Effects of Propranolol and Epinephrine on the Electrophysiology of the Heart

Myron Prinzmatal, M.D., Yuji Hashimoto, M.D., Akinori Hayashi, M.D., Kazuhiko Hori, M.D., Mitsuyoshi Nakashima, M.D., Tetsuro Fujino, M.D., and James M. Baines

Summary

Surface and intracellular electrograms and ventricular pressures were used to study the effects of epinephrine and propranolol on electrophysiological properties in the in situ heart of 21 anesthetized dogs. Five sec. after the infusion of epinephrine, the ST segment became slightly depressed. About 10 to 20 sec. after epinephrine, the ST segment became elevated and the negative T wave became more inverted. Initially, the upward convexity of phase III of the membrane action potential deepened slightly. Phase II of the membrane action potential gradually decreased in amplitude and became prolonged in duration. Phase III of the membrane action potential increased slightly. The membrane resting potential remained almost unchanged. Intracellular electrographic changes due to epinephrine were of abnormal configuration. That epinephrine may cause anginal pain is well known. Propranolol inhibits epinephrine's effects on the electrophysiologic properties of the heart. It is thought that propranolol helps to relieve the pain of angina pectoris by decreasing cardiac work and by increasing coronary blood flow.

Additional Indexing Words:
Membrane action potential Membrane resting potential Intracellular electrogram Surface electrogram Ventricular pressure Ionic transport Catecholamines

Recent studies have firmly established the value of propranolol in the treatment of angina pectoris.1-3 After the administration of propranolol, patients have less or no anginal pain. Many theories have been advanced concerning the relationship between the beneficial effects of adrenergic beta-receptor blocking compounds and the known cardiac effects of the catecholamines.

In 1930, Levine, et al.,4 found that typical anginal attacks could be provoked by the injection of epinephrine. Raab,5 in 1948, reported an

From the Cedars-Sinai Medical Research Institute and the Division of Medicine, Cedars-Sinai Medical Center, Los Angeles 90029 and the Department of Medicine, University of California School of Medicine, Los Angeles 90024.

Received for publication December 26, 1969.
increase in blood catecholamines in patients with angina pectoris after exercise. Gazes, et al., observed significantly elevated plasma levels of norepinephrine in patients with myocardial infarction and, at times, in patients with angina during pain. They suggested that the increase of catecholamines came not only from the adrenal gland but also from the myocardium and coronary vessels.

Structural and biochemical effects of catecholamines on heart muscle have been extensively studied during the past several years. Schenck and Moss, investigating catecholamines and cardiac lesions, reported the lesions consisting of focal degeneration and necrosis of myofibers and of subendocardial hemorrhage. They suggested that cellular hypoxia was most probably the basis of cardiac lesions. Clinically, Lindgren and Apthorp, et al., have proposed that thoracic sympathectomy be used in some cases of angina pectoris.

There is little in the literature on the mechanism of propranolol's beta adrenergic blocking action. However, many recent studies point to a relationship between ST-T abnormalities in angina pectoris and the blocking of beta adrenergic receptors. Raab and coworkers reported that after tying off the adrenals and eliminating the cardiac sympathetic nerve supply, the ST segment following coronary occlusion remained unchanged or showed very slight elevation. In 1962, Black and Stephenson suggested that beta-receptor blockades might be beneficial in angina pectoris because of the reduction in myocardial oxygen requirement. Apthorp, et al., claimed that ischemic abnormalities in the electrogram during effort were abolished after thoracic sympathectomy or with the administration of pronethalol which has similar actions to that of propranolol. Hamer, et al. reported that propranolol improved exercise tolerance in patients with angina pectoris. Frieden in reviewing the treatment of angina pectoris, reported that the main effect of propranolol was primarily the prevention of increased cardiac work due to adrenergic activity.

According to these reports then, the improvement of the ST-T abnormalities in angina pectoris after propranolol is probably due to the decrease in myocardial oxygen consumption. Some investigators have suggested that epinephrine affects the permeability of the cell membrane to many ions. The exchange of the potassium ion seems to be the most important.

The present study was designed to investigate: 1) the influence of epinephrine on surface and intracellular electrograms of the in situ canine heart; and 2) the influence of propranolol on the electrographic changes induced by epinephrine.
**METHOD**

Twenty-one mongrel dogs weighing 12 to 22 Kg. were used in the experiments. Thirty-four valid experiments were performed on 14 of the 21 dogs. Experiments on the remaining 7 dogs were considered invalid due to technical failures. Each dog was anesthetized with intravenous sodium pentobarbital (25 mg./Kg.). Breathing was maintained by artificial respiration. The chest was opened and the heart exposed by a method previously described. To prevent blood coagulation, 50 to 100 mg. heparin sodium was injected into the femoral vein. An artificial coronary circuit was established between the left carotid artery and the anterior descending branch of the left coronary artery (Fig. 1). The electrographic recording area was selected on that portion of the left ventricular surface which received its blood supply through the artificial circuit. Two concentric steel rings covered with polyethylene tubing were placed on the recording area. Arms extending from the rings were affixed to holders on the operating table. To minimize myocardial movement, the outer ring was sutured to the ventricular surface through the epicardium. The inner ring remained unsutured. The parietal pericardium within the small ring was removed by dissection and the exposed epicardium was continuously irrigated with Ringer’s solution at a thermostatically controlled temperature of 37°C.

A unipolar surface electrode and an intracellular electrode were applied to the approximate center of the inner ring. The unipolar electrode was made of tungsten wire about 0.1 mm. in diameter. The indifferent electrode for the surface electrogram was connected with Wilson’s central terminal. A mounted flexible glass electrode described by Woodbury and Brady was used to record the intracellular
ELECTRIC RESISTANCE OF THE MICROELECTRODE WAS ABOUT 10 TO 20 MEGOHMS. THE INDIFFERENT ELECTRODE FOR THE INTRACELLULAR ELECTROGRAM WAS PLACED ON THE EPICARDIUM AS CLOSE AS POSSIBLE TO THE INTRACELLULAR ELECTRODE TO MINIMIZE THE EXTRINSIC FACTOR.

TWENTY-SEVEN EPINEPHRINE EXPERIMENTS WERE PERFORMED ON 14 DOGS. BEFORE EACH EXPERIMENT 10 ML. OF ARTERIAL BLOOD WAS INFUSED INTO THE CORONARY CIRCUIT AT A RATE OF APPROXIMATELY 1 ML./SEC. THESE CONTROL INFUSIONS CAUSED NO SIGNIFICANT CHANGES IN SURFACE AND INTRACELLULAR ELECTROGRAMS. EPINEPHRINE SOLUTIONS CONTAINING 10 MG./L. OR 20 MG./L. WERE PREPARED BY DILUTING WITH RINGER'S SOLUTION. ONE-TENTH ML. OF THIS HIGH EPINEPHRINE SOLUTION WAS DILUTED TO 10 ML. WITH ARTERIAL BLOOD DRAWN FROM THE ANESTHETIZED ANIMAL. IN EACH DOG, THIS 10 ML. OF EPINEPHRINE SOLUTION (1 TO 2 μG.) AT A TEMPERATURE OF 37°C WAS INFUSED INTO THE ARTIFICIAL CORONARY CIRCUIT AT A RATE OF APPROXIMATELY 1 ML./SEC. THIS RATE IS WITHIN THE NORMAL RANGE OF BLOOD FLOW FROM THE AREA SUPPLIED BY THE CIRCUIT. CHANGES IN SURFACE AND INTRACELLULAR ELECTROGRAPHIC CONFIGURATIONS INVARIABLY OCCURRED WITH INFUSION OF THE EPINEPHRINE SOLUTION. WHEN THE ELECTROGRAMS RETURNED TO THEIR PRE-EPINEPHRINE VALUES, THE INFUSIONS WERE REPEATED IN EACH ANIMAL.

IN 7 OF 14 DOGS, PROPRANOLOL HYDROCHLORIDE (INDERAL, THROUGH THE COURTESY OF DR. A. SAHAGIAN-EDWARDS, AYERST LABORATORIES, NEW YORK) WAS ADMINISTERED IN DOSES OF 0.2 MG./KG. FOR ABOUT 1 MIN. ABOUT 5 TO 30 MIN. AFTER THE ADMINISTRATION OF PROPRANOLOL, INFUSIONS OF EPINEPHRINE WERE BEGUN.

RESULTS

I. INFLUENCE OF EPINEPHRINE

SURFACE AND INTRACELLULAR ELECTROGRAPHIC CHANGES CAUSED BY EPINEPHRINE INFUSIONS WERE OBSERVED IN 27 EXPERIMENTS IN 14 DOGS.

A. SURFACE ELECTROGRAMS. THE RR INTERVAL REMAINED UNCHANGED DURING THE INITIAL 20 SEC. AFTER THE INFUSION (TABLE I). AFTER 30 SEC. THE RR INTERVAL BECAME PROLONGED (p < 0.05). THE QT INTERVAL BECAME PROLONGED AFTER 10 SEC. (p < 0.01), AND AT 20 SEC. (p < 0.05). PROLONGATION OF THE QT INTERVAL WAS NOT OBSERVED AFTER 30 SEC. THE TQ SEGMENT REMAINED AT ALMOST THE PRE-INFUSION LEVEL (FIGS. 2A, 2B, 3). THE QRS DURATION REMAINED UNCHANGED IN ALL EXPERIMENTS. FIVE SEC. AFTER THE INFUSION, THE ST SEGMENT (AMPLITUDE OF THE ST SEGMENT AT 0.04 SEC. FROM THE NADIR OF THE S WAVE) BECAME SLIGHTLY DEPRESSED
Table I. Changes in Various Parameters of Surface and Intracellular Electrograms due to the Infusion of Epinephrine

<table>
<thead>
<tr>
<th></th>
<th>Pre-Infusion Value</th>
<th>Changes*** due to Epinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 sec.</td>
</tr>
<tr>
<td>ST (mV.)</td>
<td>1.65 ± 1.63 (N = 27)</td>
<td>0.47 ± 0.84 (N = 27)**</td>
</tr>
<tr>
<td>(mV.)</td>
<td>-9.15 ± 5.55 (N = 27)</td>
<td>0.40 ± 1.51 (N = 27)**</td>
</tr>
<tr>
<td>RR Interval (msec.)</td>
<td>363.1 ± 30.9 (N = 27)</td>
<td>+0.73 ± 5.48 (N = 27)**</td>
</tr>
<tr>
<td>QT Interval (msec.)</td>
<td>249.7 ± 7.8 (N = 27)</td>
<td>0.7 ± 7.4 (N = 27)</td>
</tr>
<tr>
<td>QRS Duration</td>
<td>41.1 ± 11.0 (N = 27)</td>
<td>0.6 ± 2.6 (N = 27)**</td>
</tr>
<tr>
<td>(msec.)</td>
<td>97.0 ± 6.43 (N = 24)</td>
<td>-0.80 ± 4.11 (N = 24)</td>
</tr>
<tr>
<td>MAP Amplitude (mV.)</td>
<td>-82.58 ± 12.50 (N = 24)</td>
<td>+0.27 ± 4.39 (N = 24)</td>
</tr>
<tr>
<td>MRP (mV.)</td>
<td>193.9 ± 24.8 (N = 24)</td>
<td>+1.3 ± 5.1 (N = 24)</td>
</tr>
</tbody>
</table>

***Changes = differences between the values 5, 10, 20 and 30 sec after the infusion of epinephrine and their pre-infusion values.
Values represent the mean ± 1 S.D. *=significant difference (p<0.05).
N=number of experiments. **=highly significant difference (p<0.01).
The p values were calculated by Student's t Test.

Fig. 2. Surface electrograms (upper tracings S) and intracellular electrograms (lower tracings M) recorded simultaneously from contiguous sites within the region supplied with blood through an artificial coronary circuit. Tracings labeled 1 were recorded before the epinephrine infusion. Tracings labeled 2 were recorded about 10 sec. (A) after the epinephrine infusion. Tracings labeled 3 were recorded about 30 sec. (B) after the infusion.
Tracings in C were recorded after the administration of propranolol. Tracings labeled 4 were recorded before epinephrine. Tracings labeled 5 were recorded 10 sec. after epinephrine. Tracings were photographically superimposed so that the onsets of the QRS complexes were identical in time (See text).
(p<0.01). The ST segment began to rise about 10 sec. after the infusion of epinephrine, reaching the maximum value of elevation after about 30 sec. Gradually, it returned to the pre-infusion value after 90 to 150 sec.

The initially inverted T wave became more inverted after 5 sec., reaching its deepest level 10 sec. after the infusion. The difference between the depths of the T wave before and at 10 sec. after epinephrine was $-3.35 \pm 2.62$ mV. (p<0.01). At 30 sec. the inverted T wave became less inverted than the pre-infusion value. The T wave gradually returned to its pre-infusion configuration after 90 to 150 sec.

B. Intracellular Electrograms. During the first 5 sec. after epinephrine, the amplitude and duration of the membrane action potential (MAP) and the membrane resting potential (MRP) remained unchanged (Table I). The amplitude of the MAP was measured at the highest point of the repolarization curve following the small dip after the depolarization upstroke. The duration of the MAP was measured at the 90 per cent level of the repolarization curve.

At about 10 sec., the upward convexity of phase III of the repolarization phase gradually increased, and the dip between the spike of phase I and the upward convexity of phase II did not change (Fig. 2A). The duration of the MAP became prolonged (p<0.01) (Table I).

At 30 sec., the dip of the MAP gradually deepened and the duration of phase II of the MAP became prolonged (Fig. 2B). The amplitude of phase II of the MAP gradually decreased. The amplitude of the MAP increased (p<0.01) (Table I). During 30 sec. there was no significant change in the MRP.

C. Left Ventricular Pressures. In 17 of 27 experiments the systolic left ventricular pressure (Pre-infusion value=$127 \pm 6.2$ mm.Hg) increased after
epinephrine. The increments ranged from 2 to 24 mm.Hg. The systolic left ventricular pressure began to rise after the infusion (Fig. 4). It returned to its preinfusion level after 60 to 150 sec. In the other 10 experiments, the elevation of blood pressure was not significant.

II. Influence of Propranolol on Electrographic Changes Induced by Epinephrine

Electrographic changes caused by propranolol have been described previously by this laboratory.21) In the present experiments, surface and intracellular electrographic changes due to epinephrine after the administration of propranolol were observed in 7 experiments.

A. Surface Electrograms. Epinephrine infusion after the administration of propranolol caused slowing of the heart rate. The RR interval prolonged slightly (p <0.05) (Table II). Consequently, the QT interval also prolonged slightly. The TQ segment remained at about the pre-infusion level (Fig. 2C). The QRS duration remained unchanged. The ST segment became slightly elevated. Ten sec. after epinephrine the ST segment elevated (p <0.05). The initially inverted T wave became less inverted. The difference between the depth of the T wave before and at 5 sec. after epinephrine was +0.51 ±0.50 mV. (p <0.05).

B. Intracellular Electrograms. During the first 30 sec. after epinephrine infusion, no significant changes were observed in the MAP, MRP and the
Table II. Changes in Various Parameters of Surface and Intracellular Electrograms due to Epinephrine after the Administration of Propranolol

<table>
<thead>
<tr>
<th></th>
<th>Pre-Infusion Value</th>
<th>After the Administration of Propranolol</th>
<th>Changes*** due to Epinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 sec.</td>
<td>10 sec.</td>
</tr>
<tr>
<td>ST (mV.)</td>
<td>-0.54±1.39</td>
<td>+0.20±0.28</td>
<td>+0.37±0.29</td>
</tr>
<tr>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
</tr>
<tr>
<td>T Wave (mV.)</td>
<td>-10.51±3.72</td>
<td>+0.51±0.50</td>
<td>+0.26±0.70</td>
</tr>
<tr>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
</tr>
<tr>
<td>RR Interval (msec.)</td>
<td>580.7±52.3</td>
<td>+7.1±5.7</td>
<td>+6.4±4.8</td>
</tr>
<tr>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
</tr>
<tr>
<td>QT Interval (msec.)</td>
<td>285.4±33.1</td>
<td>+1.5±2.3</td>
<td>+4.0±4.8</td>
</tr>
<tr>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
</tr>
<tr>
<td>QRS Duration (msec.)</td>
<td>38.4±3.3</td>
<td>+0.3±1.5</td>
<td>-1.0±1.3</td>
</tr>
<tr>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
</tr>
<tr>
<td>MAP Amplitude (mV.)</td>
<td>96.4±4.72</td>
<td>+1.57±1.71</td>
<td>+1.11±2.12</td>
</tr>
<tr>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
</tr>
<tr>
<td>MRP (mV.)</td>
<td>-81.98±6.23</td>
<td>-0.31±3.21</td>
<td>+0.87±3.87</td>
</tr>
<tr>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
</tr>
<tr>
<td>MAP Duration (msec.)</td>
<td>237.7±29.4</td>
<td>+1.4±5.4</td>
<td>+2.7±7.2</td>
</tr>
<tr>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
<td>(N=7)</td>
</tr>
</tbody>
</table>

Same designations as Table I.

duration of the MAP (Table II).

C. Left Ventricular Pressures. The systolic left ventricular pressure after propranolol was 91±5.1 mm.Hg before the infusion of epinephrine. After the infusion of epinephrine, the pressure was only slightly changed during 30 sec. The alterations ranged from -4 to +8 mm.Hg.

III. Changes Induced by Epinephrine alone Compared with Changes due to Epinephrine after Propranolol

The QT interval increased at 10 sec. after epinephrine alone (p<0.01) (Table I). At 10 sec. after epinephrine-plus-propranolol the increment of the QT interval was not significant (Table II).

The ST segment became elevated at 30 sec. after epinephrine alone (p<0.01) (Table I). At 30 sec. after epinephrine-plus-propranolol the elevation of the ST segment was not significant (Table II).

After epinephrine alone, the initially inverted T wave became more inverted. Later the T wave gradually became less inverted. At 30 sec. the T wave became less inverted (p<0.05) than the pre-infusion value (Table I). After epinephrine-plus-propranolol, the transient deepening was not observed. At 30 sec., the inversion of the T wave decreased (p<0.05) (Table II).

The amplitude of the MAP decreased at 30 sec. after epinephrine alone
After epinephrine-plus-propranolol, the decrement of the amplitude of the MAP was not significant (Table II).

The duration of the MAP increased at 10 sec. after epinephrine alone (Table I). After epinephrine-plus-propranolol, the increment of the duration of the MAP was not significant (Table II).

There were no significant changes in the MAP in either experiment (Tables I, II).

These findings show that propranolol almost completely inhibits the electrographic changes induced by epinephrine.

**DISCUSSION**

Electrocardiographic changes induced by epinephrine have been extensively studied clinically and experimentally. The ST-T changes have been reported to be the most clinically important findings. Gaal, et al. reported that during the first few sec. following intracoronary injections of epinephrine, both systolic and diastolic coronary blood flows increase. They suggested that this initial increase of coronary blood flow is due to a primary vasodilation. Klocke, et al. suggested the increase of myocardial oxygen uptake caused by catecholamines in the beating heart is largely due to the hemodynamic alterations produced by catecholamines. Berne reported that the decrease of coronary sinus blood oxygen tension started at approximately the time when the coronary blood flow began to rise after intracoronary injection of 1 μg. norepinephrine. These observations suggest that myocardial hypoxia due to the inability of coronary blood flow to keep pace with the increased oxygen requirement of the heart stimulated by epinephrine probably induces the ST-T abnormalities.

In the present experiments, surface and intracellular electrograms were recorded before and after infusions of epinephrine through the coronary artery of the in situ canine heart. The infusion of approximately 1 μg. epinephrine caused ST-T changes. Epinephrine injected into an artificial coronary circuit caused depression of the ST segment and an increase in the negativity of the T wave at 5 sec. (Table I). Between 10 and 30 sec., ST segment elevation was observed. This change was associated with a decrease in the amplitude of phase II of the MAP and an increase in the upward convexity of phase III of the MAP. Consequently, the configuration of the MAP became abnormal (Figs. 2A, 2B). These findings differ from those which occurred after the experimental production of coronary occlusion. In these earlier studies, relative ST elevation due to TQ depression and decrease in amplitude of the MAP with a decrease in negativity of the MAP were observed. It could,
therefore, be assumed that the ST-T changes (Figs. 2A, 2B) during about 30 sec. might not be attributable to myocardial hypoxia produced by an "oxygen-wasting" effect.

The electrographic changes at the 5 sec. period in the present experiments are similar to those reported by this laboratory in low potassium and calcium studies. In the low potassium experiments, the inversion of the T wave became greater. However, the TQ level gradually rose above the control level. In the low calcium experiments, the inverted T wave became more inverted, the terminal portion of the ST segment became slightly displaced downwardly. The TQ level remained unchanged. These changes were associated with the prolongation in the duration of the MAP which was largely due to the prolongation of phase II of the MAP.

Hoffman and Cranefield observed that in isolated heart, epinephrine caused very slight changes in the intracellular electrogram. Lavezzaro, et al. suggested that the action of epinephrine at the cellular level is probably due to changes in ionic shift. Epinephrine apparently increases the speed of ionic transport across the cell membrane. The exit of potassium seems most important and Otsuka suggested that this might be responsible for repolarization. Other investigators have reported that typical electrocardiographic changes produced by epinephrine can be largely suppressed by the administration of potassium. It has been found that epinephrine potentiates the lipid-facilitated transport of calcium ions.

The present study on the in situ canine heart demonstrates that propranolol directly inhibits ST-T abnormalities induced by catecholamines.

Acknowledgments

The authors thank Professor K. Yamada, Research Institute of Environmental Medicine, Nagoya University, Japan, for advice and suggestions; and Mr. Freddie Smith for technical services in the experiments.

References