Glucagon
ITS ENHANCEMENT OF ATRIOVENTRICULAR NODAL PACEMAKER ACTIVITY AND FAILURE TO INCREASE VENTRICULAR AUTOMATIVITY IN DOGS

By Benedict R. Lucchesi, Ph.D., M.D., David R. Stutz, B.S., and Robert A. Winfield, B.S.
With the Technical Assistance of Jeanne L. Brown and Nancy L. Nobel

ABSTRACT
The effects of glucagon on atrioventricular nodal automaticity and ventricular automaticity were studied in anesthetized open-chest dogs. After the sinoatrial node was crushed, glucagon, 4 μg/kg, produced a marked and sustained increase in the rate of A-V nodal discharge (27.6 ± 10.1 vs. 117.4 ± 6.5 beats/min) that persisted for an average of 20 minutes. The effect of glucagon was not modified by previous administration of propranolol, 2 mg/kg. Repeated administrations of glucagon, 1 μg/kg every 15 min, for a period of 2 hours, sustained A-V nodal rhythm. The effects of glucagon on ventricular automaticity were studied in unanesthetized dogs 48 and 72 hours after surgical ligation of the anterior descending coronary artery and were compared to the effects of epinephrine. Unlike the catecholamine, glucagon did not enhance ventricular automaticity in the infarcted myocardium. The results suggest that glucagon might be of therapeutic value in the management of heart block and in cardiogenic shock after acute myocardial infarction. The inability to augment ventricular ectopic activity suggests that glucagon possesses an advantage over the catecholamines as an inotropic agent.

ADDITIONAL KEY WORDS beta-receptor blockade sinoatrial arrest propranolol A-V heart block myocardial infarction epinephrine ventricular ectopic activity isoproterenol inotropic effects

Previous studies with glucagon (1-3) have demonstrated its cardiostimulatory actions and have suggested a similarity between glucagon and the catecholamines with respect to their positive inotropic and chronotropic effects. Subsequent studies by Lucchesi (4) and Glick et al. (5) have shown that glucagon is capable of exerting its positive inotropic and chronotropic effects in the presence of beta-receptor blockade produced by propranolol. Recently, Whitsitt and Lucchesi (6) reported that glucagon was capable of antagonizing the propranolol-induced decrease in atrioventricular conduction velocity. The latter observation has been confirmed by Steiner et al. (7), who also demonstrated the ability of glucagon to increase the velocity of atrioventricular conduction in dogs not subjected to beta-receptor blockade.

The results of studies in the experimental animal suggest that glucagon possesses actions similar to those of the catecholamines in augmenting cardiac contractile force and automaticity of the sinoatrial node and facilitation of transmission within the atrioventricular node (1-7). A significant difference between the cardiac actions of glucagon and of the catecholamines is that the effects of the former are not prevented by beta-receptor blockade (4-7).

Clinical studies in man have also provided
evidence for the cardiac actions of glucagon (8-10), which may be of therapeutic importance in the management of certain clinical conditions in which a positive inotropic effect is desirable.

The purpose of this study was to examine the cardiac actions of glucagon with respect to its effects on atrioventricular nodal pacemaker activity and its effects on ventricular pacemaker discharge in the dog’s heart.

**Methods**

The effects of glucagon and isoproterenol on atrioventricular nodal rhythm were studied in mongrel dogs weighing between 10 and 16 kg. The dogs were anesthetized with a mixture of albubarital 60 mg/kg, urethane 240 mg, and monethylurea 240 mg/kg (Dial-Urethane Solution, Ciba). The trachea was cannulated and the animals were ventilated with room air by a Harvard respirator. The thorax was entered through a right thoracotomy in the fourth interspace. The pericardium was opened and sutured to the chest wall to form a cradle for the heart. Bipolar silver electrodes were sutured to the heart electrically when necessary to maintain cardiac rhythm. Systemic arterial blood pressure was measured from the femoral artery by a Statham pressure transducer and the electrocardiogram was obtained via lead II limb leads. All recordings were made on a Grass Model 5 Polygraph. The effects of glucagon and isoproterenol on the automaticity of the atrioventricular node were determined after crushing the sinoatrial node with a clamp placed across the intercaval junction. The drugs were administered intravenously into the cannulated jugular vein and washed in with 2 ml of 0.9% sodium chloride.

The effects of glucagon and epinephrine on ventricular automaticity were studied in dogs after experimentally induced myocardial infarction. Dogs were anesthetized with pentobarbital sodium, 30 mg/kg iv. A cuffed endotracheal tube was inserted and the animals were ventilated artificially with room air by a Harvard respirator. The heart was exposed by entering the chest through a left thoracotomy incision in the fourth interspace. A 2-cm incision was made in the pericardium to expose the anterior descending coronary artery and a two-stage ligation was carried out according to the method described by Harris (11). The surgical incisions were closed, dressings applied, and the animals permitted to recover from the anesthetic. These animals were studied in the unanesthetized state 24 hours after ligation of the anterior descending coronary artery during the phase of spontaneous ventricular arrhythmias as well as 48 and 72 hours after infarction. On the second and third postoperative days the catecholamine sensitivity test described by Maling and Moran (12) was carried out. The lead II electrocardiogram was monitored on an oscilloscope and recorded on a Grass Model 7 polygraph while the dogs were supported in a harness and maintained in an isolated environment free of external disturbances. All drugs were administered through an indwelling catheter inserted into the left brachiocephalic vein. The indwelling catheter was connected to a length of plastic tubing which led to the outside of the animal’s enclosure, making it possible to administer the test drugs without physically disturbing the animal. The electrocardiographic recordings were analyzed according to the method described by Moran et al. (13) in which only beats of S-A nodal origin were considered as normal and all other QRS complexes were classified as ectopic ventricular beats. All beats in each successive 30-second period were counted and recorded as either sinus or ectopic beats.

Solutions of glucagon 1 used in this study were made daily by dissolving the crystalline material in 0.9% sodium chloride solution containing 0.1% tris (hydroxymethyl) aminomethane (Tris buffer) and adjusted to a pH of 8.5.

The t-tests for paired and grouped comparisons were used according to the methods described by Hill (14).

**Results**

**Effects of Glucagon on Atrioventricular Nodal Rhythm.**—The sinoatrial node was crushed in seven dogs and resulted in a ventricular nodal rhythm with a mean rate of 27.6 ± 10.1 (SEM) beats/min. Glucagon in a dose of 4 μg/kg iv resulted in an increase in the rate of the atrioventricular rhythm, the peak response in the seven dogs averaged 117.4 ± 6.5 beats/min (P < 0.025, group comparison). Twenty minutes after administration of glucagon, the atrioventricular nodal rate had declined to a mean rate of 87.4 ± 6.5 beats/min. The results are presented in Table 1. In dogs 2, 3, and 4 an idioventricular rhythm developed after the sinoatrial node was crushed and a

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1The glucagon used in this study was obtained from the Lilly Research Laboratories as crystalline glucagon (Lot 258-234 B-167-1).
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TABLE 1

Effect of Glucagon on Atrioventricular Nodal Rate (Beats/Min)

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Control A-V nodal rate</th>
<th>A-V nodal rate after glucagon, 4 μg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 min</td>
</tr>
<tr>
<td>1</td>
<td>35</td>
<td>+65</td>
</tr>
<tr>
<td>2</td>
<td>0 (7)*</td>
<td>+97</td>
</tr>
<tr>
<td>3</td>
<td>0 (12)*</td>
<td>+120</td>
</tr>
<tr>
<td>4</td>
<td>9 (9)*</td>
<td>+103</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>−76</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>−80</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>+88</td>
</tr>
</tbody>
</table>

**MEAN ± SE**

|                  | 90 ± 7 | 73 ± 12 | 13 ± 10 | 7 ± 8 |

* Idioventricular rhythm developed after the S-A node was crushed. Number in parentheses is the idioventricular rate.

† P value obtained by t-test for self-paired samples by comparing the control rate with the rates at each of the time intervals after glucagon.

Atrioventricular nodal rhythm did not become dominant until after administration of glucagon and in dogs 3 and 4 it reverted back to an idioventricular rhythm. In dog 1, electrical pacing was required 23 minutes after glucagon to maintain cardiac rhythm. A-V nodal rhythm, however, could be restored by subsequent administrations of glucagon in a dose of 4 μg/kg. Most notable was the observation that glucagon did not increase the idioventricular rate in dogs 2, 3, and 4 and did not augment automaticity from any focus other than the atrioventricular node. The effect of glucagon on the A-V nodal rhythm is illustrated in Figure 1.

Propranolol, 2 mg/kg, was administered to a second group of four dogs after the sinoatrial node had been crushed. The use of propranolol served to rule out the possibility that catecholamines, either circulating or released from cardiac sympathetic nerve fibers, could account for the enhancement of A-V nodal pacemaker activity. As shown in Table 2, glucagon, 4 μg/kg, produced an increase in the frequency of A-V nodal discharge. In 3 of the 4 dogs, propranolol abolished all automaticity, and electrical pacing had to be used to maintain cardiac rhythm before administration of glucagon. The tracings in Figure 2 illustrate the effect of glucagon on A-V nodal rhythm after administration of propranolol, 2 mg/kg. As indicated in Tables 1 and 2, the A-V nodal rate decreased progressively after the peak glucagon effect, and by the end of 23 minutes it was not significantly different from the control A-V nodal rhythm. The results were the same in animals with and without previous beta-receptor blockade with propranolol.

The sinoatrial node was crushed in five dogs that received propranolol, 2 mg/kg. When the A-V nodal rate had stabilized, each of the animals received glucagon, 1 μg/kg every 15 minutes. This regimen was continued for 2 hours (total dose of glucagon equal to 9 μg/kg) and the animals were then observed for an additional 60 minutes. In each dog, the initial dose of glucagon (1 μg/kg) resulted in a marked increase in the A-V nodal rate. The rate declined slightly during the 15-minute interval between glucagon administrations, but each subsequent injection augmented it. By repeated administration of small doses of glucagon, it was possible to maintain a stable A-V nodal rhythm in each of the five dogs throughout the 2-hour period. When glucagon was discontinued at the end of 2 hours, the A-V nodal rate decreased progressively. The data for each of the five dogs are summarized in Figure 3.

**Effects of Isoproterenol on Atrioventricular Nodal Rhythm.**—The sinoatrial node was
crushed in four dogs, and the effect on the atrioventricular nodal rhythm of isoproterenol in doses of 0.5 and 1.0 \( \mu \)g/kg was examined before and after administration of propranolol, 2 mg/kg. Isoproterenol, 0.5 \( \mu \)g/kg, produced an increase in the rate of atrioventricular nodal discharge. The mean increase from control 1 minute after isoproterenol was 83 ± 15 (SEM) beats/min \((P < 0.025)\). Two minutes after administration of isoproterenol, the increase from control in the atrioventricular nodal rate was not statistically significant. The response to 0.5 \( \mu \)g/kg of isoproterenol was blocked by the previous administration of propranolol, 2 mg/kg. Isoproterenol, 1.0 \( \mu \)g/kg, produced a mean increase in A-V

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\begin{array}{c|c|c|c|c|c}
\text{Dog no.} & \text{Control A-V nodal rate} & \text{A-V nodal rate after glucagon, 4 \( \mu \)g/kg} & \text{3 min} & \text{13 min} & \text{23 min} & \text{33 min} \\
8 & 40 & +75 & +71 & +35 & -2 \\
9 & 0 & +111 & +107 & +79 & +8 \\
10 & 0 & +89 & +79 & +12 & +4 \\
11 & 0 & +38 & +14 & 0 & 0 \\
\text{MEAN ± SE} & 78 ± 15 & 68 ± 20 & 31 ± 17 & 3 ± 2 \\
\text{P value*} & <0.025 & <0.05 & >0.05 & >0.05 \\
\end{array}
\]

* \( P \) value obtained by \( t \)-test for self-paired samples by comparing the control rate with the rate at each of the time intervals after glucagon.
Electrocardiograms, lead II, from a 12-kg male dog show the action of glucagon on the atrioventricular nodal rhythm in the presence of beta-receptor blockade. A: After destruction of the sinoatrial node and administration of propranolol, 2 mg/kg iv. Electrical pacing (120 beats/min) was necessary to maintain rhythmic activity. When electrical pacing was stopped, there was no atrioventricular nodal activity. B: Approximately 3 minutes after rapid administration of glucagon, 4 μg/kg iv; glucagon produced a sustained augmentation in the frequency of atrioventricular nodal discharge.

FIGURE 3

Effect of repeated intravenous injections of 1 μg/kg of glucagon to each of five dogs after destruction of the sinoatrial node and administration of propranolol, 2 mg/kg. The values at the point marked Control represent the atrioventricular nodal rate for each dog 10 minutes after propranolol. The subsequent points between the vertical lines represent the A-V nodal rate recorded 3 minutes after each injection of glucagon. The final points on the graph show the A-V nodal rate 60 minutes after the last injection of glucagon.

nodal rate of 106 ± 18 beats/min (P < 0.005) with the increment in nodal rate returning to the control level within 3 minutes. After the administration of propranolol, isoproterenol, 1.0 μg/kg, produced a mean increase of 7 ± 3 beats/min (P < 0.05). In contrast to the action of glucagon, the effect of isoproterenol on the rate of atrioventricular nodal discharge is terminated within 2 to 3 minutes after intravenous administration of 0.5 and 1.0 μg/kg. Secondly, the effect of isoproterenol may be prevented by the previous administration of propranolol.

Effects of Glucagon on Ventricular Automaticity
ticity in the Dog after Experimentally Induced Myocardial Infarction.—The anterior descending coronary artery was ligated in four dogs. Each animal was then studied in the unanesthetized state while resting quietly in a harness. On the first postoperative day, each animal exhibited "spontaneous" ventricular arrhythmias in which an average of 110 ± 2.5 (SEM) out of a total of 128 ± 2.4 beats/min originated from ventricular or abnormal ectopic foci. The rate of ventricular ectopic activity decreased gradually. On the second postoperative day the mean heart rate in the four dogs was 128 ± 2.9 beats/min with a mean ectopic rate of 25 ± 1.9 beats/min. There was a further reduction in the mean ectopic rate when the animals were examined on the third postoperative day. These data are presented graphically in Figure 4, along with the data comparing the effects of epinephrine (1 and 3 μg/kg) and glucagon (4 and 12 μg/kg) after myocardial infarction.

Epinephrine produced a marked increase in the rate of ectopic ventricular discharge 48 and 72 hours after myocardial infarction. This increase in ectopic activity consisted of multifocal ventricular ectopic beats, ventricular tachycardia and A-V nodal rhythms, which were more pronounced with the larger dose of epinephrine. The effects of epinephrine subsided gradually and all animals returned to the previous control state by the end of 10 minutes.

In marked contrast to the effects of epinephrine, glucagon (4 and 12 μg/kg) did not produce an increase in the rate of ventricular ectopic discharge. Although the positive chronotropic effect of glucagon is minimal in the unanesthetized dog, the rate of ventricular ectopic activity decreased from the respective control values.

**Discussion**

The results of this study provide evidence that glucagon can augment the rate of cardiac pacemaker activity originating within the region of the atrioventricular node. The effect of glucagon on the A-V nodal or junctional rhythm is not prevented by previous administration of the beta-receptor blocking agent propranolol. The results agree with previous observations made with the hormone in which its chronotropic effects on sinoatrial pacemaker activity in the presence of beta-receptor blockade (4, 5) were examined. Similarly, studies on atrioventricular nodal transmission in the dog's heart indicate that glucagon increased A-V conduction velocity, an effect which was not prevented by propranolol (6, 7). It is of further significance to note that glucagon could restore A-V nodal rhythm when all rhythmic activity had ceased after destruction of the sinoatrial node and administration of propranolol. Furthermore, in three dogs (Table 1) that had idioventricular activity after destruction of the sinoatrial node, glucagon did not augment the activity of the idioventricular pacemaker. These findings are in agreement with similar observations made...
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by Steiner et al. (7), who reported that glucagon increased the speed of A-V conduction and abolished various degrees of A-V block without increasing ventricular automaticity.

Although glucagon appears to resemble the catecholamines with respect to its chronotropic and inotropic actions (1-5) as well as its effects on atrioventricular conduction velocity (6, 7), it differs from the catecholamines in that its cardiac effects are not prevented by specific beta-receptor blockade. In addition, unlike the catecholamines, glucagon does not possess a significant capacity to influence ectopic ventricular pacemaker sites. The inability to stimulate ectopic ventricular automaticity in the dog following myocardial infarction was in marked contrast to the results obtained with epinephrine. However, it must be recalled that the vasopressor effect of epinephrine would tend to cause a reflex-induced slowing of sinoatrial pacemaker activity that would facilitate catecholamine-induced ventricular escape. The reflex-induced vagal slowing of the heart would not occur with glucagon, since the drug has little effect on systemic arterial blood pressure (4, 5). In addition, Steiner et al. (7) were unable to demonstrate an effect of glucagon on idioventricular rate in the dog during continuous vagal stimulation. It is thus unlikely that the failure to observe enhanced ventricular automaticity in the infarcted heart of the dog can be attributed to the lack of enhanced vagal slowing of the sinoatrial node.

The effectiveness of glucagon as a positive inotropic agent in man has been demonstrated (8-10). Furthermore, Parmley et al. (9) and Brogan et al. (15) have administered glucagon to digitalized patients and observed no disturbances in cardiac rhythm during myocardial stimulation with glucagon. Similarly, Linhart et al. (10) did not see the ventricular automaticity often seen with other inotropic agents such as isoproterenol and epinephrine in their studies with glucagon. The results of the present study tend to support the previous observations and suggest that glucagon may be a valuable positive inotropic agent in clinical situations in which the potential danger of enhanced ventricular automaticity exists. Thus, after acute myocardial infarction and in the presence of cardiogenic shock, glucagon may be useful as an inotropic agent. Although similar to isoproterenol in many respects, glucagon has a longer duration of action (4) and lacks the potential for stimulating ventricular ectopic foci. Glucagon might also be of value in the management of patients with A-V heart block or other rhythm disorders associated with disturbances in the region of the A-V node. Until now, the only effective way of antagonizing the undesirable cardiac depressant effects of the beta-receptor blocking agent propranolol has been through the use of isoproterenol. The effectiveness of glucagon in the presence of beta-receptor blockade suggests another possible clinical use for the pancreatic hyperglycemic factor. Although large doses of glucagon have been reported to produce nausea and vomiting, the drug appears to be remarkably free of other acute side effects (8, 9).

References


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