
**Alpha and Beta Adrenergic Effects on Human Atrial Specialized Conducting Fibers**

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SUMMARY We determined the effects of epinephrine on automaticity and action potential characteristics of right atrial specialized fibers (RAF) from human atria obtained during cardiac surgery. RAF were studied with standard microelectrode techniques during superfusion with Tyrode's solution at 37°C. A biphasic response to epinephrine was seen, rate slowing at low agonist concentrations and increasing at high concentrations. The epinephrine-induced slowing of spontaneous rate was due to a decrease in the slope of phase 4 depolarization. At the high epinephrine concentrations RAF hyperpolarized. The α-adrenergic blocker, phentolamine, shifted the dose-response curve upward and to the left and enhanced the hyperpolarization of RAF. The β blocker, propranolol, shifted the curve to the right and decreased the degree of hyperpolarization. Our study suggests the presence of α and β receptors in RAF. The α response consists of a slowing of rate, the β response of an acceleration of rate and hyperpolarization of RAF.

THE EFFECTS OF ADRENERGIC AMINES on the electrophysiologic properties of cardiac fibers have been studied extensively. Both α and β adrenergic effects on mammalian Purkinje fibers and atrial fibers have been described. Phenylephrine, primarily an α agonist, prolongs Purkinje fiber action potential (AP) duration as does norepinephrine in the presence of propranolol. This action has been referred to as α adrenergic. The β agonist, isoproterenol, and norepinephrine in the presence of phentolamine both decrease AP duration, an action referred to as β adrenergic. In studies of Purkinje fiber automaticity low concentrations of epinephrine have been shown to decrease spontaneous rate and K⁺ uptake and high concentrations to increase these variables. The decreases in spontaneous rate and K⁺ uptake are blocked by phenolamine and have been interpreted as α adrenergic; the increase in rate is blocked by propranolol and has been interpreted as β adrenergic. The epinephrine-induced increases in automaticity have been attributed to a selective effect on the kinetics of Ik, (pacemaker current), and both epinephrine effects on automaticity and on Ik are blocked by propranolol.

Despite these studies of adrenergic effects on mammalian cardiac fibers no information is yet available concerning the presence of α and β adrenergic receptors in human cardiac specialized conducting fibers. For this reason we studied the effects of epinephrine and of α and β blockade on human atrial fibers. We found changes in automaticity consistent with the presence of α and β receptors.

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Methods

Atrial tissue was obtained from the hearts of 23 patients undergoing corrective cardiac surgery. Prior to surgery informed consent was obtained. Fourteen patients were 8 months to 11 years old (mean: 4·5 years) and underwent surgery for a variety of congenital heart diseases (table 1). None of these patients was in congestive heart failure at the time of surgery. One patient had an elevated mean right atrial pressure (10 mm Hg). One patient had a previous history of paroxysmal atrial tachycardia during cardiac catheterization. Two patients in this group were on digoxin therapy for treatment of prior congestive failure. Nine patients were 23 to 54 years old (mean: 40 years). The clinical diagnoses are listed in table 1. One patient was in congestive heart failure and atrial fibrillation at the time of surgery. Three patients had elevated mean right atrial pressures (20.7 ± 8.4 mm Hg, mean ± se). Two were receiving digoxin therapy, 3 nitroglycerin, and 2, propranolol.

The preparations obtained from these two patients were included in protocols utilizing epinephrine and propranolol (see below). For all patients receiving cardioactive drugs, therapy was terminated at least 24 hours prior to surgery.

At surgery, approximately 1 cm² of atrial myocardium was removed from the anterior free wall of the right atrium as part of the routine cannulation procedure for cardiopulmonary bypass. This was made available for electrophysiology study. The tissue was immersed in cooled Tyrode's solution immediately after excision from the atrium and rapidly brought to the laboratory. It was mounted in a Lucite chamber and superfused with Tyrode's solution warmed to 37°C. and equilibrated with 95% O₂, 5% CO₂. The composition of the Tyrode's solution (mM/L) was: NaCl, 137; NaHCO₃, 12; NaH₂PO₄, 1.8; MgCl₂, 0.5; CaCl₂, 2.7; KCl, 4; dextrose, 5.5. Na ethylene-diaminetetra-acetic acid (EDTA) was included in the Tyrode's in a final concentration of 5 x 10⁻⁴ M. This had no effect on action potential characteristics or automaticity. The superfusate flow rate was 15–17 ml/min.

The tissues were impaled with machine-pulled 3M KCl filled glass capillary microelectrodes having tip diameters < 1 μ and resistances of 10–25 megohms. The electrodes were coupled by a 3M KCl interface to an Ag-AgCl bar which led to an amplifier having a high input impedance and input capacity neutralization. The output was displayed on a cathode ray oscilloscope (Tektronics Model 565). The tissue chamber was connected to ground through a salt bridge and an Ag-AgCl junction. The methods used to calibrate the equipment have been described previously. ⁹

Experimental Protocols

The tissue was stimulated at a cycle length of 1000 msec through Teflon coated bipolar silver wire electrodes. ⁹ Measurements were made of action potential (AP) amplitude, maximum diastolic potential (MDP) and maximum upstroke velocity of phase 0 depolarization (Vₘₐₓ). The measurements for each tissue sample were obtained from 20–40 impalements in the first subendocardial cell layer. All impalements were made at least 3 mm away from the cut edges of the preparation. This mapping of the tissue was necessary not only to determine the condition of the fibers, but to ascertain the presence of specialized conducting fibers having the potential to exhibit pacemaker activity. ¹⁰, ¹¹

The specialized conducting fibers having "fast response," ¹², ¹³ action potentials were identified easily on the basis of a prominent plateau preceding phase 3 repolarization, and the occurrence of phase 4 depolarization and automaticity on discontinuation of electrical stimulation. In working atrial myocardial fibers, the plateau is very brief, and phase 4 depolarization does not occur. ¹⁰ For fibers having "slow response" action potentials, ¹⁰, ¹⁴ which included five of the total 23 preparations, the distinction between working myocardial and specialized fibers was not readily made on the basis of the two criteria described. As shall be shown, however, the response of fibers with the slow response to epinephrine did not differ from that of fibers with the fast response. In prior publications, we described the action potential characteristics of normal¹⁵ and depressed fast responses and slow responses¹⁶ in human atrial fibers. Distinctions were made on the basis of membrane potential and the effect of procaine amide and the slow channel blocker, verapamil. The action potentials described as "slow responses" in this study fulfill the resting and action potential criteria determined for slow responses in the prior study. In addition, as in our prior study, all slow responses were recorded from atria that were markedly dilated. Atrial size was estimated by the surgeon at the time of cardiac surgery. Size was stated to be 1–4, with 1 being normal and 4 markedly dilated. For comparisons of normal and markedly dilated atria, only those preparations graded as 1 or 4 were compared.

After determining the control AP characteristics for each preparation, the drive stimulus was discontinued and the tissue was allowed to initiate spontaneous activity. Escape time was variable and periods as long as 120 min were required for a spontaneous rhythm to start and stabilize. In all preparations the fiber impaled had the characteristics of a "pacemaker" cell, that is a smooth transition from slow depolarization of phase 4 to the more rapid depolarization of phase 0. The following control measurements were recorded: activation voltage measured from "0" reference potential to the point of inflection between phase 4 and phase 0; MDP, measured from the "0" potential to the point

| Table 1. Clinical Diagnoses of the Patients from Whom Atrial Tissues Were Obtained |
|---------------------------------|------------------------|
| Mean age 4.5 years              | Atrial septal defect   |
|                                 | Ventricular septal defect |
|                                 | Endocardial cushion defect |
|                                 | Transposition of the great vessels |
|                                 | Tetralogy of Fallot |
|                                 | Pulmonary stenosis |
|                                 | Double outlet right ventricle |
| Mean age 40 years               | Ventricular septal defect |
|                                 | Left atrial myxoma |
|                                 | Single ventricle |
|                                 | Rheumatic heart disease |
|                                 | Atherosclerotic heart disease |
of maximum membrane potential occurring at the end of phase 3 or beginning of phase 4; AP amplitude, measured from the MDP to the peak of the overshoot; mean slope of phase 4 depolarization, derived by subtracting activation voltage from MDP and dividing the difference (Δ, in mV) by the time (in sec) between the points at which these two voltages were measured. The spontaneous rate was expressed in beats/min. Preparations in which the rhythm was irregular were not included. In nine of the experiments, following the control period, the atrial fibers were superfused with epinephrine (1-epinephrine bitartrate, Sigma) $1 \times 10^{-11}$ to $1 \times 10^{-4}$M. After 20 min of superfusion with each concentration of the drug, all the above mentioned characteristics were recorded. A steady state effect of the drug was reached within 10 min of the start of superfusion.

To study the effects of α-adrenergic blockade, in five experiments, phentolamine (Regitine – HCl; Ciba-Geigy) $1 \times 10^{-4}$M, was added to the superfusate after the control period. The preparation was superfused with the antagonist, alone, for 40 min, after which a second set of control readings was taken. The fibers then were superfused with epinephrine as described above in the continuous presence of phentolamine.

To study the effects of β-adrenergic blockade, in nine experiments, d,l-propranolol (Ayerst) $2 \times 10^{-4}$M, was used and the same protocol as with phentolamine was followed.

We report here experiments in which the microelectrode impalements were maintained throughout the study. The

<table>
<thead>
<tr>
<th>TABLE 2. Control Action Potential Characteristics and Automaticity (mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
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<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>AP Amplitude (mV)</td>
</tr>
<tr>
<td>AV ($-mV$)</td>
</tr>
<tr>
<td>MDP ($-mV$)</td>
</tr>
<tr>
<td>$\Delta/t^*$ (mV/sec)</td>
</tr>
<tr>
<td>Spontaneous rate (beats/min)</td>
</tr>
</tbody>
</table>

A represents control values for the experiments in which epinephrine was used alone. B includes controls from experiments using epinephrine and phentolamine. C includes control data from experiments using epinephrine and propranolol. The differences between A, B and C are not significant ($P >0.05$). N = the number of experiments.

$\Delta/t^*$ = slope of phase 4 (mV/sec).

Abbreviations: AP = action potential; AV = activation voltage; MDP = maximum diastolic potential.

effects of epinephrine with or without the blocker were analyzed using a paired t-test. When data from one group were compared to data from another, a t-test for grouped data was used. Results are expressed as mean ± standard error.

Results

Control action potentials before discontinuation of the drive stimulus were as follows: four preparations showed normal fast response$^{10,12}$ action potentials (MDP, $-79.5 \pm 1.2$ mV; AP amplitude, $96.4 \pm 5.1$ mV; $V_{\text{max}}$, $223 \pm 22$ V/sec); 14 preparations, depressed fast response

Effect of varying concentrations of epinephrine ($1 \times 10^{-11}$ to $1 \times 10^{-4}$ M) on the response of human atrial fibers to the drug. The results are expressed as mean ± SE of percent change from control (control = O). The preparations were subdivided into two groups on the basis of the age of the patients (panel A), and on the basis of the atrial size (panel B). In all the subgroups, epinephrine induced slowing of spontaneous rate at low concentrations and increased rate at higher concentrations. No difference was noted among the subgroups.

![Figure 1](http://circ.ahajournals.org/)

![Figure 2](http://circ.ahajournals.org/)
action potentials (MDP, \(-71.0 \pm 1.0 \text{ mV}\); AP amplitude, \(82.1 \pm 1.9 \text{ mV}; V_{\text{max}}, 133 \pm 11.8 \text{ V/sec}\); in five preparations the membrane potential was less than \(-60 \text{ mV}\) (\(-55.1 \pm 1.8 \text{ mV}\)) and the fiber either could not be stimulated or the elicited AP were slow responses. Following cessation of the drive and the attainment of a stable spontaneous rhythm (which required up to 120 min) the action potential characteristics for the spontaneously occurring action potentials were recorded. These are reported in Table 2. Note that despite the differing AP characteristics before the onset of spontaneous activity (see above) the AP characteristics for all fibers that functioned as pacemakers were quite similar.

The results of the experiments in which epinephrine alone was studied are shown in Table 3. Low concentrations of epinephrine (10^{-11} through 10^{-9}M) induced a significant decrease in the slope of phase 4 depolarization and with this a slowing of spontaneous rate. At these concentrations, no significant changes in MDP, activation voltage and AP amplitude were recorded. At the higher epinephrine concentrations the spontaneous rate and the slope of phase 4 increased, as did MDP and AP amplitude. Epinephrine effects on activation voltage were variable, not consistent in direction and statistically insignificant.

The effects of epinephrine on spontaneous rate are shown in figure 1. In panel A, the preparations were divided into two groups on the basis of the age of the patients from whom they were obtained. In panel B, they were divided on the basis of the size of the atrium. In all the subgroups a biphasic response to epinephrine was observed: slowing of rate occurred at low concentrations, and rate increased at higher concentrations. In addition, no significant difference was noted between the curves obtained for the different subgroups. The nature of the control AP (fast or slow response) before discontinuation of the drive and the escape time interval did not alter the dose-response curve, nor did prior treatment with the pharmacologic agents mentioned.

In those fibers superfused with phentolamine and epinephrine, the antagonist (1 \times 10^{-4}M) alone had no effect on automaticity or AP characteristics (Table 4). Low epinephrine concentrations, (1 \times 10^{-11} to 1 \times 10^{-7}M) had no effect on the slope of phase 4, spontaneous rate, MDP, activation voltage and AP amplitude. At higher concentrations the slope of phase 4 and rate increased, as did MDP. The hyperpolarization at epinephrine 1 \times 10^{-4}M was significantly greater in the presence of the \(\alpha\) antagonist \((P < 0.05)\) than in the presence of epinephrine alone.

Propranolol, 2 \times 10^{-4}M, had no effect on the atrial fibers.

### Table 3. Effects of Epinephrine on Action Potential Characteristics and Automaticity of Human Atrial Fibers (mean ± SE)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>10^{-11}</th>
<th>10^{-10}</th>
<th>10^{-9}</th>
<th>10^{-8}</th>
<th>10^{-7}</th>
<th>10^{-6}</th>
<th>10^{-5}</th>
<th>10^{-4}</th>
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<tbody>
<tr>
<td>Amplitude (mV)</td>
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<td>64.9</td>
<td>65.9</td>
<td>66.0</td>
<td>67.3</td>
<td>68.5</td>
<td>75.0*</td>
<td>81.2*</td>
<td>83.3*</td>
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<td>42.0</td>
<td>41.8</td>
<td>42.0</td>
<td>44.2</td>
<td>45.1</td>
<td>48.0</td>
<td>46.3</td>
</tr>
<tr>
<td>MDP (-mV)</td>
<td>58.3</td>
<td>57.6</td>
<td>57.8</td>
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<td>58.4</td>
<td>60.4</td>
<td>65.5*</td>
<td>70.0*</td>
<td>70.9*</td>
</tr>
<tr>
<td>(\Delta t) (mV/sec)</td>
<td>11.5</td>
<td>6.2*</td>
<td>5.9*</td>
<td>6.0*</td>
<td>5.4*</td>
<td>4.5*</td>
<td>27.1*</td>
<td>62.7*</td>
<td>78.3*</td>
</tr>
<tr>
<td>Spontaneous rate (beats/min)</td>
<td>27.1</td>
<td>16.5*</td>
<td>14.5*</td>
<td>14.7*</td>
<td>13.4*</td>
<td>12.2*</td>
<td>42.0*</td>
<td>72.8*</td>
<td>82.4*</td>
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For abbreviations see Table 2.

### Table 4. Effects of Phentolamine (1 \times 10^{-4}M) on Epinephrine-Induced Changes in Action Potential Characteristics and Automaticity (mean ± SE)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Phentolamine</th>
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<th>10^{-10}</th>
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<td>57.8</td>
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<td>55.0</td>
<td>56.6</td>
<td>73.0*</td>
<td>82.2*</td>
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<tr>
<td>AV (-mV)</td>
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<td>42.2</td>
<td>42.2</td>
<td>42.2</td>
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<td>43.2</td>
<td>46.6</td>
<td>46.8</td>
<td>45.6</td>
</tr>
<tr>
<td>MDP (-mV)</td>
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<td>55.2</td>
<td>55.0</td>
<td>54.8</td>
<td>55.0</td>
<td>55.4</td>
<td>59.6</td>
<td>64.0*</td>
<td>72.4*</td>
</tr>
<tr>
<td>(\Delta t) (mV/sec)</td>
<td>9.3</td>
<td>9.5</td>
<td>9.4</td>
<td>9.6</td>
<td>9.7</td>
<td>9.1</td>
<td>8.5</td>
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<td>60.1*</td>
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<tr>
<td>Rate (beats/min)</td>
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<td>25.2</td>
<td>26.6</td>
<td>25.6</td>
<td>25.6</td>
<td>25.2</td>
<td>22.8</td>
<td>41.0*</td>
<td>76.2*</td>
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For abbreviations see Table 2.

*\(p < 0.05\) compared to control.

The number of observations is listed in parentheses.
Table 5. Effects of Propranolol (2 × 10⁻¹⁰M) on Epinephrine-induced Changes in AP Characteristics and Automaticity (mean ± SE)

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>10⁻¹⁴</th>
<th>10⁻¹⁶</th>
<th>10⁻¹⁸</th>
<th>10⁻²⁰</th>
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<tbody>
<tr>
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<td>63.6</td>
<td>62.4</td>
<td>62.0</td>
<td>60.8*</td>
<td>60.6*</td>
<td>62.1</td>
<td>63.3</td>
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<td>±2.6</td>
<td>±3.0</td>
<td>±3.1</td>
<td>±2.8</td>
<td>±3.6</td>
<td>±2.7</td>
<td>±2.2</td>
<td>±3.8</td>
</tr>
<tr>
<td>AV (mV)</td>
<td>43.1</td>
<td>43.7</td>
<td>43.6</td>
<td>44.1</td>
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<td>(±SE)</td>
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<td>±2.7</td>
<td>±3.3</td>
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<td>±2.7</td>
<td>±1.9</td>
<td>±2.2</td>
<td>±2.3</td>
<td>±2.0</td>
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<tr>
<td>MDP (mV)</td>
<td>55.8</td>
<td>59.8</td>
<td>60.9</td>
<td>60.5</td>
<td>58.6</td>
<td>58.1</td>
<td>60.6</td>
<td>60.4</td>
<td>59.1</td>
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<tr>
<td>(±SE)</td>
<td>±2.2</td>
<td>±2.1</td>
<td>±2.3</td>
<td>±2.6</td>
<td>±2.4</td>
<td>±2.9</td>
<td>±2.7</td>
<td>±2.6</td>
<td>±2.4</td>
</tr>
<tr>
<td>Δt (mV/sec)</td>
<td>10.2</td>
<td>10.1</td>
<td>7.1*</td>
<td>6.6*</td>
<td>5.5*</td>
<td>4.2*</td>
<td>4.1*</td>
<td>4.6*</td>
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</tr>
<tr>
<td>(±SE)</td>
<td>±0.9</td>
<td>±0.9</td>
<td>±1.3</td>
<td>±1.2</td>
<td>±1.0</td>
<td>±1.1</td>
<td>±1.1</td>
<td>±1.0</td>
<td>±1.4</td>
</tr>
<tr>
<td>Rate (beats/min)</td>
<td>27.3</td>
<td>27.3</td>
<td>18.6*</td>
<td>17.3*</td>
<td>15.0*</td>
<td>11.7*</td>
<td>10.8*</td>
<td>13.2*</td>
<td>15.6*</td>
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<tr>
<td>(±SE)</td>
<td>±1.9</td>
<td>±2.0</td>
<td>±3.3</td>
<td>±3.0</td>
<td>±2.7</td>
<td>±3.2</td>
<td>±3.6</td>
<td>±3.3</td>
<td>±3.7</td>
</tr>
</tbody>
</table>

*P <0.05 compared to control.
†Δt/Δ = slope of phase 4 (mV/sec).
The number of observations is listed in parentheses. The same impalement was maintained throughout the nine experiments but in four cases, the fiber became quiescent at low epinephrine concentrations.

In propranolol-superfused fibers, epinephrine (1 × 10⁻¹¹ to 1 × 10⁻¹⁰M) significantly decreased the slope of phase 4 and spontaneous rate. There was no concomitant change of MDP and activation voltage. Epinephrine, 1 × 10⁻⁸M, increased the slope of phase 4, MDP and AP amplitude. The increase in MDP was significantly smaller than it was in fibers superfused with epinephrine alone (P < 0.05).

Two preparations in this group were obtained from patients who had received prior propranolol therapy. No significant difference could be seen in the response of these fibers as compared to the rest of the group.

The effects on spontaneous rate of epinephrine alone and in the presence of phenolamine or propranolol are shown in figure 2. In the fibers superfused with epinephrine alone, low agonist concentrations (1 × 10⁻¹¹ to 1 × 10⁻¹⁰M) induced a slowing, and high concentrations (1 × 10⁻⁸ to 1 × 10⁻⁷M) induced an acceleration of the spontaneous rate. In the phenolamine-superfused fibers, low epinephrine concentrations (1 × 10⁻¹¹ to 1 × 10⁻¹⁰M) did not slow the spontaneous rate significantly. At the higher epinephrine concentrations (1 × 10⁻⁴ to 1 × 10⁻³M) automaticity increased and the peak rate attained at 1 × 10⁻⁴M was slightly greater than in the experiments in which the agonist alone was used. In the presence of propranolol, the slowing of rate induced by epinephrine was sustained through higher agonist concentrations (1 × 10⁻¹¹ to 1 × 10⁻⁸M). The magnitude of the decrease of rate observed with low epinephrine concentrations was not changed by the addition of propranolol. The peak rate attained at 1 × 10⁻⁴M in propranolol-superfused fibers was significantly lower than the peak response observed in phenolamine-superfused fibers (P < 0.05).

Figure 3 shows the effects of epinephrine on MDP and spontaneous rate for those experiments in which epinephrine alone was used. From a control value of 27.1 ± 6.5 beats/min the rate slowed to a minimum of 12.2 ± 4.6 beats/min at 10⁻⁷M; however, the MDP did not change significantly from the control value of −58.3 ± 1.3 mV. At the higher epinephrine concentrations the rate increased to a maximum of 82.4 ± 11.1 beats/minute and the fiber was hyperpolarized. To determine whether the hyperpolarization might be the result of the increased rate alone, as opposed to a β adrenergic effect, ten experiments were done in which the fibers again were stimulated electrically and MDP was measured in the absence of epinephrine. An increase in stimulus rate, from 30 up to 100 beats/min failed to increase MDP. Hence, it is apparent from table 2 and these results that the changes in rate were mediated by changes in the slope of phase 4 and that the increase in MDP was a β-adrenergic effect and was not induced by the change in spontaneous rate.

A representative experiment in which epinephrine alone was superfused is shown in figure 4.

Discussion

Epinephrine can induce both slowing and acceleration of the spontaneous rate of human atrial fibers. The slowing caused by low concentrations of epinephrine was suppressed by the addition of phenolamine, an α-adrenergic antagonist. In the presence of propranolol, a β-adrenergic antagonist, the slowing of rate was sustained through higher agonist concentrations. These results (fig. 2) suggest the presence of alpha and beta adrenergic receptors in human atrium.

The nature of these receptors and the mechanism whereby their stimulation induces either slowing or acceleration of spontaneous rate has not been fully described. In our study, epinephrine exerted its chronotropic effects by affecting the slope of phase 4 depolarization. These results are consistent with previous reports on sheep and dog Purkinje fibers.1, 4, 13, 14

Posner et al.5 have stated that the negative chronotropic effect of epinephrine on Purkinje fibers may be due to inhibition of the Na-K pump. This would imply a depolarization of the cell at low catecholamine concentrations, an effect that Posner et al. state does occur. However, Rosen et al.4 in studies of canine Purkinje fiber showed a slowing of rate with epinephrine in low concentrations but no depolarization. Similarly, our present study on atrial fibers failed to...
show any depolarization as spontaneous rate decreased. Hence, it appears that the epinephrine-induced slowing of spontaneous rate is due to changes in the slope of phase 4 depolarization, without attendant changes in membrane potential. The basis for this change in slope is uncertain; whether it is due to an action on ATPase or — as has been suggested — to an increase in cellular cyclic guanosine monophosphate (GMP) and an associated decrease in cAMP remains open to question.

The basis for the increase in rate at higher epinephrine concentrations is better known. Beta receptor stimulation induces activation of adenylate cyclase and an increase in intracellular cyclic AMP. In Purkinje fibers, epinephrine accelerates pacemaker activity by causing a more rapid and complete deactivation of $i_{k1}$, an effect blocked by pronethalol and propranolol. Calculations of the pacemaker potential have shown that the more rapid inactivation of $i_{k1}$ can account for the increased frequency induced by epinephrine.

In atrial fibers, the increased spontaneous rate has been attributed to an increase in inward current. In frog atrium, Brown and Noble found that epinephrine induced a large increase in $i_{k1}$ (the outward $K^+$ current), accounting for the observed hyperpolarization. The increase in inward current, due perhaps to an increase in intracellular cyclic AMP, would be responsible for the increased pacemaker activity, the positive inotropic action, and possibly the increased AP amplitude.

The hyperpolarization induced by high epinephrine concentrations was enhanced by pronethalol and inhibited by propranolol, suggesting that this effect is $\beta$-receptor mediated. In canine Purkinje fibers, Rosen et al. found that

**Figure 2.** Effects of pronethalol ($1 \times 10^{-4}$M) and propranolol ($2 \times 10^{-7}$M) on the response of human atrial fibers to epinephrine. In this figure the results are expressed as mean ± se of percent change from control (control = 0). The percent change in rate of pronethalol-superfused fibers is significantly different from the change in fibers superfused with epinephrine $1 \times 10^{-11}$ to $1 \times 10^{-7}$M alone ($P < 0.02$). The change in rate of pronethalol-superfused fibers is significantly different from the change in propranolol-superfused fibers at all epinephrine concentrations ($1 \times 10^{-11}$ to $1 \times 10^{-4}$M; $P < 0.05$).

**Figure 3.** Effects of epinephrine ($1 \times 10^{-11}$ to $1 \times 10^{-4}$M) on the spontaneous rate and the maximum diastolic pressure (MDP) of atrial fibers.

**Figure 4.** Effects of epinephrine on a spontaneously firing human atrial fiber. Panel A) control MDP = 80.3 mV; spontaneous rate = 36.9/min.; slope of phase 4, 23.4 mV/sec. Panel B) epinephrine, $10^{-8}$M; MDP = 10.8 mV; rate, 58.6/min.; slope of phase 4, 6.17 mV/sec. Panel C) epinephrine, $10^{-6}$M; MDP = 10.3 mV; rate, 55.3/msec.; slope of phase 4, 55.3 mV/sec. Panel D) epinephrine, $10^{-4}$M; MDP = 10.1 mV; rate, 55.3/msec.; slope of phase 4, 130 mV/sec.
the hyperpolarization was neither alpha nor beta mediated. This divergence may be due to differences in sensitivity to adrenergic amines related to tissue type or species.

The clinical relevance of \( \alpha \) and \( \beta \) adrenergic effects of catecholamines on human atrial fibers is difficult to assess. It is possible that under normal conditions the basal catecholamine level available to the receptors is greater than the concentrations which cause a slowing of rate. If this is the case, sympathetic stimulation and/or circulating catecholamines would be expected to increase rate only. However, in situations in which tissues or neuronal stores of catecholamines are depleted, the basal state of the tissue might be such that its baseline level of responsiveness on the dose-response curve is further to the left (as figure 1). If this were the case, addition of catecholamines and/or sympathetic stimulation might increase or decrease rate.

It also has been observed clinically that heart rate may, at times, slow following catecholamine infusion. In general, this is attributed to reflex mechanisms.\(^{2}\) It is intriguing to speculate that in addition there might - at the cellular level - be a mechanism whereby slowing or acceleration would follow addition of catecholamines. Although our experimental observations are consistent with such a premise, its validity must await further experimental verification.

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