Effects of Glucagon on Atrioventricular Conduction and Ventricular Automaticity in Dogs

By Charles Steiner, M.D., Andrew L. Wit, Ph.D., and Anthony N. Damato, M.D.

ABSTRACT

The effects of glucagon, 50 μg/kg, on atrioventricular (A-V) conduction and ventricular automaticity were studied in 14 dogs. Atrial pacing was used to control the heart rate. The His bundle electrogram was recorded, and the interval from the pacing impulse (P) to the His bundle spike (H), the P-H interval, was used as a measure of A-V conduction. Ventricular automaticity was estimated in four dogs by recording vagal escape time and idioventricular rate after 60 seconds of continuous vagal stimulation. In three dogs with experimentally produced, complete heart block the effect of glucagon on idioventricular rate was estimated. When the heart rate was 250/minute, glucagon decreased the P-H interval by 30 ± 3%, from 126 ± 5 to 85 ± 5 msec (P<0.01). When the heart rate was 310/minute, eight dogs demonstrated second-degree A-V block before glucagon; after glucagon, seven of the eight showed 1:1 A-V conduction. Glucagon increased heart rate by 38 ± 3.5%, from 148 ± 6.6 to 205 ± 8 beats/min (P<0.01). Propranolol, 2 mg/kg, did not block these effects on rate and A-V conduction. The vagal escape time and idioventricular rate with vagal stimulation and idioventricular rate in complete heart block did not change significantly after glucagon. Since glucagon profoundly increased the speed of A-V conduction without increasing ventricular automaticity, it may be useful in the treatment of A-V block especially in the presence of propranolol.

ADDITIONAL KEY WORDS

complete heart block  propranolol  vagal escape time

beta-receptor blockade  cyclic AMP

The effects of catecholamines on the heart are well known. These effects have been shown to be mediated via beta-receptor stimulation (1). Recent studies aimed at delineating the biochemical mechanism of beta-receptor stimulation have implicated the adenyl cyclase system as a prime participant (2). It is well known that the catecholamines are potent activators of this system (3). If activation of adenyl cyclase is the mechanism by which catecholamines exert their stimulating effects on beta receptors, other substances that increase the production of cyclic 3',5'-AMP from ATP may also exert stimulating actions on the heart similar to those of beta receptors. In two recent studies Glick et al. (4) and Lucchesi (5) have found that another potent activator of the adenyl cyclase system, the pancreatic hormone glucagon, possesses positive inotropic and chronotropic effects, thereby confirming and extending reports of earlier investigators (6-8). However, these effects could not be eliminated by blocking beta receptors, indicating a possible difference in the mechanism of catecholamines and glucagon on the heart.

The catecholamines are also known to exert
marked effects on certain electrophysiological properties of the heart; namely, they increase the speed of impulse transmission through the atrioventricular (A-V) node and increase the automaticity of latent pacemakers in the specialized conducting system of the ventricle (9-12). These effects are also believed to be mediated by beta-receptor stimulation and may also involve the adenyl cyclase system. Since glucagon has been shown to exhibit catecholamine-like effects on cardiac rate and force of contraction, it was of interest to determine its effects on these electrophysiological properties and to determine whether its effects if any, could be blocked by beta-receptor blockade.

**Methods**

The effects of glucagon on atrioventricular conduction and ventricular automaticity were studied in 14 mongrel dogs weighing 15 to 25 kg. The dogs were anesthetized with pentobarbital, 30 mg/kg, and after the trachea was cannulated, they were ventilated with room air by a Harvard respirator.

A rigid teflon catheter 10 inches long was passed into the left ventricle, via the right carotid artery, and connected directly to a Statham P23d strain gauge. Left ventricular pressure and its first time derivative (dP/dt) were recorded on an Electronics for Medicine switched-beam recorder.

In seven dogs the chest was entered through the fourth right interspace, and the pericardium was opened and sutured to the chest wall to form a cradle for the heart. Bipolar stainless steel wires (0.08 inches in diameter) with teflon insulation, except at the very tip, were placed into the region of the His bundle across the right atrial free wall and atrial cavity as described by Scherlag et al. (13). The position of the His bundle was estimated by palpation of the coronary sinus and tricuspid valve. With the wires in this position, a His bundle electrogram (Fig. 1) could be recorded; this consists of an atrial electrogram, followed by a sharp spike representing activity in the common bundle (H) and later by the ventricular electrogram.

In seven dogs the chest was not opened, and the His bundle electrogram was recorded via a catheter. Under fluoroscopic guidance, a tri- pectoral pacing catheter was placed across the tricuspid valve with its tip in the apex of the right ventricle. While recording between the two proximal electrodes, the catheter was moved back and forth across the inflow tract of the right ventricle until a clear and stable His bundle electrogram could be found (14). The low-frequency components below 500 cycles/sec were filtered to increase baseline stability and allow recognition of complexes resulting from depolarization of the specialized fibers (15). The recording of a His bundle electrogram enables the A-V conduction time to be determined with a higher degree of accuracy and reproducibility than by simply measuring the P-R interval. The electrical activity from the common bundle forms a discrete spike, signifying the end of A-V conduction time, and enables this variable to be separated from the conduction time in the His-Purkinje system of the ventricle, intraventricular conduction being represented by the H-S interval. In this study the beginning of A-V conduction was taken as the pacing artifact (P), although we...

**Figure 1**

Effect of glucagon on the P-H interval. P = pacemaker artifact, H = His bundle spike; A = atrial electrogram, S = ventricular electrogram, L2 = lead II of the electrocardiogram, and HBE = His bundle electrogram. Top: control, P-H interval = 116 msec. Bottom: after 50 µg/kg glucagon, P-H interval = 80 msec.
realize that our measurements include intraatrial conduction. The P-H interval is used rather than the A-H interval because the pacemaker spike is discrete and can be readily identified at any heart rate, even if the spike falls within the ventricular electrogram. Also, in no case was the interval between the pacing artifact and onset of the atrial electrogram found to vary by more than 1 to 2 msec, a change which is insignificant in comparison to the total intervals being measured. Atrial pacing was performed using an American Electronic Laboratories (model 104 A) stimulator. The stimuli were delivered via a bipolar catheter placed just below the junction of the right atrium and the superior vena cava.

Glucagon (Eli Lilly, lyophilized glucagon hydrochloride with accompanying diluent) was administered in varying doses intravenously. The sinus rate and A-V conduction time during atrial pacing at 200, 250, and 310/min were recorded before and after the glucagon administration. The conduction times were measured within 2 minutes after drug administration and then every 10 to 20 minutes for up to 60 minutes after administration of the drug to estimate its duration of action. In five dogs the effect of glucagon on A-V conduction was measured after beta-receptor blockade by propranolol, 2 mg/kg, (Ayerst Laboratories). Beta-receptor blockade was considered complete if the isoproterenol, 2 to 3 µg/kg, did not produce a significant inotropic or chronotropic effect.

The effect of glucagon on ventricular automaticity was assessed in three ways. First, the right vagus was isolated in the neck and sectioned. Bipolar electrodes were placed on the peripheral cut end and 6- to 10-v rectangular pulses of 3-msec duration were applied at a frequency of 30/sec (Grass Instruments Stimulator S8). The vagal escape time (16-18) (the time from the onset of vagal stimulation to the first ventricular escape beat) was recorded before and 2 to 5 minutes after the administration of varying doses of glucagon. Only those dogs that had a stable, reproducible vagal escape time with the same idioventricular focus appearing each time were used. Ten experiments were performed on four dogs.

In twelve experiments on five dogs vagal stimulation was continued for 60 seconds and the idioventricular rate recorded at that time. Glucagon was given and the procedure repeated within 2 minutes. The idioventricular rates were used only if the same focus was controlling the ventricles.

In three dogs complete heart block was produced by injecting 0.1 ml of 40% formaldehyde into the region of the His bundle (19). Once

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C = control, G = glucagon, N = not paced at this rate, and B = heart block with dropped beats. P value obtained by t-test for paired samples.
a stable idioventricular rhythm was established, and at least 30 minutes after the production of complete heart block, glucagon was given, and its effects on the idioventricular rate were recorded. In all these studies on automaticity, when more than one experiment was performed on the same dog, there was an interval of at least 60 minutes between doses of glucagon.

In each series of experiments, three dogs were given the diluent alone (1 ml).

**Results**

**Effects of Glucagon on Atrioventricular Conduction and Heart Rate**

Glucagon was administered to 11 dogs as a single bolus or in cumulative doses with the total dose being given in less than 10 minutes. As the results in the open- and closed-chested dogs did not differ, they will be presented together. Five of these dogs had both vagi cut, but as the results in these dogs were the same as those with the vagi intact, they will also be presented together. The maximal effect on A-V conduction time (P-H interval) along with its effects on heart rates is shown in Table 1. The H-S interval is not reported as it was not affected by glucagon administration.

Glucagon increased mean heart rate by 38%. Of the dogs whose heart rate was slow enough to allow pacing at 200/min before glucagon, only five could be paced after glucagon because of the increase in heart rate. In these five dogs the P-H interval decreased by an average of 28%. At a control pacing rate of 250/min, three dogs showed second-degree heart block. However, they all demonstrated 1:1 A-V conduction after glucagon administration. In the eight dogs that could be paced with 1:1 A-V conduction both before and after glucagon at 250/min, the P-H interval decreased by an average of 30%. Figure 1 shows the pronounced shortening of the P-H interval in the His bundle electrogram of one dog in this series. When pacing at 310/min, eight of the eleven dogs showed second-degree heart block but after glucagon ten of the eleven dogs demonstrated 1:1 A-V conduction.

In Figure 2 2:1 heart block is evident in the control tracings of a typical experiment, as indicated by the absence of a His bundle deflection and QRS complex after every al-

![Figure 1](image1.png)

**Abbreviations as in Figure 1.** Top: control tracing showing 2:1 A-V block, with a His bundle spike appearing only after the conducted beats. Bottom: after 50 μg/kg glucagon, tracing shows 1:1 A-V conduction, each pacemaker artifact being followed by a His bundle spike.
Effect of Increasing Doses of Glucagon on Heart Rate and Atrioventricular Conduction

Each dose given at 2-minute intervals with the total dose being given in less than 10 minutes.

The effects of increasing doses of glucagon are shown in Table 2. The doses were given in increments every 2 minutes with the total dose being given in less than 10 minutes. The maximal or near maximal effect on the P-H interval was obtained with relatively small doses (5 to 10 µg/kg). In experiment 7 and 8 it is shown that very small doses (2 to 4 µg/kg) may produce significant effects in A-V conduction even before they produce marked effects on heart rate.

In three dogs given only the amount of diluent given with doses of glucagon greater than 30 µg/kg, atrial fibrillation was noted. In the dogs with atrial fibrillation and bradycardia, the P-H interval was increased as compared to the control in a manner similar to that described by other investigators. The administration of small doses of glucagon (5 to 10 µg/kg) to these dogs resulted in a marked increase in heart rate, but no increase in P-H interval. This may be related to the increase in contractility of the atrial musculature produced by glucagon and, in turn, to the increased atrial rate when compared to the rate of the ventricle.

In the three dogs with 1:1 conduction before and after glucagon, the average decrease in P-H interval was 30%. It can be seen from Table 1 that all dogs showed a substantial decrease in P-H interval and that most dogs could be paced at a faster rate with 1:1 A-V conduction after glucagon had been administered.

The alternate pacing spike. This block was abolished by administration of 50 µg/kg of glucagon as can be seen in the lower tracing where each pacing spike is now followed by the His bundle deflection and ventricular depolarization. In the three dogs with 1:1 conduction before and after glucagon, at a cardiac rate of 310/min the average decrease in P-H interval was 30%. It can be seen from Table 1 that all dogs showed a substantial decrease in P-H interval and that most dogs could be paced at a faster rate with 1:1 A-V conduction after glucagon had been administered.
EFFECT OF GLUCAGON ON ATRIOVENTRICULAR CONDUCTION AFTER BETA-RECEPTOR BLOCKADE

Five dogs were given propranolol, 2 mg/kg, to produce effective beta-receptor blockade. This caused an increase in A-V conduction time so that only two of five dogs could be paced at 250/min, and none could be paced at 310/min without some degree of block. After glucagon (Table 3) all dogs showed 1:1 A-V conduction at heart rates of both 250 and 310/min. In the two dogs who could be paced at 250 beats/min before and after glucagon the decrease in the P-H interval was 43% and 40%. Figure 3 shows the results of one propranolol experiment. After 2 mg/kg of propranolol at a paced rate of 250/min, this dog exhibited Wenckebach periodicity, and every fourth beat was dropped. The completeness of the beta-receptor blockade is demonstrated by the persistence of block, even after 2 μg/kg of isoproterenol. The administration of 50 μg/kg of glucagon quickly restored 1:1 A-V conduction. In the five dogs, heart rate increased by an average of 48% (Table 3). Therefore the effects of glucagon on heart rate and A-V conduction were not blocked by effective beta-receptor blockade.

The duration of action of glucagon on A-V conduction is shown in Figure 4. The duration of action is dose-dependent. The effect of a 50 μg/kg dose decreased significantly after 20 to 30 minutes and returned approximately to baseline by 60 minutes. The four dogs given 20 μg/kg had all returned to control levels by 30 minutes.

The increase in dP/dt after 50 μg/kg of glucagon was of the same order as that described by Lucchesi (5) and by Glick et al. (4) (Fig. 5).

EFFECT OF GLUCAGON ON VENTRICULAR AUTOMATICITY

The change in vagal escape time (Table 4) is not statistically significant.

The effect of glucagon on idioventricular rate (Table 4) also showed a small but not statistically significant increase. Figure 6 shows the effects of vagal stimulation on a typical
The idioventricular rate in stable, complete heart block showed no significant change. Figure 7 demonstrates the effects of glucagon, experiment showing a small decrease in vagal escape time and a slight increase in heart rate.

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The duration of the effect of glucagon on A-V conduction. Abscissa: time in minutes after a single intravenous injection of glucagon. Ordinate: decrease in P-H interval expressed as a percent of the control level. In the four dogs given 20 µg/kg, all had returned to control levels in 30 minutes. In the five dogs given 50 µg/kg, all had returned to within 5% of control by 60 minutes.

50 µg/kg, on a dog in complete heart block. The marked increase in sinus rate and dP/dt can be seen with a very slight increase in idioventricular rate. At no time after the administration of glucagon in any of these experiments were ventricular premature contractions noted.

Discussion

This study shows that glucagon increases the speed of A-V conduction and abolishes various degrees of A-V block without increasing ventricular automaticity. The decrease in the P-H interval may be due to an increased rate of conduction in the atria, at the atrial A-V node region, in the A-V node itself, or at the A-V node to His bundle junction. Using our techniques, we could not localize the effect more precisely, and this important aspect must await microelectrode studies.

The increased chronotropic effect on the sinus node is in agreement with other investigators (4, 5, 7). In this study the chronotropic effect was not blocked or diminished by beta-receptor blockade. Glick et al. (4) found a decrease in the chronotropic effect of glucagon, but no change on the inotropic effect, after beta-receptor blockade and suggested that these two effects may be produced by different mechanisms. Our findings are in agreement with Lucchesi (5) who also showed no change in the chronotropic response to glucagon after propranolol. These effects of glucagon on the sinus and A-V nodes are qualitatively similar to the effects

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A-V CONDUCTION AND VENTRICULAR AUTOMATICITY

![Graphs and data showing changes in LVP and GLUCAGON](image)

**FIGURE 6**

Vagal escape time (VET) decreased slightly after glucagon, 50 μg/kg. The idioventricular rate (IVR) after 60 seconds of continuous vagal stimulation increased very slightly. These very small changes are not significant.

![Graphs and data showing changes in HR and LVP](image)

**FIGURE 7**

The effect of glucagon on the idioventricular rate in a dog in complete heart block. HR = heart rate, other abbreviations as in Figure 3. Top: control. Bottom: after glucagon which increased the sinus rate (P waves in L2) from a control of 110 to 200 beats/min. Left ventricular dP/dt also increased. A similar increase was seen in those cases where the idioventricular rate did not increase.

investigators believe that this effect can explain many of the known actions of the catecholamines on the heart, although this matter is far from settled (22). It has also been suggested that adenyl cyclase may be the adrenergic receptor or closely involved in adrenergic receptor activation (2). If adenyl cyclase activation and cyclic 3',5'-AMP formation are indeed involved in adrenergic receptor activation and form the common denominator for both the catecholamines and glucagon effects on the heart, the ability of propranolol to block the actions of the former without impairing the effects of the latter must be explained. Propranolol in doses as high as 3 mg/kg did not prevent the glucagon...
facilitation of A-V conduction. Previous reports by Lucchesi (5), and confirmed in this study, also indicate a failure of propranolol to block the inotropic and chronotropic effects of glucagon. It is possible that the activation of the beta receptor requires a series of steps with the catecholamines and glucagon acting at different sites in the pathway. Propranolol may block at the catecholamine receptor site, whereas glucagon may act after this site. However, this is a matter of conjecture.

If glucagon acts through beta-receptor stimulation, it also becomes difficult to explain its failure to increase ventricular automaticity. When the sinus pacemaker is inhibited by vagal stimulation, injection of 1 to 2 μg/kg of isoproterenol results in a marked shortening of ventricular pacemaker escape times and a multifocal ventricular tachycardia (18). This effect is prevented by beta-receptor blockade (23). These actions of isoproterenol may be explained by the effect of the catecholamines on increasing the slope of spontaneous phase-4 depolarization of Purkinje fibers in the ventricles (9, 10, 21). Our results indicate that glucagon does not shorten ventricular pacemaker escape time nor does it induce ventricular tachycardia, and thus it probably does not increase phase-4 depolarization of the Purkinje fiber.

Glucagon, then, appears to have effects similar to those of catecholamines on the sinus and A-V nodes but differs from drugs with known beta-receptor stimulating actions (e.g., isoproterenol) in two important ways. First, its effects are not inhibited by beta-receptor blocking drugs, and second, it does not appear to have a significant effect on latent pacemakers in the His-Purkinje system. This suggests that the cardiac effects of glucagon may not be due to stimulation of the beta receptors, but may be caused by a separate, direct effect of the hormone itself.

The ability of this drug to increase the rate of A-V conduction and inotropism without increasing ventricular automaticity makes glucagon a potentially useful drug in certain clinical circumstances. For example, it may prove to be of value after acute myocardial infarction with conduction disturbances where the increase in ventricular automaticity makes the use of catecholamines undesirable. Because propranolol is becoming widely used clinically, the occurrence of heart block in a patient receiving propranolol will become more common, and glucagon may be useful in these patients.

References
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