen in the following four figures, the atrial flutter cycle length prolonged from 193 milliseconds before drug administration to 203 milliseconds after 90 seconds of drug infusion, to 218 milliseconds after 120 seconds, to 246 milliseconds after 150 seconds, and to 292 milliseconds after 180 seconds, followed soon by termination of the atrial flutter.

In Fig 7, the four panels show atrial electrograms recorded along with ECG lead II from the same selected sites shown in Fig 6. The panels show the atrial electrograms recorded at 90, 120, 150, and 180 seconds from the onset of the drug administration. Electrograms from site a are recorded near the superior area of slow conduction, and electrograms from sites c through e span the entire width of the inferior area of slow conduction. During drug administration, even though there is a 99-millisecond increment in the atrial flutter cycle length compared with control, conduction time between the reference site and site a remains unchanged, as does conduction time between sites b and c, c and d, and e and f. There is an increase of 10 milliseconds between electrode sites a and b because of a prolongation in conduction in the area of slow conduction located in the upper portion of the sulcus terminalis. Conduction times between sites d and e prolonged 60 milliseconds. When comparing conduction times between the stable atrial flutter and Fig 7D, 60% of the increase in the atrial flutter cycle length was accounted for by slowing of conduction between electrode sites d and e, and 90% of the increase was accounted for by slowing between electrode sites c and e.

Fig 8 shows the activation maps for each panel shown in Fig 7. Maps A, B, C, and D are the sequence of activation maps at 90, 120, 150, and 180 seconds from
Fig 9. Tracings of ECG lead II and atrial electrograms recorded from same electrode sites shown in Fig 6. The electrograms were recorded 1 second after electrograms from Fig 7D (ie, 181 seconds after onset of moricizine administration) and show the last beats before termination. The last site activated from this electrodes sites was site d, located just at the center of the area of slow conduction. s indicates ventricular stimulus artifact.

the onset of moricizine administration, respectively. In map A, there was a 10-millisecond cycle length increase compared with the stable atrial flutter before drug administration, and it was the result of slowing of conduction in the area of slow conduction located at the upper portion of the sulcus terminalis. The remainder of the right atrial free wall is activated as before drug administration (see Fig 6). In subsequent maps, all the increase in atrial flutter cycle length is explained by further slowing of conduction in the inferior area of slow conduction. Map B shows a 25-millisecond increase in cycle length compared with the stable atrial flutter and a 15-millisecond increase in cycle length compared with map A. The increase in cycle length is the result of slowing of conduction in the area of slow conduction between electrode sites c and e. Map C shows an increase in the crowding of isochronous lines on the right atrial free wall as conduction continues to slow in that region. Map D shows the activation sequence of a still longer atrial flutter cycle length (284 milliseconds). Note the further crowding of isochrons in the inferior area of slow conduction. As also evident in the representative atrial electrogram recordings (Fig 7), the conduction time in the remainder of the right atrial free wall is similar despite changes in the cycle length of the atrial flutter.

Fig 9 shows the atrial electrograms recorded from the same selected right atrial sites just before drug-induced termination of atrial flutter. Numbers are given in milliseconds and demonstrate cycle length changes. The absence of changes in morphology and polarity of the atrial electrograms demonstrates that there were no changes in the activation sequence in the reentrant circuit (this was consistent for all the electrograms analyzed).

Fig 10 shows the last four activation maps before drug-induced termination of atrial flutter with return to sinus rhythm. The first map (map A) is similar to the last one of Fig 8, with a cycle length of 284 milliseconds. The cycle length increases to 292 milliseconds in map B, and as previously described, there is an increase of one isochron in the inferior area of slow conduction. Map C shows the second-to-last beat and is similar to the previous map. Map D shows the termination of the atrial flutter. The circulating wave front blocks at 164 milliseconds (relative to prior activation of the reference site) in the midportion of the inferior area of slow conduction.

Summary of Data From All Open Chest Studies

It is noteworthy that the areas of slow conduction in all seven episodes of atrial flutter were always in areas where the circulating reentrant wave front crossed perpendicular to the longitudinal orientation of the atrial muscle fibers. This suggests an important role for anisotropic conduction and the effects of moricizine on this form of conduction. Also of note is that when there was more than one area of relatively slow conduction (present in four of the seven studies), conduction time across both areas of slow conduction did not increase uniformly. Rather, conduction time increased far more in one area of slow conduction than in the other, and it was always in the area of the major slowing that the last circulating wave front blocked. Thus, the prolongation of the atrial flutter cycle length was explained either by further slowing of conduction in an area of slow conduction in the reentrant circuit (episodes 1, 2, and 5) or by further slowing of conduction in two areas of slow conduction, with slowing being more prominent in one of the areas (episodes 3, 4, 6, and 7). The prolongation of conduction time in the remainder of the reentrant circuit was 10.9 ± 8.7% (range, 0% to 24.2%) of the total change in the atrial flutter cycle length. In all seven episodes, the termination of atrial flutter occurred in an area of slow conduction.

Discussion

Previous studies have shown that moricizine prolongs cardiac conduction in all cardiac tissues but has little or no effect on the effective refractory period of the atria or ventricles. Thus, in this study, the fact that moricizine prolonged intra-atrial conduction time and did not affect the atrial effective refractory period measured at the Bachmann’s bundle region and the posterior inferior left atrial electrode sites is not surprising. The reason why moricizine prolonged the atrial effective refractory period measured at the sulcus ter-
minalis site, a site that usually is in the atrial flutter reentrant circuit in this model,24-32 and the significance of this nonuniform effect of moricizine on atrial refractoriness is not apparent. However, the striking effect of moricizine in this study is its preferential effect on conduction in the area(s) of slow conduction in the atrial flutter reentrant circuit.

Relation of Interruption of Atrial Flutter to the Wave Length Hypothesis

Traditionally, it has been thought that the wavelength of excitation, defined as the product of the refractory period multiplied by the conduction velocity, has been very important in understanding the effects of antiarrhythmic drugs on reentrant rhythms.41-44 In fact, over the years, and as summarized recently,44 it has been postulated that the effects of antiarrhythmic drugs on reentrant rhythms could be explained by their effects on the wavelength (ie, their effects on the product of conduction velocity and the refractory period). This hypothesis assumes (1) that any drug-induced slowing of conduction velocity that may occur is uniform; (2) that drug interruption of the reentrant rhythm occurs when a drug causes an increase in the wavelength such that the circulating reentrant wave front encounters tissue in the reentrant circuit that is not excitable because it is still refractory; and (3) that a drug that decreases conduction velocity (and thereby prolongs the cycle length of the reentrant rhythm—in our case, atrial flutter) is less likely or, in fact, unlikely to terminate the reentrant rhythm because it decreases the wavelength and therefore the degree of interaction between the head of the reentrant excitation wave front and the tail of refractoriness of the previous reentrant excitation wave front. According to the classic interpretation of the wavelength theory, for a drug that slows conduction velocity to terminate a reentrant rhythm, it is necessary that it also cause prolongation of refractoriness that more than compensates for the decrease in conduction velocity (ie, it increases the wavelength).

In the present study, the effects of moricizine in prolonging the atrial flutter cycle length were explained virtually entirely by the further slowing of conduction in the area(s) of slow conduction in the reentrant circuit. Furthermore, moricizine interrupted atrial flutter by causing block of the circulating reentrant wave front in an area of slow conduction. Therefore, in this model, moricizine works to interrupt atrial flutter in a manner that is not easily explained by the classic wavelength hypothesis. Thus, interruption may not be related solely or even in part to an increased degree of interaction between the reentrant wave front and the tail of refractoriness. In fact, it seems most likely to be related to a change in the safety factor for conduction in an area of slow conduction in the reentrant circuit.

It is of interest that the best understood reentrant rhythm in humans—AV reentrant tachycardia involving an accessory AV connection—is well known to be interrupted by drugs that first slow the tachycardia rate by prolonging conduction time virtually exclusively in an area of slow conduction in the reentrant circuit, the AV node. Ultimately, these same drugs interrupt this rhythm by causing block of the circulating reentrant wave front in this area of slow conduction.52 That this should be true for reentrant rhythms that depend on a functional area of slow conduction, ie, an area of slow conduction that does not serve this role during sinus rhythm, is of great interest. In fact, as emphasized by Spinelli and Hoffman,46 the nature of conduction in reentrant circuits is not uniform, so the effects of antiarrhythmic agents on conduction should not be expected to be uniform in all segments of the reentrant pathway. Spinelli and Hoffman also provided data demonstrating that the wavelength theory cannot always explain the effects of drugs on reentrant arrhythmias (ie, they still demonstrated an excitable gap when the tachycardia was interrupted).

In addition, the data presented here suggest that the traditional way of looking at the effects of antiarrhythmic drugs needs to be expanded. Thus, the fact that moricizine works primarily in an area of slow conduction in this model while having little, if any, effect on conduction velocity in other parts of the reentrant circuit suggests that there is something special about the nature of conduction in this region of the reentrant circuit and its interaction with antiarrhythmic drugs. Because the area of slow conduction in this model appeared in regions in which the circulating wave front crossed perpendicular to the longitudinal orientation of the pectinate atrial muscle fibers, it suggests that anisotropic conduction may be important in generating these functional areas of slow conduction.56

Whether the observed effects of moricizine in this model of atrial flutter are unique to this particular drug or are more general remains to be seen. However, the data from Hoffman and Spinelli46 and Wu and Hoffman47 and data from several studies in canine models of atrial flutter27-32,48-50 suggest that the effects of antiarrhythmic drugs in terminating this arrhythmia cannot be solely explained by their effects on the wavelength. Therefore, although the effects of other antiarrhythmic agents in this model must be studied systematically, this study provides exciting new observations on the mechanism of drug action to interrupt reentrant excitation in a functionally determined reentrant circuit. In addition, it suggests a new way of thinking about the action of antiarrhythmic agents to interrupt reentrant rhythms.

Possible Effects of Moricizine on the Atrial Flutter Reentrant Circuit

Success or failure of conduction in cardiac tissue is determined by the local source-sink relations in the tissue. With this in mind, one possible explanation for moricizine's effect in our atrial flutter model is that it does not affect membrane excitability to the same degree in all segments of the reentrant pathway. It may selectively reduce excitability to a larger degree in an area of slow conduction. Thus, moricizine may introduce inhomogeneities in membrane excitability around the reentrant pathway. Quan and Rudy51 have shown in a simulation study of reentry that nonuniform distribution of membrane excitability provides conditions for the development of conduction block. Moreover, the inducibility of block was proportional to the degree of inhomogeneity, being greatest at the site of the steepest excitability gradient. A nonuniform effect of moricizine on the membrane (source) could, therefore, be the basis for interruption of the reentrant rhythm. This mechanism is also consistent with our finding that moricizine slowed conduction primarily in the area of slow conduc-
tion, with minimal or no slowing effect on velocity elsewhere in the reentrant circuit.

Another possible explanation of moricizine’s effect on the reentrant circuit of our atrial flutter model is that it acts to reduce membrane excitability uniformly in the reentrant pathway. This implies that the development of block preferentially in an area of slow conduction results from nonuniformities in passive properties of the tissue along the reentrant circuit. It is conceivable that in the area of slow conduction, passive structural properties exist that constitute a large electrical load (sink) for the reentrant wave front. When membrane excitability is compromised by moricizine, the source can no longer supply the current necessary to maintain conduction through this region, and block occurs. As suggested by computer simulations, nonuniformities in load that may lead to block result from inhomogeneities in cell-to-cell coupling or in the effective cross-sectional area of the reentrant pathway. Both structural properties reflect the anisotropy of cardiac tissue (different effective cross section and different distribution of gap junctions encountered by a wave front propagating along the fibers or transverse to the fibers). A nonuniform cross section may also reflect branching of fibers or sharp changes in the curvature of the reentrant wave front such as occur at pivot points.

Of course, interruption of the circulating reentrant wave front by moricizone could be caused by a combination of both a nonuniform effect of the drug on membrane excitability and inhomogeneities in the distribution of load along the pathway. Both mechanisms can bring about conduction block without eliminating the excitable gap, and their mode of action cannot be explained solely by their effect on the wavelength of refractoriness. Our finding that block always seems to occur transverse to the fiber axis suggests an important role of passive structural properties that reflect the underlying architecture of the tissue.

Clearly, this study does not provide the data to explain the precise mechanism by which moricizone slowed and then interrupted the atrial flutter. However, it does provide new insights into how drugs may work to interrupt functionally determined reentrant circuits.

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