The Cellular Electrophysiologic Mechanism of the Dual Actions of Disopyramide on Rabbit Sinus Node Function

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with the technical assistance of Avile McCullen

SUMMARY To determine the contribution of disopyramide’s suggested opposing direct depressant and indirect acceleratory actions on sinus node function, we studied the effects of disopyramide, $1 \times 10^{-7}$ to $1 \times 10^{-4}$ $M$, on isolated rabbit sinus node preparations using standard microelectrode techniques. Transmembrane potentials were recorded simultaneously from the sinus node and adjoining crista terminalis area. Disopyramide, as much as $1 \times 10^{-5} M$, had no effects on the sinus cycle length. At a concentration of $1 \times 10^{-4} M$, sinus cycle length was significantly prolonged due to prolongation of the sinus nodal action potential duration. During cholinergic blockade with atropine, $1 \times 10^{-6} M$, disopyramide, $1 \times 10^{-7}$ to $1 \times 10^{-4} M$, significantly prolonged sinus cycle length as a result of a prolongation of the sinus nodal action potential duration and a decrease of the slope of phase 4 depolarization. During cholinergic stimulation with carbamyl choline, $1 \times 10^{-6} M$, disopyramide, $1 \times 10^{-7}$ to $1 \times 10^{-4} M$, tended to reverse carbamyl choline–induced prolongation of the sinus cycle length (NS). This acceleratory action of disopyramide was caused by a significant increase of the slope of phase 4 depolarization. Disopyramide, $1 \times 10^{-7}$ to $1 \times 10^{-4} M$, had no significant effects on corrected sinus node recovery time or sinoatrial conduction time under any conditions studied. We conclude that disopyramide has a direct depressant action on normal sinus node cells at the upper therapeutic and toxic levels, which is enhanced during cholinergic blockade, and that disopyramide’s acceleratory action appears only at much lower concentrations and only during cholinergic stimulation.

DISOPYRAMIDE is a useful antiarrhythmic agent that has significant effects against a variety of experimental and clinical arrhythmias of both atrial and ventricular origin. Its spectrum of antiarrhythmic effects is similar to that of quinidine in rabbit right atria, canine Purkinje fibers and in the specialized conduction system in man. However, the mechanisms of electrophysiologic action of disopyramide on sinus node function in man are controversial. Birkhead and VaughanWilliams suggested that disopyramide has dual effects on sinus nodal automaticity, resulting in a potentially unpredictable effect on sinus node function. One effect was thought to be mediated by a direct depressant action of the drug on sinus node cells, causing a slowing of heart rate, and the other action to be mediated by disopyramide’s anticholinergic action (that is, atropine-like action), which would remove cholinergic inhibitory action, causing an acceleration of heart rate. These properties of disopyramide could similarly affect in a dual manner the sinus node recovery time. Therefore, the purpose of the present study was to test the hypothesis that disopyramide has dual actions on sinus nodal automaticity, and, if so, to determine the cellular mechanisms of the dual action. We used standard microelectrode techniques to record transmembrane potentials using isolated rabbit right atrial preparations before and after superfusion with disopyramide, under control (resting), activated and blocked cholinergic tone to determine the cellular electrophysiologic mechanisms of disopyramide’s actions on the sinus nodal pacemaker cells.

**Methods**

Rabbits that weighed 1.5–3 kg were stunned by a blow on the head. The hearts were then rapidly excised and dissected in cool, oxygenated, modified Tyrode’s...
solution. The right atrium, including the sinus node area, was carefully dissected free and pinned in a Lucite tissue chamber according to the method of Paes de Carvalho et al. The composition of the modified Tyrode’s solution (mM/l) was: NaCl 135, KCl 4.5, NaH2PO4 1.8, CaCl2 2.7, MgCl2 0.5, dextrose 5.5, NaHCO3 24 in triple-distilled, deionized water. The tissue was superfused at a constant rate of 8 ml/min with modified Tyrode’s solution that was equilibrated with 95% oxygen and 5% carbon dioxide. The temperature of the bath was maintained at 35 ± 0.2°C. This temperature facilitated location of the site of the dominant pacemaker and made continuous intracellular microelectrode impalement for longer periods more feasible, because with lower temperatures the rate of spontaneous sinus rate tends to decrease. The pH of the Tyrode’s solution was 7.4 ± 0.02. Machine-pulled glass capillary microelectrodes filled with 3 M potassium chloride were impaled in the area of sinus node and the adjacent (within 2 mm) crista terminalis (fig. 1).

Transmembrane action potentials were simultaneously recorded through these microelectrodes, which had tip resistances of 15–30 MΩ. These electrodes were coupled by a silver-silver chloride wire leading to amplifiers with high input impedance and variable capacity neutralization (AM-2 and ME-3221, Biodyne Electronics Laboratory). The amplified transmembrane potentials were displayed on a dual-beam cathode ray oscilloscope (RM 565, Tektronics). These action potentials were also displayed on a storage oscilloscope (R5103N, Tektronics) and on a multichannel recorder (Electronics for Medicine DR8). The records were photographed on 35-mm film (Grass C-4 camera) and on photographic paper (Electronics for Medicine) (fig. 1).

Recordings were made during spontaneous sinus rhythm and after atrial pacing at cycle lengths of 300 and 400 msec for 30 seconds to measure sinus node recovery time. In addition to direct measurements, sinoatrial conduction time was also estimated by an indirect method. This was accomplished by applying atrial premature stimuli with various coupling intervals during spontaneous sinus rhythm. Atrial pacing was performed using a closely coupled bipolar silver electrode positioned immediately adjacent (1 mm) to the microelectrode at the crista terminalis site. Pacing and premature stimulation were done using a specially built programmable digital stimulator that has the capacity of triggering. Applied stimuli were rectangular pulses of twice diastolic threshold with 2 msec duration.

To record transmembrane potential from the dominant pacemaker cell in sinus node, we impaled 10–20 cells within 1 mm2 of the sinus node region. The cell, which showed the earliest activation, the steepest slope of diastolic depolarization, the slowest rate of rise of phase 0 depolarization and smooth transition from phase 4 to phase 0, was defined as the dominant pacemaker cell in the sinus node.

**Drug Superfusion**

To evaluate the relative efficacy of disopyramide’s two antagonistic actions, we studied the effects of this drug during cholinergic blockade and cholinergic stimulation. During effective cholinergic blockade, a direct depressant action of disopyramide can be evaluated unaffected by any interference or masking effect due to the drug’s possible anticholinergic acceleratory effect. Similarly, under conditions of cholinergic stimulation, when this stimulation had already produced heart rate slowing, one can thus readily expose or unmask disopyramide’s atropine-like action by observing an actual reversal of the heart rate slowing.

**Protocol**

Twenty-seven preparations were classified into

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**Figure 1.** (left) The sites of recordings and stimulation from rabbit right atrial preparation. SAN = sinoatrial node; CT = crista terminalis; SVC = superior vena cava; IVC = inferior vena cava; RA = right atrial muscles; AS = atrial septum; CS = coronary sinus; TV = tricuspid valve. 1 and 2 = microelectrodes. (right) Simultaneous recording of transmembrane action potentials from the sinus node and crista terminalis during spontaneous sinus rhythm. Top tracing denotes zero reference potential. Records 1 and 2 are recordings of the sinus node and crista terminalis action potential, respectively. The bottom tracing is the rate of rise of phase 0 depolarization the crista terminalis. The vertical bar in the bottom right is a calibrated signal of 100 V/sec.
three groups. In group 1 (10 preparations), disopyramide was superfused alone at progressively increasing concentrations from $1 \times 10^{-7}$ to $1 \times 10^{-4} M$. In group 2 (six preparations), atropine, $1 \times 10^{-6} M$ was continuously superfused along with increasing concentrations of disopyramide as in group 1 to evaluate the effects of disopyramide during cholinergic blockade. This concentration of atropine effectively blocks cholinergic receptor sites in both rabbit sinus node and guinea pig right atrial preparations. In fact, our preliminary studies show that atropine, $1 \times 10^{-6} M$, completely blocks heart rate slowing induced by carbamyl choline, $1 \times 10^{-9} M$. In group 3 (11 preparations), carbamyl choline, $1 \times 10^{-9} M$, was superfused along with increasing concentrations of disopyramide as in group 1 to evaluate the effects of disopyramide during cholinergic stimulation. This concentration of carbamyl choline caused an approximately 15% reduction of the sinus rate. Such a level of cholinergic stimulation was appropriate for evaluating disopyramide’s “anticholinergic” properties. Higher concentrations of carbamyl choline caused severe slowing of the sinus rate, an effect that would have prevented the detection of disopyramide’s “mild” anticholinergic properties on the sinus node. Each step was maintained for 20 minutes. After the final concentration was superfused, the preparations were then superfused for 1 hour with drug-free Tyrode’s solution.

Recordings during spontaneous rhythm, atrial premature stimulation and after atrial overdrive pacing were obtained at the end of 20 minutes of superfusion in each step, and then the solution was immediately switched over to higher concentrations.

In each experiment, we attempted to maintain a continuous impalement in the dominant pacemaker cell in the sinus node during the control period and during superfusion with drugs. However, often we could not because of the continuous movement of the preparation and perhaps because of the small diameter of sinus nodal cells. In five experiments (at least one in each group), however, we maintained single cell impalement throughout the entire study period. In experiments in which we had considerable difficulty in maintaining single impalement during the control period, we recorded three to five adjacent cells (within 1 mm) that had the characteristics of the dominant pacemaker cell. The results were pooled and compared with the results obtained after drug exposure. If the impalement was lost just before the termination of the experiment, these studies were rejected and are not included in the statistical analysis.

**Data Analysis and Definitions**

The following variables were measured from the recordings during spontaneous rhythm: sinus cycle length (the mean of 10 consecutive spontaneous sinus beat); characteristics of sinus node action potentials, including maximum diastolic potential, takeoff potential measured at the cross point of the steepest slope of phase 0 and the slope of phase 4, slope of diastolic depolarization, and action potential duration at 50% and 100% repolarization (fig. 2); characteristics of crista terminalis action potentials, including resting membrane potential, total amplitude of the action potential, maximum rate of rise of phase 0 depolarization, and action potential duration at 50% and 90% repolarization; and direct sinoatrial conduction time (the time from the beginning of sinus node action potential to the beginning of crista terminalis action potential). In addition, from the recordings during atrial overdrive pacing and premature stimulation, corrected sinus node recovery time was determined by subtracting basic sinus cycle length from the cycle length of the first spontaneous beat that appears after the cessation of the overdrive pacing at 150 and 200 beats/min for 30 seconds. During overdrive pacing, we verified that each paced impulse entered and depolarized the sinus node cells. Estimated sinoatrial conduction time was calculated according to the method of Strauss et al.

Statistical analysis was done by using two-way analysis of variance and by paired t test. A p value < 0.01 was taken as the level of significance in the analysis of variance, and a p value < 0.05 was taken as the level of significance in the paired t test. All values are expressed as the mean ± SEM.

**Results**

**Spontaneous Sinus Cycle Length**

During control (group 1), significant prolongation of spontaneous sinus cycle length occurred only after exposure to $1 \times 10^{-4} M$ disopyramide. At this concentration, mean cycle length was prolonged 83 msec over control (table 1). The maximum percent increase was 16% (fig. 3).

Cholinergic blockade with atropine (group 2) significantly shortened (12%) sinus cycle length. Superfusion with increasing concentration of disopyramide in the presence of atropine (group 2) significantly increased sinus cycle length in a concentration-dependent manner at all disopyramide concentrations ($1 \times 10^{-7}$ to $1 \times 10^{-4} M$) compared with control (table 1). The maximum prolongation was 124 msec, which oc-

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Variables measured from sinus nodal action potentials. MDP = maximum diastolic potential; TP = takeoff potential; phase 4 slope = slope of diastolic depolarization; APD 50 and APD 100 = action potential duration at 50% and 100% repolarization, respectively.
TABLE 1. The Effects of Disopyramide on Spontaneous Sinus Cycle Length

<table>
<thead>
<tr>
<th>Group</th>
<th>Before drug</th>
<th>Control</th>
<th>Disopyramide</th>
<th>Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>10^{-7} M</td>
<td>10^{-6} M</td>
</tr>
<tr>
<td>SCL (msec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n = 11)</td>
<td>—</td>
<td>455.1 ± 21.5</td>
<td>456.8 ± 21.0</td>
<td>464.3 ± 19.1</td>
</tr>
<tr>
<td>2 (n = 6)</td>
<td>435.0 ± 26.1†</td>
<td>381.6 ± 19.9</td>
<td>412.6 ± 21.2†</td>
<td>395.4 ± 19.7*</td>
</tr>
<tr>
<td>3 (n = 10)</td>
<td>443.0 ± 18.1*</td>
<td>493.0 ± 59.3</td>
<td>460.3 ± 22.0</td>
<td>464.3 ± 33.0</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Compared with control:
* p < 0.05.
† p < 0.01.
‡ p < 0.005.
Abbreviation: SCL = sinus cycle length.

curred at 1 × 10^{-4} M of disopyramide. The maximum percent increase was 33% (fig. 3).

Cholinergic stimulation with carbamyl choline (group 3) significantly prolonged sinus cycle length (13%). This prolongation however, tended to be reversed with simultaneous superfusion with low concentrations of disopyramide (table 1). The maximum shortening of sinus cycle length was 33 msec. This occurred at 1 × 10^{-7} M of disopyramide. The percent decrease in cycle length was 7% (p < 0.05) (fig. 3).

Higher concentrations of disopyramide (more than 1 × 10^{-5} M) did not further shorten the sinus cycle length (table 1). In fact, a prolongation of the sinus cycle length back to the control (carbamyl choline) level occurred.

All of these effects on spontaneous sinus cycle lengths were fully reversible within 1 hour of superfusion with drug-free Tyrode’s solution.

Action Potential Characteristics of Sinus Node Cells

There were no significant changes in either maximum diastolic potential and estimated takeoff potential under any condition studied in any groups (table 2).

There was no significant change in the slope of phase 4 depolarization in group 1 at all disopyramide concentrations (1 × 10^{-7} M — 1 × 10^{-4} M). Cholinergic blockade with atropine in group 2 increased the slope of phase 4 depolarization from 55 to 71 mV/sec (table 2). A significant reduction in the slope, however, occurred at all concentrations of disopyramide (table 2). The maximum decrease in this variable occurred at 1 × 10^{-4} M of disopyramide; this amounted to a 43% reduction over control (fig. 4). In contrast, during cholinergic stimulation (group 3), carbamyl choline significantly decreased the slope, from 56 to 42 mV/sec (table 2). This effect was reversed with superfusion of disopyramide at concentrations of 1 × 10^{-7} M and 1 × 10^{-6} M (table 2). The maximum increase in this value occurred at 1 × 10^{-4} M of disopyramide; this amounted to 18% increase compared to control (fig. 4). Higher concentrations of disopyramide decreased the slope back to control (table 2). All of

Figure 3. Effect of disopyramide on spontaneous sinus cycle length. We used, as control sinus cycle length, the cycle length before disopyramide in group 1, atropine alone in group 2 and carbamyl choline alone in group 3. C = control. A significant increase in sinus cycle length occurred only at 1 × 10^{-4} M of disopyramide in group 1. However, in group 2, all concentrations of disopyramide significantly increased the sinus cycle length. In group 3, disopyramide, 1 × 10^{-4} M, shortened the sinus cycle length.
TABLE 2. The Effects of Disopyramide on Action Potential Characteristics of Sinus Node

<table>
<thead>
<tr>
<th>Group</th>
<th>Before drug</th>
<th>Control</th>
<th>Disopyramide</th>
<th>Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>10⁻⁷ M</td>
<td>10⁻⁶ M</td>
</tr>
<tr>
<td>MDP (mV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>—</td>
<td>−60.5 ± 2.0</td>
<td>−58.3 ± 3.9</td>
<td>−57.7 ± 4.6</td>
</tr>
<tr>
<td>2</td>
<td>−59.7 ± 2.3</td>
<td>−59.1 ± 2.4</td>
<td>−57.6 ± 2.4</td>
<td>−59.0 ± 2.0</td>
</tr>
<tr>
<td>3</td>
<td>−59.2 ± 2.0</td>
<td>−59.2 ± 2.0</td>
<td>−58.8 ± 2.1</td>
<td>−58.7 ± 2.2</td>
</tr>
<tr>
<td>TP (mV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>—</td>
<td>−43.7 ± 1.8</td>
<td>−40.3 ± 2.9</td>
<td>−38.4 ± 3.6</td>
</tr>
<tr>
<td>2</td>
<td>−42.7 ± 2.9</td>
<td>−42.9 ± 3.2</td>
<td>−41.1 ± 3.8</td>
<td>−41.4 ± 3.7</td>
</tr>
<tr>
<td>3</td>
<td>−44.2 ± 2.4</td>
<td>−43.2 ± 2.9</td>
<td>−41.3 ± 2.6</td>
<td>−39.8 ± 3.1</td>
</tr>
<tr>
<td>Phase 4 slope (mV/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>—</td>
<td>50.4 ± 3.2</td>
<td>44.5 ± 2.5</td>
<td>46.7 ± 2.8</td>
</tr>
<tr>
<td>2</td>
<td>55.3 ± 6.2*</td>
<td>70.7 ± 6.9</td>
<td>48.0 ± 3.6*</td>
<td>48.8 ± 3.5*</td>
</tr>
<tr>
<td>3</td>
<td>55.8 ± 3.0*</td>
<td>42.5 ± 3.6</td>
<td>46.0 ± 2.9*</td>
<td>48.0 ± 4.1*</td>
</tr>
<tr>
<td>APD 50 (msec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>—</td>
<td>129.1 ± 6.1</td>
<td>125.0 ± 8.5</td>
<td>137.9 ± 11.0</td>
</tr>
<tr>
<td>2</td>
<td>122.9 ± 3.7</td>
<td>121.4 ± 2.4</td>
<td>122.0 ± 2.6</td>
<td>123.8 ± 2.4*</td>
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<tr>
<td>3</td>
<td>123.3 ± 4.0</td>
<td>127.5 ± 6.3</td>
<td>131.0 ± 6.2</td>
<td>131.7 ± 8.1</td>
</tr>
<tr>
<td>APD 100 (msec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>—</td>
<td>216.8 ± 10.5</td>
<td>210.0 ± 13.3</td>
<td>215.7 ± 10.5</td>
</tr>
<tr>
<td>2</td>
<td>224.3 ± 10.9</td>
<td>219.3 ± 6.8</td>
<td>216.0 ± 7.3</td>
<td>222.5 ± 3.3</td>
</tr>
<tr>
<td>3</td>
<td>215.8 ± 7.0</td>
<td>216.7 ± 8.1</td>
<td>228.0 ± 6.6</td>
<td>230.0 ± 11.6*</td>
</tr>
</tbody>
</table>

Values are mean ± sem; group 1, n = 11; group 2, n = 6; group 3, n = 10.

Compared with control:

*p < 0.05.

†p < 0.01.

‡p < 0.005.

Abbreviations: MDP = maximum diastolic potential; TP = takeoff potential; APD 50 = action potential duration at 50% repolarization; APD 100 = action potential duration at 100% repolarization.

These changes in the slope of phase 4 depolarization were fully reversible within 1 hour of superfusion with drug-free Tyrode’s solution.

Disopyramide significantly prolonged the action potential duration both at 50% and 100% repolarization in all three groups. This prolongation was almost concentration-dependent, and greater prolongation occurred with higher disopyramide concentrations (table 2, fig. 5).

These changes in action potential duration were also fully reversible within 1 hour of superfusion with drug-free Tyrode’s solution.

Figure 4. Effect of disopyramide on the slope of phase 4 depolarization during spontaneous sinus rhythm. No significant changes occurred in group 1. All concentrations of disopyramide significantly decreased the slope in group 2. In contrast, in group 3, disopyramide in concentrations of 1 × 10⁻⁷ M and 1 × 10⁻⁶ M significantly increased the slope.
Thus, disopyramide at a concentration of $10^{-6} \, M$ caused significant acceleration of sinus cycle length in group 3 (fig. 3), and this was associated with a significant increase in the slope of phase 4 depolarization (fig. 4). In contrast, disopyramide in a dose of $10^{-6} \, M$ caused significant slowing of sinus cycle length in group 2 (fig. 3) and this was associated with a concomitant decrease in the slope of phase 4 depolarization (fig. 4). In group 1, during resting cholinergic tone, disopyramide up to $10^{-5} \, M$ had no effect on either sinus cycle length or the slope of phase 4 depolarization (figs. 3 and 4).

**Corrected Sinoatrial Node Recovery Time**

The effect of disopyramide on corrected sinoatrial node recovery time varied in each preparation; the range was 64–116 msec. In a few preparations in groups 2 and 3, disopyramide prolonged corrected sinoatrial node recovery time when superfused at $1 \times 10^{-4} \, M$. However, in each group as a whole, there were no significant changes in this variable under any condition or at any disopyramide concentrations.

**Sinoatrial Conduction Time**

No significant changes in both directly measured (67–78 msec) and estimated sinoatrial conduction time occurred in any group during any disopyramide concentration.

**Action Potential Characteristics of Crista Terminalis Cells**

Table 3 is a summary of the action potential characteristics of crista terminalis cells. Disopyramide at all concentrations studied (up to $1 \times 10^{-4} \, M$) had no effects on the resting membrane potential. The amplitude of action potential was significantly decreased at $1 \times 10^{-4} \, M$ of disopyramide in all three groups. In group 3, disopyramide, $1 \times 10^{-3} \, M$, also decreased the action potential amplitude. The maximum rate of rise of phase 0 depolarization significantly decreased at $1 \times 10^{-4} \, M$ of disopyramide in all three groups.

Disopyramide significantly prolonged action potential duration both at 50% and 90% repolarization in all three groups. This prolongation was concentration-dependent. Greater prolongation occurred with higher disopyramide concentrations, particularly at 90% repolarization (table 3).

All of these changes were fully reversible within 1 hour of superfusion with drug-free Tyrode’s solution.

**Discussion**

**The Effects of Disopyramide on Spontaneous Sinus Cycle Length**

The results of the present study demonstrate that disopyramide has two opposing effects on the rabbit sinoatrial node. One effect, which appears at low concentration of disopyramide (up to $1 \times 10^{-6} \, M$), tends to accelerate the sinus rate. The second effect, which appears at high disopyramide concentrations (more than $1 \times 10^{-5} \, M$), slows the sinus rate. We found that disopyramide’s dual action is influenced by the level of cholinergic activity of the sinus nodal cells. The accelerator action of disopyramide is enhanced during cholinergic receptor stimulation and the drug’s inhibitory action is more prominent during cholinergic receptor.
blockade. Thus, the net effect of disopyramide on rabbit sinus nodal discharge rate critically depends on both the concentration of the drug and on the level of underlying cholinergic tone at the sinus node. A concentration of $1 \times 10^{-5} M$ of disopyramide was found where acceleratory and inhibitory actions of the drug appeared to cancel each other, causing no apparent net effect on the sinus rate. Similar dual actions of disopyramide on heart rate have been found in man” and in guinea pig right atrial preparations.26

The ability to record transmembrane potentials in sinus nodal cells with the microelectrode technique allowed to correlate changes in transmembrane electrical activity of the pacemaker cells with the known chronotropic effects of the drug.

The prolongation of sinus cycle length with disopyramide during resting cholinergic tone (group 1) appeared to be brought about merely by a prolongation of sinus nodal action potential duration (fig. 6). This mechanism of disopyramide’s slowing of the pacemaker frequency in the sinus node is different from that seen on the automaticity of Purkinje fibers initiated from high levels of resting membrane potential.10,11 Disopyramide slows the rate of automatic impulse initiation in the Purkinje fibers (with much lower concentrations than those needed to cause slowing in sinus rate), by decreasing primarily the slope of spontaneous diastolic depolarization. The lack or little sensitivity of slow response action potentials in Purkinje fibers to disopyramide14 are consonant with our findings; however, we do not know the effects of disopyramide on the automatic activity of Purkinje fibers with slow response action potentials.

Thus, pacemaker currents that arise from a relatively higher resting membrane potential (more negative), as is the case in normal Purkinje fibers, apparently are more sensitive to disopyramide’s depressant effect than pacemaker currents that arise from lower resting membrane potential (less negative), as in the sinoatrial nodal pacemakers.

During cholinergic blockade, the sinus cycle lengthening was produced by prolongation of sinus nodal action potential duration and by a slight but significant decrease in the slope of diastolic depolarization (fig. 6). The decrease in the slope caused by disopyramide during cholinergic blockade was different from that seen during control, in which no change in the slope occurred. This may be caused by disopyramide’s nonspecific depressant action on sinus nodal pacemaker cells, particularly when cholinergic receptors are already blocked and the potential of positive chronotropic action of disopyramide is thus effectively minimized or nil. The nonspecific depressant action of disopyramide on the pacemaker current of the sinus node is clearly demonstrated at very high concentrations ($1 \times 10^{-3} M$) of disopyramide, where complete sinus arrest occurs. This is in sharp contrast to the effects of verapamil, a “specific” slow-channel blocker, where sinus arrest occurs at much lower molar concentrations than with disopyramide.27

In contrast, during cholinergic stimulation, when the slope of diastolic depolarization has already been decreased by the effect of carbamyl choline, low concentrations of disopyramide tend to reverse this inhibitory effect by increasing the slope, causing a slight shortening of sinus cycle length. The slight prolongation of sinus nodal action potential duration seen at this low concentration of disopyramide did not seem to affect the sinus cycle length, since the slope factor was more pronounced. Since the other variables did not change, this increase in the slope may well be the cellular mechanism of disopyramide’s anticholinergic

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**Table 3. The Effects of Disopyramide on Action Potential Characteristics of Crista Terminalis**

<table>
<thead>
<tr>
<th>Group</th>
<th>Before drug $V_{max}$</th>
<th>Control $V_{max}$</th>
<th>Disopyramide $10^{-7} M$</th>
<th>Control $V_{max}$</th>
<th>Disopyramide $10^{-6} M$</th>
<th>Control $V_{max}$</th>
<th>Disopyramide $10^{-5} M$</th>
<th>Control $V_{max}$</th>
<th>Disopyramide $10^{-4} M$</th>
<th>Washout $V_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMP</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>$-84.2 \pm 1.6$</td>
<td>$-86.2 \pm 2.7$</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(mV)</td>
<td>2</td>
<td>$-83.8 \pm 2.0$</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>$-80.4 \pm 0.4$</td>
<td>$-80.0 \pm 0.8$</td>
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Values are mean ± SEM; group 1, n = 11; group 2, n = 6; group 3, n = 10.

Compared with control:

*p < 0.05.

**p < 0.01.

3p < 0.005.

Abbreviations: RMP = resting membrane potential; APA = amplitude of action potential; $V_{max}$ = maximum rate of rise of phase 0 depolarization; APD 50 = action potential duration at 50% repolarization; APD 90 = action potential duration at 90% repolarization.
acceleratory action. However, as the concentration of disopyramide increased, the slope tended to decrease, with a concomitant prolongation of action potential duration, resulting in a prolongation of sinus cycle length.

The Effects of Disopyramide on Other Sinus Node Functions

As a marker of the sinus node function, we measured corrected sinus node recovery time after overdrive pacing.

Befeler et al.\textsuperscript{13} reported that sinus node recovery time was shortened after disopyramide administered intravenously in patients with cardiac disease without changing basic sinus rate.\textsuperscript{13} They suggested that the shortening of sinus node recovery time may be related to a vagolytic action of disopyramide. However, Birkhead and Vaughan Williams\textsuperscript{15} showed that sinus node recovery time was prolonged together with a slowing of the heart rate after i.v. disopyramide in humans pretreated with atropine.\textsuperscript{15} They noted that disopyramide exerts a depressant effect on sinus node during cholinergic blockade.

In the present study, disopyramide had no significant effects on corrected sinus node recovery time. Although it tended to prolong corrected sinus node recovery time during blockade (group 2), those changes were not statistically significant. These findings suggest that the effect of disopyramide on sinus node recovery time may in part depend on the underlying cholinergic tone; however, the cellular mechanisms of disopyramide’s effect on sinus node recovery time is unknown.

The few studies of the effect of disopyramide on sinoatrial conduction time in man\textsuperscript{16, 20} have yielded variable results. Since sinoatrial conduction time in man is estimated indirectly, we evaluated the effect of disopyramide on this variable by both direct and indirect methods. No significant changes were found either in the estimated or in the directly measured sinoatrial conduction time under various states of cholinergic tone and at the concentrations of disopyramide that we studied.

The Effects of Disopyramide on the Action Potential Characteristics of Crista Terminalis Cells

Disopyramide decreased, in a concentration-dependent manner, the amplitude of the action potential and the maximum rate of rise of phase 0 depolarization, with a minimal reduction in the level of resting membrane potential. This typical local anesthetic action, thought to be brought about by a reduction in the amplitude of fast inward sodium current, has also been seen in canine cardiac Purkinje fibers.\textsuperscript{10, 11} Disopyramide’s inhibitory action on the upstroke velocity of phase 0 and on the amplitude of the action were independent of the underlying cholinergic tone. We also found a significant prolongation in the action potential duration, which also occurs in canine Purkinje fibers.\textsuperscript{9, 11}

Clinical Implications

There has been considerable disagreement about the electrophysiologic effects of disopyramide, especially on sinus node function.\textsuperscript{13-16} This variability may be attributed to the relative efficacy of disopyramide’s opposing dual effects and to the underlying cholinergic tone. The results of the present study suggest that disopyramide has dual actions on isolated normal sinus node of the rabbit at therapeutic concentrations, and the response to these dual actions mostly depend on the underlying cholinergic tone of the tissue and on the concentration of the drug.

Our studies were made on isolated normal rabbit sinus node preparations, and we do not know if similar effects would also occur in intact man, particularly in intact man with sick sinus syndrome. If similar effects do occur in man, then one might speculate the mechanism of disopyramide’s paradoxical slowing of sinus rate at therapeutic levels, in a subset of patients with sinus node dysfunction.\textsuperscript{16} Such patients may lack adequate cholinergic responsiveness or sensitivity,\textsuperscript{20} and as a result of this abnormality, disopyramide cannot exhibit its anticholinergic acceleratory action, allowing the drug to manifest only its direct depressant action, causing slowing of the heart rate. Furthermore, depression of sinus nodal discharge rate with therapeutic concentrations of disopyramide may reflect the
presence of occult sinus node dysfunction; but this speculation has not been established.

Acknowledgment

The authors express their gratitude to Lance LaForteza for graphics, to Patricia Edwards for photography, and to Joyce Nunn for secretarial assistance.

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