Effects of Glucagon on a Multistressed Circulation*

Gaeton T. Nola, B.S.;** Ricard E. Kerber, M.D.;† Pamela E. Stacks; and Donald C. Harrison, M.D.

The effectiveness of intravenous glucagon in improving myocardial function during conditions when exceptional loads have been added has been evaluated in three groups of eight instrumented, anesthetized, open-chest dogs. Glucagon (5 mg/kg/min) was infused continuously for 20 minutes after a series of hemodynamic stresses had been applied. These stresses consisted of cardiovascular depression secondary to propranolol (2 mg/kg) and volume loading (20 ml/kg); experimental myocardial infarction produced by coronary artery ligation; and ligation of the thoracic aorta. Depression due to beta blockade alone resulted in significant increases in mean left atrial pressure and systemic vascular resistance and decreases in left ventricular dp/dt, right ventricular contractile force, heart rate, and cardiac output. The induction of myocardial infarction caused significant increase in mean atrial pressures and marked decreases in left ventricular systolic pressure, cardiac output, and stroke volume, while ligation of the thoracic aorta after myocardial infarction produced marked elevation of systemic vascular resistance, mean aortic pressure, left ventricular systolic pressure and decreases in heart rate as well. Significant hemodynamic improvement after the administration of glucagon was observed during each stress or combination of stresses, and consisted of marked increases in left ventricular dp/dt, right ventricular contractile force, heart rate, and cardiac output and decreases in mean right and left atrial pressures and in systemic vascular resistance. Elevation of aortic pressure and left ventricular systolic pressure, in addition, was seen in maximally stressed animals. Glucagon also attenuated rises in atrial pressure produced by volume loading of stressed animals. Improvement in hemodynamic variables was probably not due to the positive chronotropic actions of the drug, but due to its positive inotropic effects, since pacing to rates equivalent to those attained by the administration of glucagon did not improve significantly the hemodynamic status of the animals.

During the years following the first description of the cardiovascular effects of glucagon by Farah and Tuttle,† glucagon has been shown to have positive inotropic and chronotropic effects on the hearts of animals,⁴⁄̴ and of human beings.⁴⁄̴³ During this time several studies have been carried out to demonstrate its hemodynamic properties and effectiveness in enhancing cardiac function under many conditions of added stress or load. Most of these studies utilized bolus injections of glucagon to produce the desired hemodynamic effect. It has been demonstrated subsequently that although glucagon's action was mediated via adeny] cyclase activation² like that of norepinephrine, its action was not blocked by beta adrenergic blocking drugs such as propranolol²⁴ nor did glucagon act through release of endogenous catecholamines.³ Studies have shown also that glucagon possesses antiarrhythmic potential while not increasing myocardial automaticity by enhancing AV nodal pacemaker activity.⁵ Moreover, in clinical and experimental models, glucagon has been demonstrated to enhance cardiac function after acute myocardial infarction and concomitant failure.⁶⁄⁷⁄⁸⁄⁹⁄¹⁰⁄¹¹⁄¹²⁄¹³ while reported results are somewhat ambiguous when dealing with chronic heart failure.⁹

This study evaluates further the effectiveness of glucagon in reversing profound hemodynamic depression resulting from multiple, acute stresses or additional loads on the heart and circulation produced by beta blockade, acute experimental myocardial infarction, and large increases in preload and afterload. Furthermore, the experiments were designed to determine the effects of prolonged infusion of glucagon rather than the effect noted...
after a single bolus.

**METHODS**

Studies were performed on 24 mongrel dogs weighing 10 to 20 kg. The animals were anesthetized with a mixture of alpha-chorolose (80 mg/kg) and urethane (500 mg/kg) with small supplemental doses administered as necessary during the course of each study to maintain a light plane of anesthesia.

A midsternal thoracotomy was performed and the animals were instrumented for hemodynamic measurements. Polyethylene 260 catheters were introduced into the central aorta via the right femoral artery and into the right atrium via the left femoral vein in order to monitor central aortic and right atrial pressures, respectively. Left atrial pressure was measured through a catheter via a stab wound in the appendage. All pressure catheters were connected to Statham P23Db pressure transducers. Left ventricular pressure was monitored using a Whittaker Model 1017 (variation 0026) implantable blood pressure transducer introduced directly into the left ventricle through a stab wound through the apex of the heart and secured by means of a purse-string suture. This transducer has a full scale pressure range of ±10 to ±500 mm Hg with an output signal of 30 mV (300 mm Hg). Range of thermal error is ±2 mm Hg/C*; linearity: ±1 percent full scale, maximum; and frequency response is dc to 5 kHz ±1 percent. The rate at which left ventricular pressure develops, LV dp/dt, was recorded directly from the left ventricular pressure curve by means of an RC differentiator with a frequency response to 35 cps; this parameter was used as an indication of myocardial contractility. Additionally, a Honeywell myocardial force transducer was sewn to the anterior wall of the right ventricle as a measure of right ventricular contractility. The right femoral vein was cannulated for drug administration and blood samples.

Mean aortic blood flow, or cardiac output, was measured by means of a gated sine-wave electromagnetic flowmeter (Biotronix), placed distal to the coronary arteries on the ascending aorta. Each flowprobe was calibrated using a mechanical flow simulating device with body temperature controlled heparinized blood. Standard lead II of the electrocardiogram was monitored continuously. All recordings were made on a Beckman Model R direct-writing oscillograph. Stroke volume was calculated by dividing mean cardiac output by heart rate, and systemic vascular resistance by dividing the difference of mean aortic and mean right atrial pressures by the cardiac output.

Ventilation was maintained with a Harvard respirator through auffed endotracheal tube and was regulated to insure a physiologic pH and correct oxygenation. Blood samples taken from the femoral arterial cannula were analyzed for PO2, PCO2, and pH using a Model AME-1 Astrup ultramicro apparatus. The pH electrode was calibrated daily with standard solutions, and duplicate pH determinations on blood samples were found to vary no more than ±0.01 pH units. The PO2 was determined with a modification of the Clark PO2 electrode, and duplicate determinations varied no more than 3 mm Hg. The animals were kept within physiologic range with regard to these parameters. Ranges of average pH for the three groups were from 7.37 ± .13 to 7.43 ± .18; ranges of PO2 were 95.5 ± 7.6 to 113.9 ± 22.6 mm Hg; and mean PCO2 ranged from 18.2 ± 0.9 to 28.7 ± 5.1 mm Hg. Venous blood samples from the femoral vein were taken, and the serum potassium levels were determined with an IL Model 143 flame photometer. No significant changes were seen in serum potassium after glucagon administration.

Combinations of experimentally induced hemodynamic stresses were performed on three groups of eight dogs each (Table 1). All animals were subjected to myocardial depression with propranolol (2.0 mg/kg, over two minutes) and all were given a constant infusion of glucagon (5.0 µg/kg/min for 20 minutes, a total of 100 µg/kg) after the circulation had been maximally depressed. Every animal was volume loaded with 20 ml/kg of 6 percent dextrose before propranolol was given, as an initial stress; an equal volume of heparinized blood was then removed to return blood volume to normal. Subsequently blood volume was increased in like manner by infusing this blood (at 37°C) back into the animal after propranolol and during glucagon infusion so that the stress of the volume load was evaluated alone, superimposed upon beta blockade, and during glucagon. Isoproterenol (0.25 µg/kg) was administered as a bolus before and after propranolol to test quantitatively for beta blockade, followed by a 15 minute waiting period for stabilization and elimination of the drug. In order to control heart rate, fishhook type pacing electrodes and a Grass stimulator were used to increase heart rate by chronotropic depression due to beta blockade and before glucagon so that the effects of increased heart rate alone on the various stresses could be compared to the effects of glucagon (inotropic as well as chronotropic).

In addition to the stresses of increased preload (volume load) and beta blockade, animals in groups 2 and 3 were also subjected to acute myocardial infarction, which was produced by ligation before volume load and propranolol were administered. Coronary arterial branches of the anterior descending and circumflex branches of the left coronary artery, not visibly supplying the septum, were ligated so that an infarct of approximately 35 percent by weight was restricted to the apex and lower half of the left ventricular wall. Ligation time was usually 20 minutes. To suppress ventricular arrhythmias during ligation, lidocaine, 0.5 mg/min was infused using a Harvard infusion pump, and 1 ml quantities of 1 mg/ml lidocaine were applied directly to the myocardial surface every five minutes. After completion of ligation and discontinuance of lidocaine, a 30-minute recovery period was allowed for elimination of the drug from the system (lidocaine half-life in plasma is approximately 13 minutes) and clinical effects last for only 10 to 20 minutes) and for stabilization of all monitored parameters postinfarction. It has been observed in earlier control studies where dogs were

**Table 1—Protocol Summary.**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Animals</th>
<th>Stress</th>
<th>MI</th>
<th>Coaret</th>
<th>VL</th>
<th>Beta-Blockade</th>
<th>Glucagon</th>
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<td>+</td>
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</table>

Abbreviations: MI = Myocardial infarction, coronary ligation; VL = Volume load.

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*Crystalline glucagon was obtained from Eli Lilly and Company. The drug was dissolved in its accompanying diluent, a solution containing glycerin (1.6 percent) and phenol (0.2 percent).
infarcted in an identical manner and monitored for three hours that 30 minutes postinfarction was sufficient for stabilization, and thereafter, no significant changes in the circulation resulted for 3 hours and termination of the experiment.16

The percentage of nonperfused area of the myocardium was determined by injecting Evans blue dye into the right and left coronary ostia of the intact, excised heart. The left ventricular wall and interventricular septum were separated and weighed. The nonperfused portion of the free left ventricle, unstained by dye, was dissected out and weighed. The percentage infarction was expressed as the percent weight of the total left ventricle (including septum).

The animals comprising group 3 were stressed further by ligating the descending thoracic aorta after infarction, and before volume loading and propranolol, thus increasing afterload in addition to group 2 stresses. Otherwise the protocol remained the same as in groups 1 and 2. Sufficient stabilization times of 10 to 20 minutes were allowed after each applied stress so that cardiovascular parameters were stable before each subsequent stress or before glucagon was infused (see Table 1 for a summary of experimental groups and protocol).

**DATA SECTION**

**Effects of Hemodynamic Stresses on the Circulation**

Acute volume loading with 20 ml/kg of 6 percent dextran caused significant rises in mean right and left atrial pressures in all groups both before and after the animals were stressed. Group percentage increases ranged from 50 percent to 180 percent. Mean aortic pressure (AoP) rose significantly only after propranolol; mean left ventricular systolic pressure (LVP) was also increased with a volume load. Left ventricular dp/dt (LV dp/dt) increased with volume load, but as further hemodynamic stresses were applied no significant change was observed; marked changes in right ventricular contractile force (RVCF) and heart rate (HR) were not observed. Cardiac output (CO) and stroke volume (SV) increased significantly, mean percentage changes ranging from 30 percent to 120 percent for CO and from 30 percent to 130 percent for SV. Systemic vascular resistance (SVR), however, was decreased with volume load alone and also when "moderate" stress was preexisting (beta blockade and MI).

Significant increases in mean right and left atrial pressures were consistently observed post-MI (group 2) and post-MI + coarct (group 3) and ranged from 30 percent to 130 percent. While MI alone caused marked decreases in LVP (10 percent), CO (15 percent), and SV (20 percent), "maximal" stress with the addition of aortic ligation further produced significant increases in mean AoP (20 percent) and LVP (17 percent) and a decrease in HR (10 percent). A 40 percent (but not significant) rise in SVR was noted.

Beta blockade, along with its concomitant hemodynamic depression, was produced by propranolol (2.0 mg/kg) and was essentially complete in that all significant hemodynamic responses to bolus injection of isoproterenol (0.25 μg/kg) were not observed after the administration of propranolol. Cardiovascular depression due to blockade consisted of significant increases in mean left atrial pressure (65 percent to 120 percent) and SVR (40 percent to 100 percent) in all three groups and marked decreases in LV dp/dt (55 percent to 60 percent), RVCF (30 percent), HR (25 percent to 30 percent), and in CO (25 percent to 45 percent).

**Hemodynamic Effects of Glucagon in Stressed Animals**

Significant hemodynamic improvement was seen during a constant infusion of glucagon (5.0 μg/kg/min) under each stress or combination of stresses. Glucagon caused significant decreases in both mean right (25 percent to 30 percent) and left (30 percent to 55 percent) atrial pressures in all animals under "moderate," "severe," and "maximal" stress (Fig 1). Also, in all groups LV dp/dt decreased (90 percent to 180 percent) as did RVCF (80 percent to 145 percent); HR increased (50 percent to 60 percent) with "moderate" and "se-
EFFECTS OF GLUCAGON ON MULTISTRESSED CIRCULATION

FIGURE 2. The effects of glucagon on left ventricular dp/dt (LV dp/dt) (top) and right ventricular contractile force (RVCF) (bottom).

vere" stress, and CO increased (60 percent to 85 percent) with "severe" and "maximal" stress (Fig. 2, 3). Mean AoP fell (15 percent) in group 1 ("moderate" stress) and group 2 ("severe" stress) animals after glucagon, while LVP did not change significantly except in group 3 ("maximal" stress) animals, in which a marked increase (25 percent) was noted. In all the groups of stressed animals, glucagon caused a significant decrease in SVR (25 percent to 40 percent) (Fig 3), and SV was observed to increase (50 percent) only while under "severe" hemodynamic stress. Moreover, glucagon administration seemed to lessen filling pressure changes due to volume load under stress, in that smaller increases in atrial pressures were noted secondary to volume loading. Before glucagon administration all animals were paced to heart rates comparable to those attained with glucagon. It was observed that such an increase in heart rate alone in a depressed animal increased atrial pressures and did not change LV dp/dt, RVCF, CO, SVR, nor SV significantly, unlike the results of glucagon. The duration of action of glucagon in these groups of animals usually ranged from 20 to 30 minutes after the infusion of glucagon was stopped.

FIGURE 3. The effects of glucagon on cardiac output (CO) (top) and systemic vascular resistance (SVR) (bottom).

DISCUSSION

The administration of glucagon as a bolus injection, or by series of bolus injections, has previously been shown to produce a positive inotropic and chronotropic response. In our studies, in which a series of cardiovascular stresses were produced, glucagon was given as a continuous intravenous infusion, and it was also shown that glucagon has positive inotropic and chronotropic actions on the heart. Thus, our studies confirm the results with glucagon from a variety of previous reports in which single cardiovascular stresses were studied.

In this study, circulatory depression was produced by the administration of large doses of propranolol. Elevations in ventricular filling pressures, reductions in heart rate and cardiac output, and elevation of peripheral vascular resistance were produced by this beta blockade. In these animals, volume loading produced further deterioration of cardiovascular function. The intravenous infusion of...
glucagon resulted in increases in heart rate and myocardial contractility, an increase in cardiac output, and lowering of ventricular filling pressures. Although beta adrenergic blockade was produced to such an extent that multiple injections of isoproterenol produced no positive inotropic actions, glucagon continued to be active. Therefore, it is concluded that glucagon exerts its inotropic and chronotropic effects by a mechanism different from that of isoproterenol. It has been suggested that this agent is active by a mechanism other than that mediated through catecholamines and our studies confirm these observations. Thus, in patients who might be receiving propranolol and experience some type of circulatory stress, glucagon would appear to be the agent of choice for treatment.

A second level of circulatory stress was produced by ligation of coronary arteries to produce myocardial infarction in addition to the stress of total beta blockade by propranolol. The combination of these two circulatory stresses produces even greater depression of cardiac function. In these studies, glucagon given by infusion continued to be effective in lowering ventricular filling pressures, elevating cardiac output, and increasing heart rate and contractility. Thus, the inotropic and chronotropic effects of glucagon were evident in this "severely" stressed circulation.

In addition to the other circulatory stresses, ligation of the aorta to increase afterload was performed in a third group of animals. The circulatory stresses produced in these animals resulted in further marked depression of the overloaded and seriously damaged heart. Nevertheless, glucagon given by infusion continued to enhance circulatory function and produce decreases in atrial pressures, while increasing cardiac output and cardiac contractility.

Our studies were designed to determine whether or not glucagon would continue to be effective when given as a continuous intravenous infusion. At all levels of circulatory stress, glucagon proved to be an effective myocardial stimulant producing both positive inotropic and chronotropic effects over prolonged periods of time when given by infusion. These studies confirm the action of the drug when given as a single bolus, and extend these findings to reaffirm in a more direct manner the clinical observation that long-term administration by intravenous infusion will be effective in enhancing cardiac function. Clinical studies using infusions of glucagon ranging from two minutes to five days for treatment of low cardiac output states, congestive heart failure, and ventricular failure following acute myocardial infarction have reported clinical improvement with moderate (25 percent) inotropic enhancement.

The beneficial effects of glucagon were clearly not due to increases in heart rate alone. When atrial pacing rates equivalent to those obtained by infusion of glucagon were achieved, there was little improvement in hemodynamics. No significant changes in left ventricular dp/dt, contractile force as measured by strain gauge, or cardiac output occurred. In fact, during atrial pacing, there was elevation of left and right atrial pressure, as opposed to the decline seen during the infusions of glucagon. This perhaps indicated a deleterious effect of increasing heart rate alone. The improvement in the hemodynamic status of the animals in all levels of stress was related to the positive inotropic effects of glucagon.

It was apparent that progressive graded increases in cardiac insults produced by pharmacologic depression, myocardial infarction, and acute aortic ligation to increase afterload did not markedly attenuate the response to infusions of glucagon. In one group of animals, namely those treated with large doses of propranolol to block adrenergic receptors, the intravenous administration of glucagon produced only slight increases in cardiac output and falls in left atrial pressure. However, in the group of animals in which severe cardiovascular stress had been produced, both of these parameters changed in a highly significant manner. Thus, glucagon's effectiveness was greater as acute circulatory depression was increased. This is more apparent when percent changes are presented than when absolute changes are considered. However, the effects of glucagon may be different in cases of more chronic myocardial stress. Clinical and experimental studies have shown little or no improvement with this drug in cases of long-standing cardiogenic shock or chronic heart failure.

An interesting incidental finding was the appearance of ventricular premature beats during the administration of glucagon in six animals in groups 2 and 3. Cohn and associates found that bolus doses of glucagon abolished digitalis-induced ventricular irritability in 26 of 36 dogs, an effect they concluded was attributable primarily to a glucagon-induced sinus tachycardia, with "overdrive suppression" of the arrhythmia. Also noted in their studies was a transient rise and then a fall in serum potassium levels. In our studies, no consistent changes in serum potassium were observed. This probably was the result of the slower rate of glucagon administration which was used. This may also account for the ventricular irritability which was encountered, although other possible mecha-
nisms may explain this observation.

In summary, prolonged intravenous infusions of glucagon produce positive inotropic and chronotropic response in animals subjected to circulatory stresses. Moderate circulatory stress was produced by the administration of doses of propranolol large enough to block the circulatory response to isoproterenol. In these animals, glucagon produced improvements in cardiac function. In other groups of animals, acute myocardial infarction was produced by coronary artery ligation and the aorta was ligated to change afterload. Glucagon continued to exhibit positive inotropic and chronotropic effects in these animals. Atrial pacing to rates equivalent to those achieved by the intravenous administration of glucagon did not result in improvement in hemodynamics. Thus, we conclude that in addition to its positive chronotropic actions, glucagon has positive inotropic effects which constitute the primary mechanism for enhancement of cardiac function.

REFERENCES
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8 Matloff JM, Parmley WW, Manchester JH, et al: Hemo-

Editorial Expression

This study confirms the inotropic effect of glucagon in acutely induced hemodynamic stress of varying severity. There has not been extensive clinical experience with this agent in the treatment of low output states. Nevertheless, glucagon appears to be a useful agent when given as an intravenous infusion to patients with congestive heart failure or cardiogenic shock unresponsive to digitalis, diuretics, or isoproterenol. The effective doses of 2-4 mg/hour are frequently accompanied by nausea and vomiting. These side effects can be suppressed by antiemetic agents. An alternate approach suggested by Polumbo et al1 is to use a combination of isoproterenol 60 μg/hour and glucagon 0.75-1.5 mg/hour, thereby obtaining the additive inotropic effect of each agent and diminishing the side effects of these drugs. Glucagon potentiates the hypoprothrombinemic effect of warfarin. Other side effects include hypoglycemia and, rarely, hyperglycemia.

Frank I. Marcus, M.D.
Tucson