

EFFECT OF GLUCAGON ON ARRHYTHMIAS INDUCED BY CORONARY ARTERY OCCLUSION AND OUABAIN IN DOGS

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Summary : The effect of glucagon in arrhythmias induced by coronary artery occlusion and ouabain was studied in dogs. Intravenous administration of glucagon ($50 \mu\text{g}/\text{kg}$) to 6 dogs with more than 70% ectopic activity after coronary artery occlusion, resulted in significant ($P < 0.01$) decrease in ectopics and increase in heart rate. Infusion of glucagon ($2.5 \mu\text{g}/\text{kg}/\text{min}$) for 30 min caused complete elimination of ectopic activity during infusion period. In another series of 7 experiments, glucagon failed to abolish the ouabain-induced ectopic beats. In fact the hormone itself caused a significant ($P < 0.01$) increase in ectopic activity and heart rate. However, in 7 dogs with complete heart block produced after ouabain, conversion to normal sinus rhythm was observed after glucagon.

Key words : glucagon arrhythmias ouabain coronary occlusion

INTRODUCTION

Glucagon, a polypeptide hormone secreted from the alpha cells of islets of Langerhans of pancreas, has recently been investigated for its cardiovascular action. Its positive inotropic action has been confirmed by numerous workers both in laboratory animals and man (5,8). It is not a cardiac depressant (4). Electrophysiological studies on heart have demonstrated increased A-V conduction velocity and A-V nodal automaticity after glucagon (1,12,17). However, conflicting results have been obtained in studies evaluating the action of glucagon on ventricular automaticity. Steiner *et al.* (18) and Lucchesi *et al.* (12) reported no increase in ventricular automaticity after glucagon in dogs, while increase in ventricular automaticity along with increase in S-A nodal and A-V nodal discharge rates have also been demonstrated in experimental animals (11,19) and man (7). A number of investigators have demonstrated that glucagon exerts an antiarrhythmic effect on arrhythmias produced by digitalis (1,14,17) and coronary artery occlusion (13). In addition, the usefulness of glucagon in patients with acute myocardial infarction has also been reported (3,16). The present study was undertaken to investigate the effect of glucagon in arrhythmias induced by coronary artery occlusion and ouabain in dogs.

MATERIAL AND METHODS

Coronary artery occlusion-induced arrhythmias; Adult mongrel dogs of either sex weighing 10 to 19 kg were anaesthetized with 30 mg/kg pentobarbitone sodium intravenously. A cuffed endotracheal tube was inserted in the trachea, and after instituting artificial ventilation under positive pressure, a left thoracotomy was performed in the left fourth intercostal space. The anterior descending branch of the left coronary artery was ligated in two stages as described by Harris (6). On the first postoperative day, glucagon was administered intravenously (50 $\mu\text{g}/\text{kg}$) to six animals with at least 70% ectopic activity as detected by E.C.G. In another set of 7 dogs glucagon was administered by slow intravenous infusion for half an hr, at the rate of 2.5 $\mu\text{g}/\text{kg}/\text{min}$. The E.C.G. recordings were made after 5, 20 and 30 min of single injection and at the same intervals during infusion.

Ouabain-induced arrhythmias; Mongrel dogs of either sex; (7 to 17 kg) were anaesthetized with pentobarbitone as above. An initial dose of ouabain (40 $\mu\text{g}/\text{kg}$) was given intravenously, and 30 min later, an additional dose (20 $\mu\text{g}/\text{kg}$) was given. Further, the dose was increased by 10 $\mu\text{g}/\text{kg}$ every 15 min till the average dose was 80 $\mu\text{g}/\text{kg}$. Glucagon (50 $\mu\text{g}/\text{kg}$) was administered immediately after the last dose of ouabain. E.C.G., recordings were made before, and after 5, 10 and 15 min of glucagon injection. The experiments were divided into two groups i.e. those where ouabain produced tachyarrhythmias and those where it produced heart block.

RESULTS

Arrhythmias after coronary artery occlusion; In all of the six coronary artery ligated dogs intravenous bolus injection of glucagon (50 $\mu\text{g}/\text{kg}$) produced a marked reduction in ectopic beats. The antiarrhythmic effect lasted from 5 to 20 min of injection. The effect of glucagon disappeared after 30 min of injection. In all the six dogs, there was an increase in ectopic rhythm, including appearance of ventricular tachycardia after 30 min of injection of glucagon. The results are given in Table I and illustrated in Fig. 1.

In another series of 7 experiments, intravenous infusion of glucagon (2.5 $\mu\text{g}/\text{kg}/\text{min}$) for 30 min caused complete elimination of ectopic activity along with increase in heart rate during infusion period, but ectopic beats reappeared in all the experiments after 30 min of stopping the infusion.

Ouabain-induced arrhythmias; Intravenous administration of glucagon (50 $\mu\text{g}/\text{kg}$) failed to abolish ouabain-induced tachyarrhythmias in 7 dogs; rather the hormone itself

caused a significant ($P < 0.01$) increase in ectopic activity. The mean ectopic activity in ouabain treated dogs was 175.1 ± 16.05 which increased to 234.1 ± 8.25 after glucagon injection (Table II). In 7 dogs, which developed complete heart block following ouabain, conversion to normal sinus rhythm was observed following glucagon administration (Fig. 2). However, 30 min after glucagon few ectopics did appear in all the animals.

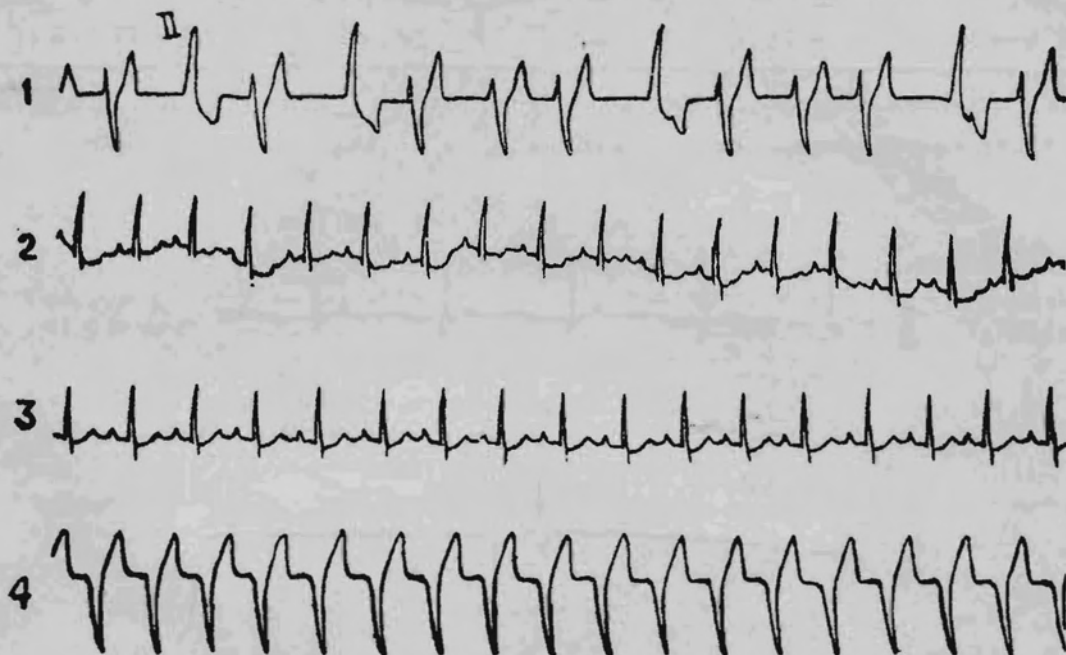


Fig. 1 : E.C.G. (Lead II) record showing effect of glucagon on ventricular arrhythmias produced by coronary artery occlusion.

- (1) Ventricular arrhythmias after coronary artery occlusion.
- (2) 5 min after glucagon.
- (3) 20 min after glucagon.
- (4) 30 min after glucagon (reappearance of ectopics).

TABLE I : Effect of glucagon ($50 \mu\text{g}/\text{kg}$) on heart rate and ectopic rhythm in dogs (6) on the second day after occlusion of coronary artery.

*Before (beats/min. Mean \pm S.E.)		After (beats/min. Mean \pm S.E.)			P value
		5 Min.	20 Min	30 Min.	
Heart rate	208.3 ± 7.85	253.3 ± 10.87	234.0 ± 10.80	248.7 ± 8.46	$P < 0.01$
Ectopic beats	176.2 ± 9.36	7.63 ± 7.55	—	229.7 ± 9.62	$P < 0.01$

*Standard for comparison (Paired "t" test)

TABLE II : Effect of glucagon (50 $\mu\text{g}/\text{kg}$) on heart rate and ectopic rhythm in ouabain induced arrhythmias in dogs (7).

	Beats/min (Mean \pm S.E.)			P values
	Control	After ouabain	After glucagon	
Heart rate	*149.6 \pm 10.94	217.4 \pm 16.35	248.9 \pm 9.84	P < 0.01
Ectopic beats	—	**175.1 \pm 16.05	234.1 \pm 8.25	P < 0.01

*Standard for comparison for heart rate
 **Standard for comparison for ectopic beats } Paired "t" test.

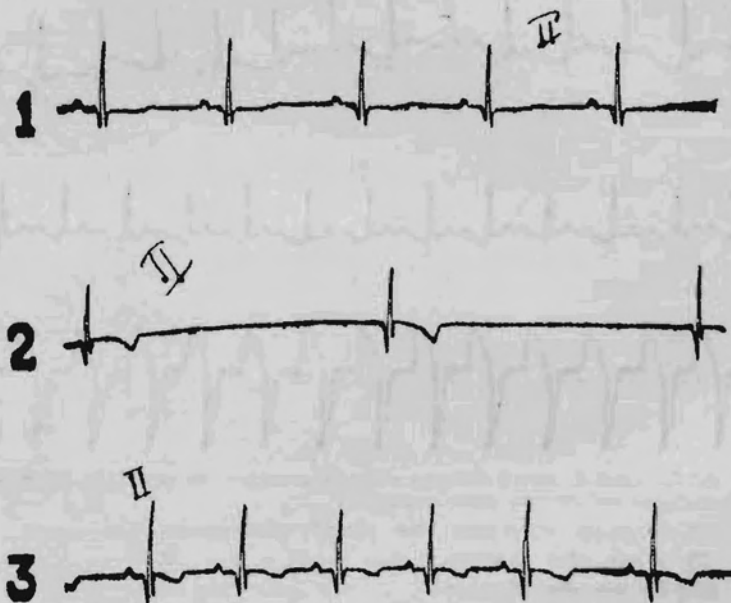


Fig. 2 : E.C.G. record showing the effect of glucagon (50 $\mu\text{g}/\text{kg}$) on heart block produced by ouabain in dog
 (1) Control Lead II record.
 (2) Heart block after ouabain.
 (3) After glucagon (normal rhythm).

DISCUSSION

Although the antiarrhythmic effect of glucagon on arrhythmias produced by digitalis (1,14) and coronary artery occlusion (13) has been reported. The available reports to show its effect on ventricular automaticity (12,18,19) are conflicting.

In the present study, administration of glucagon caused complete suppression of ectopics with restoration of normal sinus rhythm in dogs after coronary artery occlusion. However, the effect was short-lived. Similar observations have been made by Madan (13) in dogs using 30 and 100 $\mu\text{g}/\text{kg}$ glucagon. There were two interesting findings in the present study - (a) an increased ectopic activity following a short lived anti-arrhythmic activity of glucagon and (b) positive chronotropic effect of glucagon during anti-arrhythmic as well as arrhythmic phases of action. It could be surmised that the strong positive chronotropic action of glucagon might indirectly suppress ventricular automatic sites, resulting in antiarrhythmic action. However, this does not appear to be so. It seems that glucagon has two independent actions - (a) positive chronotropic activity and (b) a short-lived immediate anti-arrhythmic followed by arrhythmogenic activity. The former action is on the pacemaker and the latter on the ventricular automaticity.

In the present study the effect of glucagon was analysed separately on the two types of ouabain-induced arrhythmias- tachyarrhythmias and bradyarrhythmias. In cases of tachyarrhythmias, glucagon failed to restore sinus rhythm, rather the hormone itself caused a marked increase in ectopic activity. A positive chronotropic effect was seen after glucagon in all the animals. These findings are not in agreement with the antiarrhythmic action of glucagon reported by other workers in ouabain-induced arrhythmias in dogs (1, 2, 20). These workers suggested that the positive chronotropic effect of glucagon plays a great role in the antiarrhythmic action by out running the ectopic pacemaker and by effectively reducing ventricular automaticity through overdrive suppression phenomenon. However, in the present study, the ectopic activity was not reduced inspite of a positive chronotropic activity of glucagon. In dogs with ouabain-induced complete heart block, glucagon administration produced immediate conversion to normal sinus rhythm. There was also significant increase in the heart rate. These results are in agreement with those of Lucchesi *et al.* (12) who have also reported a complete abolition of A-V block by glucagon. Thus in the presence of A-V block, it promotes A-V conduction (10,12,18) and increases sinus automaticity.

The present study shows that glucagon (a) has a short lived antiarrhythmic action and a delayed arrhythmogenic action in coronary artery ligation induced arrhythmias, (b) aggravates ouabain-induced tachyarrhythmias, (c) reverses ouabain-induced bradyarrhythmias, and (d) has a positive chronotropic action.

The positive chronotropic action and arrhythmogenic actions and the beneficial action of glucagon in ouabain-induced bradyarrhythmias may be related to its action on

adenylate cyclase system increasing cardiac cyclic AMP concentration (9,15). The antiarrhythmic action may possibly be due to short-lived decrease in ventricular automaticity.

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