Glucagon-Enhanced Ventricular Automaticity in Dogs

ITS CONCEALMENT BY POSITIVE CHRONOTROPISM

By R. D. Wilkerson, J. K. Pruett, and E. F. Woods

With the Technical Assistance of T. E. Grover

ABSTRACT

Ventricular automaticity was studied in dogs with intact atrioventricular conduction systems and in dogs with surgically interrupted conduction systems before and after glucagon, 50 μg/kg. Results of these studies are in agreement with previous studies. When the influence of rate-dependent suppression of ventricular automaticity was nullified by comparing automaticity during periods of equal heart rates, highly significant increases in automaticity were observed in both preparations after glucagon administration. One index of automaticity, the number of ventricular beats occurring in a 30-second period following onset of vagal stimulation, increased from 8.7 ± 2.6 to 14.7 ± 3.1 after glucagon administration, an increase of 60%. The number of ventricular beats in a 30-second period following cessation of ventricular pacing increased from 8.6 ± 2.5 to 14.9 ± 2.1 after glucagon administration in dogs with heart block, an increase of 73%. Automaticity increases were also noted using other indexes. Beta-receptor blockade with propranolol failed to abolish automaticity changes effected by glucagon. This study demonstrated increases in ventricular automaticity produced by glucagon that heretofore had been overlooked, because a rate-dependent decrease in ventricular automaticity secondary to the positive chronotropic effect of this hormone masked the increases in automaticity.

KEY WORDS atrial pacing propranolol vagal escape complete heart block sinus rate ventricular pacing vagus nerves overdrive suppression tyramine

It has been recognized that glucagon possesses potent chronotropic and inotropic actions (1-3) similar to the well-known cardiac actions of the catecholamines. More recently, it has been suggested that the mechanisms of action of glucagon and the catecholamines are similar in that both may act by stimulating adenyl cyclase (4, 5). The actions of these hormones must, however, be mediated through different receptors, since beta-receptor blockade with propranolol has no effect on glucagon action (6).

In addition to the probability of different sites of action for glucagon and the catecholamines, recent reports indicate a difference in their effects on ventricular automaticity. Several authors have reported that glucagon has no effect on ventricular automaticity (7-9), whereas it has long been accepted that catecholamines are potent stimulants of ventricular automaticity. Disagreement does exist concerning the effect of glucagon on this parameter. Lipski et al. (10), in a preliminary report, noted an increase in ventricular automaticity after glucagon administration in dogs with intact conduction systems. Daniell

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et al. (11) reported similar results in dogs with chronic complete heart block. In the latter study, an increase in ventricular automaticity in dogs with acute complete heart block was noted for only 1 minute after glucagon administration. In a recent report from this laboratory, glucagon was shown to enhance the automaticity of isolated canine Purkinje fibers, a strong indication that it should increase ventricular automaticity in the in situ heart (12).

Increased sinus rate alone has been shown to depress ventricular automaticity (13, 14). This phenomenon, termed overdrive suppression, is easily noted as a period of ventricular asystole with slow recovery to a regular idioventricular rate during vagal stimulation (14). The duration of the asystole and recovery periods has been shown by Vassalle et al. (14) to be directly related to the sinus rate prior to vagal stimulation; the greater the sinus rate, the longer the period of ventricular asystole and recovery.

The purpose of this study was to examine the effects of rate-dependent inhibition of ventricular pacemakers on ventricular automaticity changes produced by glucagon in the dog heart.

Methods

Twenty-seven dogs of either sex weighing 10–20 kg were anesthetized with pentobarbital sodium, 30 mg/kg, iv. Positive pressure respiration was maintained with room air by a Harvard respirator. Catheters were placed in a femoral artery and attached to a Statham pressure transducer for the measurement of arterial blood pressure and in a femoral vein for drug injection. A standard lead II electrocardiogram (ECG) was monitored for rate measurements and pacemaker-site approximations. The dogs were divided into two groups: group 1 consisted of 10 animals with intact conduction systems, and group 2 consisted of 17 animals with complete heart block.

In group 1 the vagi were isolated in the cervical region and crushed. Shielded electrodes (Harvard Apparatus Co.) were placed on the distal ends of these nerves for subsequent stimulation. In the experiments reported here, only the right vagus was stimulated. The chest was opened via a midsternal incision, and a Walton-Brodie isometric strain-gauge arch with an adjustable foot was sutured to the anterior aspect of the right ventricle (15). The muscle segment subtended by the feet of the gauge was stretched approximately 40%. Contractile force and blood pressure recordings were used only as indicators of drug response, and changes in these parameters are not reported in this paper. Pacing electrodes were attached to the right atrium in the area of the sinus node for atrial pacing by a Grass S-4 stimulator.

Animals were allowed to stabilize for 30 minutes following surgery. Three successive determinations of ventricular automaticity were performed at 3-minute intervals by stimulating the distal end of the right vagus with a second Grass S-4 stimulator at a frequency of 30 impulses/sec, 3-msec duration. Stimulus intensity was adjusted to produce sinus arrest in each animal. Each determination was made during 1 minute of vagal stimulation following 2 minutes of sinus rhythm. The time to ventricular escape (period of ventricular asystole), the number of ventricular beats occurring in the first 30 seconds after onset of vagal stimulation, and the time (in seconds) necessary for ten ventricular beats to occur were taken as measures of ventricular automaticity. Decreases in ventricular asystole time and the time necessary for ten ventricular beats to occur and increases in the number of ventricular beats in 30 seconds were considered indications of enhanced ventricular automaticity. The results of the three determinations were averaged to obtain control values for ventricular automaticity. A study was considered valid only if no conducted beats were observed on the ECG.

Five minutes after the last control determination, glucagon 50 μg/kg (Eli Lilly, Glucagon Hydrochloride with accompanying diluent) was administered intravenously. The first determination of ventricular automaticity following glucagon administration was made when the drug effect had stabilized, as evidenced by a stable contractile force recording which usually occurred 1–2 minutes after glucagon injection. The second and third determinations were made at 3-minute intervals after the first determination using the same method employed in the control period.

In each experiment, a minimum of 80 minutes was allowed for glucagon action to subside. Hearts were then paced through atrial electrodes for 2 minutes at a rate equal to the sinus rate attained during glucagon stimulation. Ventricular automaticity during vagal stimulation after atrial pacing was evaluated by measuring the same parameters used in control and glucagon stimulation periods. Again, three determinations were made and the results were averaged to obtain driven values.

Preparation of animals in group 2 was similar to that for animals in group 1 with the following...
exceptions: (1) the chest was opened via a right thoracotomy; (2) complete heart block was produced by a heart cautery of the His bundle (16); (3) pacing electrodes were placed on the right ventricular free wall instead of the right atrium; (4) no vagal electrodes were employed. In ten animals, after all recorded parameters had stabilized, ventricular pacing was commenced at a rate equal to the sinus rate of the dog (as determined by ECG P-P intervals) and continued for 2 minutes. This rate is referred to as the control rate of the animals. Pacing was abruptly stopped, and the recovery to a regular ventricular rate was observed. The same indexes of ventricular automaticity used for group 1 were used for group 2, namely, asystole time, time necessary for ten ventricular beats to occur, and the number of ventricular beats occurring in 30 seconds after interruption of pacing. This procedure was repeated three times, and the results were averaged to obtain control values. As in group 1, glucagon (50 µg/kg iv) was administered and, after the drug effect had stabilized, sinus rate was noted from the ECG. Ventricular pacing was immediately initiated at this rate, referred to as the glucagon rate. Pacing was stopped after 2 minutes and recovery of automaticity observed. After the effect of glucagon had subsided, ventricular pacing was initiated at the same rate employed during glucagon action for 2 minutes and then stopped to determine the effects of this rapid rate alone on ventricular automaticity. Again, three determinations of ventricular automaticity were made and averaged. Values obtained in the above manner are referred to as driven rate values.

The pacing rates described for group 2 are summarized at this point to avoid confusion when interpreting the results. It should be noted that in group 2 three ventricular pacing rates were employed with each animal. First, a control rate which was equal to the control sinus rate of each animal. Second, a glucagon rate which was equal to the maximum sinus rate obtained during glucagon action and was utilized during the period of glucagon stimulation. Third, a driven rate, which was equal to the glucagon rate but was employed after glucagon action had subsided.

In addition, in five animals with complete heart block, the effect of glucagon on ventricular automaticity was tested in the presence of beta-receptor blockade produced by propranolol. In these experiments, propranolol 0.5 mg/kg, was administered to produce beta-receptor blockade, and this blockade was tested by injection of tyramine, 50 µg/kg. In all experiments, this dose of propranolol was sufficient to block the action of tyramine. After beta-receptor blockade was shown to be effective, glucagon, 50 µg/kg, was administered and, at the time of peak action, sinus rate was noted. Ventricular pacing was commenced at this rate for 2 minutes and abruptly stopped to evaluate automaticity. Three determinations were made and averaged to obtain glucagon values. After a 60-minute waiting period, all parameters had returned to control levels. Ventricular pacing was again commenced at the same rate employed during glucagon action and maintained for 2 minutes. Pacing was abruptly stopped to evaluate ventricular automaticity. Again, three determinations were made and averaged to obtain propranolol values. After the third determination, tyramine was again administered in the same dose as above to assure that beta-receptor blockade was still effective. Results obtained during glucagon action were compared to those obtained during propranolol action alone to determine the influence of catecholamine release on glucagon action.

The procedure followed for group 2 was intended to parallel as closely as possible procedures followed for group 1 so that results from the two preparations could be evaluated by the same criteria. However, no attempt was made to determine idioventricular rates for group 1, while in group 2 this rate was ascertained from ECG R-R intervals.

Two longitudinal studies were carried out on dogs with heart block to ascertain changes in automaticity which might have occurred spontaneously during the approximate time (90 minutes) necessary to complete each experiment. This was accomplished by making hourly evaluations of ventricular automaticity in two control animals. These hourly evaluations consisted of six individual determinations to simultaneously determine whether cumulative effects of overdrive suppression might be present. This was accomplished by statistical comparison of the first and third and first and sixth determinations in each case; a lack of statistical significance in each case would indicate the absence of cumulative effects.

In both experimental groups, all determinations during glucagon stimulation were made between 2 and 12 minutes after administration of the drug. In all experiments, arterial blood samples were obtained at regular intervals, and pH was measured on an Instrumentation Laboratories Blood Gas Analyzer. No significant changes in pH occurred in the course of individual experiments. All recordings were made on a Honeywell 1508 Visicorder and simultaneously recorded on magnetic tape with a Honeywell model 7600.

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1Propranolol was supplied by Ayerst Laboratories.
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TABLE 1

<table>
<thead>
<tr>
<th>Glucagon Effect in Ten Dogs with Intact Conduction Systems</th>
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<tbody>
<tr>
<td>Sinus rate</td>
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<tr>
<td>C</td>
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<tr>
<td>Mean</td>
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<td>st</td>
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</tbody>
</table>

Percent change: +53 † | −42 † | −40 ‡ | +11 † | +60 ‡ | −10 † | −33 ‡ |

C = control; G = glucagon; D = driven; Vent = ventricular.

†Atrial pacing at rate equal to maximum sinus rate attained during glucagon action.
‡Comparison made between control and glucagon.

magnetic tape recorder. All statistical computations were made by self-paired t-test analysis on a Wang model 700 computer.

Results

Glucagon Effect in Dogs with Intact Conduction Systems.—Data from these group 1 dogs are summarized in Table 1. Glucagon increased sinus rate from a control mean of 156.9 ± 8.1 beats/min to 239.5 ± 9.8 beats/min, a highly significant increase of 53% (P < 0.001). This was the only rhythm change noted; there were no premature ventricular beats in any experiment. Rate increases for individual experiments ranged from 25% to 93%. Only one of the three indexes of automaticity employed, the time necessary for ten ventricular beats to occur, indicated a significant increase in automaticity when results of the control period were compared with those of glucagon action, and this change was only of borderline significance. In this case, glucagon reduced the time from 28.5 ± 3.5 seconds to 25.6 ± 3.3 seconds, a decrease of 10% (P < 0.05). Asystole time was decreased by glucagon from 5.9 ± 1.3 seconds to 3.4 ± 1.5 seconds, but this change was not statistically significant (P < 0.10). The number of ventricular beats during the 30-second period after onset of vagal stimulation increased from 13.3 ± 2.7 to 14.7 ± 3.1, not a statistically significant increase (P < 0.20).

Comparisons made between the period of glucagon action and the period with hearts paced through atrial electrodes at rates equal to sinus rates during glucagon action, using the same indexes of automaticity, indicated statistically significant changes in all indexes. The time necessary for ten ventricular beats to occur after onset of vagal stimulation was decreased from 38.1 ± 4.9 seconds to 25.6 ± 3.3 seconds by glucagon, a change of 33% (P < 0.001). Asystole time was decreased by glucagon from 5.7 ± 2.1 seconds to 3.4 ± 1.5 seconds (P < 0.05); the number of ventricular beats during the 30-second period after onset of vagal stimulation was increased from 8.7 ± 2.6 to 14.7 ± 3.1 by glucagon (P < 0.001).

The results of a typical experiment from this group are illustrated in Figure 1, where it may be noted that the recovery of ventricular automaticity after vagal stimulation is greatly accelerated by glucagon when periods of equal heart rate (B and C) are compared, but little effect is evident if glucagon action is compared to control (A and B).

Glucagon Effect in Dogs with Acute Complete Heart Block.—Data from these group 2 dogs are summarized in Table 2. Glucagon increased sinus rate from 162.5 ± 6.7 to 252 ± 10.9 beats/min, an increase of 55% (P < 0.001). Spontaneous ventricular rate was similarly increased from 52 ± 3.2 beats/min to 75.4 ± 3.1 beats/min, a 10% increase (P < 0.025). The number of ventricular beats occurring in the first 30 seconds after ventricular pacing increased from 11.9 ± 2.1 during the control period to 14.9 ± 2.1 during glucagon

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Effect of glucagon on ventricular automaticity in an animal with intact conduction system. Tracings shown here are standard lead II electrocardiograms. A: control sinus rate (130 beats/min); B: glucagon action (sinus rate = 220 beats/min); C: atrial pacing (rate = 220 beats/min). Vagal stimulation was commenced at the arrow in each panel.

TABLE 2

Glucagon Effect in Ten Dogs with Acute Complete Heart Block

<table>
<thead>
<tr>
<th></th>
<th>Sinus rate</th>
<th>Asystole time (sec)</th>
<th>No. vent beats in 30 sec</th>
<th>Time to 10 vent beats (sec)</th>
<th>Spontaneous vent rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>G†</td>
<td>D†</td>
<td>C</td>
<td>G</td>
</tr>
<tr>
<td>Mean</td>
<td>162.5</td>
<td>252.0</td>
<td>252.0</td>
<td>11.9</td>
<td>14.9</td>
</tr>
<tr>
<td>SE</td>
<td>6.7</td>
<td>10.9</td>
<td>10.9</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Percent change</td>
<td>+ 55†</td>
<td>- 31†</td>
<td>- 78§</td>
<td>+ 25†</td>
<td>+ 73§</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001†</td>
<td>&lt; 0.40†</td>
<td>&lt; 0.025†</td>
<td>&lt; 0.025†</td>
<td>&lt; 0.001§</td>
</tr>
</tbody>
</table>

C = control; G = glucagon; D = driven; Vent = ventricular.
*Ventricular pacing rate equal to control sinus rate.
†Ventricular pacing rate equal to maximum sinus rate attained during glucagon action.
‡Comparison made between control and glucagon.
§Comparison made between driven and glucagon.
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Effect of glucagon on ventricular automaticity in an animal with complete heart block. Tracings shown here are standard lead II electrocardiograms. A: control rate (150 beats/min); B: glucagon rate (200 beats/min); C: driven rate (200 beats/min). Ventricular pacing was stopped at the arrow in each panel.

action, a statistically significant increase ($P < 0.025$) of 25%. When values at equal heart rates were compared (driven rate vs. glucagon rate), the number of beats during the 30-second period was increased from $8.6 \pm 2.5$ to $14.9 \pm 2.1$ by glucagon, a much more significant increase ($P < 0.001$) of 73%. The time necessary for ten ventricular beats to occur after ventricular pacing was decreased from $27.9 \pm 3$ seconds during the control period to $24.5 \pm 3.1$ seconds during glucagon action, a change of borderline significance ($P < 0.05$). This same index showed a much greater change when values for the glucagon rate were compared to those obtained at the driven rate; in this case, the time necessary for ten beats to occur was decreased from $41.1 \pm 7.6$ seconds to $24.5 \pm 3.1$ seconds by glucagon, a highly significant change ($P < 0.01$). Asystole time, the third index of automaticity, was decreased from a control value of $4.5 \pm 1$ seconds to $3.1 \pm 1.1$ seconds by glucagon, not a statistically significant change. When values at equal heart rates were compared (driven rate vs. glucagon rate), this parameter was significantly decreased ($P < 0.025$) from $14.1 \pm 4.4$ seconds to $3.1 \pm 1.1$ seconds by glucagon.

Results of a typical experiment from this group are illustrated in Figure 2, which shows that the recovery of automaticity was greatly accelerated by glucagon. This enhanced automaticity is evident whether the glucagon effect is compared to the effect during the-
control period (B vs. A) or the paced period (B vs. C).

Glucagon Effect on Ventricular Automaticity after Beta-Receptor Blockade.—In five animals after treatment with propranolol, glucagon increased ventricular rate from $31.0 \pm 3.6$ to $37.8 \pm 3.5$ beats/min, a statistically significant increase of 22% ($P < 0.005$). Asystole time was decreased from $13.4 \pm 4.7$ seconds to $5.7 \pm 3.5$ seconds by glucagon, but this change was not statistically significant. The number of ventricular beats occurring in the first 30 seconds after ventricular pacing was stopped increased from $2.5 \pm 0.6$ during propranolol action alone to $5.7 \pm 1.2$ after the administration of glucagon, indicating a significant increase in ventricular automaticity ($P < 0.025$). Similarly, the time necessary for ten ventricular beats to occur was decreased from $51.9 \pm 3.6$ seconds to $39.4 \pm 3.4$ by the administration of glucagon, indicating a significant increase in ventricular automaticity ($P < 0.025$).

In two control dogs with heart block, ventricular automaticity was evaluated periodically over a period of time equal to the duration of each experimental study. It was observed that automaticity was stable throughout this time as evidenced by lack of a statistically significant difference when observations at the beginning, middle, and end of this period were compared by self-paired t-test analysis. Furthermore, each evaluation was repeated six times, and comparisons were made of these results as described above. These comparisons showed no significant cumulative effect of overdrive suppression. That is, the first determination in each case was not significantly different from the third or sixth determination.

**Discussion**

Previous studies have led to some confusion concerning the effects of glucagon on ventricular automaticity. Steiner et al. (7) and Cohn et al. (9) reported that glucagon had no effect on ventricular automaticity in dogs with intact conduction systems. These investigators compared the rapidity of ventricular escape prior to and after administration of glucagon. Lucchesi et al. (8), using dogs with crushed sinoatrial nodes, also showed that glucagon had no effect on ventricular automaticity. On the other hand, Lipski et al. (10), using the vagal stimulation technique, found increased automaticity in dogs. Likewise, Daniell et al. (11) reported increased ventricular automaticity up to 30 minutes after glucagon administration in dogs with chronic complete heart block but only up to 1 minute in dogs with acute complete heart block. This latter finding is indeed confusing in light of a more recent report that the effects of glucagon on ventricular rate and other cardiovascular parameters in dogs with acute heart block are the same as those in dogs with chronic heart block (17). A further indication of increased ventricular automaticity was reported by Pruett et al. (12). This study demonstrated that automaticity in spontaneously beating false tendons was increased by administration of glucagon.

In most previous studies, evaluation of changes in ventricular automaticity in animals with intact conduction systems and animals with complete atrioventricular block have involved different methods. The most often used index of automaticity in animals with intact conduction systems has been ventricular escape time after vagal stimulation (7, 9, 10). Usually this has been assessed in terms of asystole time, but Cohn et al. (9) modified this procedure to measure the number of ventricular beats occurring in the first 30 seconds after onset of vagal stimulation (7, 9, 10). This study agrees well with those of Steiner et al. (7) and Cohn et al.
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(9) when data from the control periods are compared with those obtained after glucagon administration in dogs with intact conduction systems. Like those investigators, we were unable to show a change in ventricular automaticity using previously reported indexes. Lipski et al. (10), on the other hand, were able to show increased automaticity under these conditions. This latter group, however, noted premature ventricular beats or ventricular tachycardia in 55% of the animals studied, a finding in disagreement with most other workers (8, 9, 18).

When steps were taken to rule out effects of glucagon's positive chronotropic action on ventricular automaticity, a significant increase in automaticity was noted by all indexes. Here the animal was tested at equal heart rates during and after glucagon action. These results seem to indicate that the rate-dependent suppression of ventricular automaticity produced by the positive chronotropic action of glucagon effectively masks changes in ventricular automaticity produced by the hormone. The effect of this suppressive action of rate alone is apparent in Figure 1 when A is compared to C. When A is compared to B, it may be seen that the stimulant effect of glucagon on ventricular automaticity is hardly distinguishable. On the other hand, when the suppressive action of increased sinus rate is eliminated by making comparisons at equal heart rates (comparing B to C), it is evident that glucagon does, indeed, increase ventricular automaticity.

Experiments performed on dogs with acute complete heart block produced results similar to those for dogs with intact conduction systems. Although significant increases in automaticity were observed in two indexes between control and glucagon values, statistical significance was enhanced when rate was held constant. This fact is well illustrated in Figure 2, where increased ventricular automaticity after glucagon is evident when A and B are compared. This automaticity change is much more pronounced, however, when B and C are compared.

A fourth indication of increased ventricular automaticity after glucagon administration noted in this study was an increase in idioventricular rate in dogs with heart block. Increases of this magnitude have been reported previously in dogs with acute heart block, but these changes were not statistically significant (11). Similarly, Hurwitz (17) has reported increased ventricular rate in experiments on dogs with both acute and chronic heart block.

The inability of propranolol to block the effects of glucagon on ventricular automaticity in the present study is in agreement with previous reports indicating that propranolol does not block the inotropic (2, 6) or chronotropic (6, 7) responses to glucagon. Similarly, Stein et al. (7) and Whitsitt and Lucchesi (19) have shown that enhanced atrioventricular conduction produced by glucagon is not blocked by propranolol. Thus, although glucagon-induced catecholamine release has been reported, this action would seem unimportant with respect to the cardiac actions of glucagon (20). In the present study, the seemingly more pronounced changes in ventricular automaticity produced by glucagon after beta-receptor blockade may be due to the depressed state of automaticity resulting from propranolol administration.

It is not felt that glucagon-induced changes in serum potassium influenced automaticity changes reported in the present study. Cohn et al. (9) observed a transient hyperkalemia that peaked approximately 1 minute after glucagon administration and returned to near the control level 4 minutes later. Thus the triple determinations of automaticity made in the present study represent observations at near peak, during the fall, and after serum potassium had returned to control as indicated by the results of Cohn's group. Averaging of the results of these three determinations minimized the effect of the changing serum potassium level on automaticity. Furthermore, statistical comparisons made between the first and second, first and third, and second and third determinations showed no significant difference in these values, which indicated a stable level of automaticity.

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It would seem contradictory that an agent such as glucagon, which increases ventricular automaticity, could be effective in treating digitalis toxicity as Cohn et al. (9) have reported. When one considers, however, that the effect of glucagon on ventricular automaticity is masked by the rate-dependent suppression of automaticity produced by its positive chronotropic action, it is easily seen that no contradiction exists. In suggesting a mode of action of glucagon in digitalis toxicity, Cohn and his group (9) could not correlate this antiarrhythmic action with a glucagon reversal of the increased ventricular automaticity due to digitalis intoxication. Rather, it was suggested that the positive chronotropic action of glucagon plays a large role in this conversion by "outrunning" the ectopic pacemaker and by effectively reducing ventricular automaticity through the overdrive suppression phenomenon. The present study indicates that rather than a depression of automaticity by glucagon through the overdrive suppression mechanism, there is effectively no change in ventricular automaticity. That is, the direct stimulant effect of the hormone on automaticity is cancelled by the rate-dependent suppression in automaticity secondary to the glucagon-induced positive chronotropism. Thus one is left simply with increased sinus rate because glucagon over-rides the ventricular arrhythmia, just as atrial pacing at a rapid rate might be expected to do (21).

In conclusion, it has been shown that glucagon increases ventricular automaticity, but this increase may be masked by a rate-dependent depression of ventricular automaticity effected by the potent positive chronotropic action of the hormone.

References
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