Glucagon in Heart Failure
and in Cardiogenic Shock

Experience in 50 Patients

By ROBERT LVOFF, M.B., B.S., M.R.A.C.P.,
and DAVID E. L. WILCKEN, M.D., M.R.C.P., M.R.A.C.P.

SUMMARY
Intravenous glucagon, in doses of 2.5–15 mg/hour, was administered to 50 patients for periods of 1–7 days. Forty patients had either intractable heart failure or cardiogenic shock or both; the remaining 10 had less severe heart disease. In all patients glucagon was added to conventional therapy. Twenty-two of the 40 with very severe heart failure showed a clinical improvement, and 18 were discharged from the hospital; 16 of the 18 patients who did not respond died in the hospital. Only two of the 10 with less severe heart disease improved with glucagon but all could be discharged from the hospital. Glucagon did not initiate or aggravate a tendency to arrhythmias in any of the 17 patients with acute myocardial infarction. In two patients with bradycardia and cardiac failure due to beta-adrenergic blocking drugs, glucagon increased heart rate and there was clinical improvement in heart failure. However, there was no effect in two patients with digitalis-induced nodal bradycardia and heart failure. Nausea was the most troublesome side effect and this could usually be controlled by intramuscular prochlorperazine (Stemetil) which was given routinely before the infusion in all except postoperative patients and repeated as required during the infusion. The results show that glucagon has a definite place in the management of patients with severe heart failure when used as an adjunct to conventional therapy.

Additional Indexing Words:
Inotropic effects Myocardial infarction Arrhythmias after myocardial infarction
Conduction abnormalities Digitalis intoxication Bradyarrhythmias
Beta-adrenergic blockade Postoperative myocardial depression Insulin release
Cyclic AMP

THE FIRST DESCRIPTION of the cardiovascular effects of glucagon in man1 together with earlier animal work2-4 gave promise that glucagon might find an established place in cardiovascular therapeutics. However, human studies reported since 1968 have not resulted in any clear definition of either the preferred mode of administration or the efficacy of glucagon in different clinical situations and its current status in the treatment of cardiovascular disease.5, 6

In a previous paper7 we reported our initial experience with the use of continuous infusions of glucagon in the treatment of severe heart failure. The present paper describes our further experience in a variety of clinical situations in 50 patients, 40 of whom had either intractable heart failure or cardiogenic shock.

Materials and Methods
There were four groups of patients, 36 males and 14 females, ranging in age from 21 to 79 years.
Group 1: Patients with chronic congestive heart failure unresponsive to all other therapy, which included digitalization and an oral dosage of furosemide of at least 200 mg/day together with 100 mg/day of spironolactone (12 patients, including four in cardiogenic shock). The diagnoses were congestive cardiomyopathy (five), ischemic heart disease (five), and chronic rheumatic heart disease (two).

Group 2: Patients with acute myocardial infarction complicated by either cardiogenic shock (15 patients—group 2A) or by severe congestive heart failure with major arrhythmias (two patients—group 2B). All 15 patients with cardiogenic shock had failed to respond to an isotrotenol infusion.

Group 3: Patients with postoperative myocardial depression occurring after open-heart surgery for valve replacement (11 patients). In nine, the aortic valve was replaced, and in one the mitral valve. One additional patient had aortic valve replacement plus mitral valvotomy.

Group 4: Miscellaneous group of 10 patients. There were six patients with cardiomegaly and controlled heart failure, two with complete heart block, one with severe ischemic heart disease and congestive heart failure aggravated by propranolol (Inderal) who later developed digitalis intoxication, and one with ischemic heart disease and digitalis intoxication.

The criteria used to define cardiogenic shock were persistent hypotension with a blood pressure usually below 85 mm Hg systolic accompanied by cyanosis, sweating, cold extremities, mental clouding, and oliguria.4,9 Established criteria were used for the diagnosis of acute myocardial infarction.4,10 Postoperative myocardial depression was considered present if cardiogenic shock or acute heart failure unresponsive to conventional therapy developed within 48 hours of operation.

The methods used were the same as described in our earlier report.7 Glucagon (Eli Lilly and Co.) freshly dissolved in a 5% dextrose solution, was given as a continuous intravenous infusion at an initial rate of 5 mg/hour. The diluent provided was not used, to avoid the possibility of administering excessive amounts of phenol.11

To prevent nausea, an intramuscular injection of 12.5 mg of prochlorperazine (Stemetil) was given before starting glucagon, and in most patients in whom nausea developed later it was possible to control this with further prochlorperazine and continue the infusion; several injections were usually necessary throughout the infusion period. Prochlorperazine was not required in postoperative patients (group 3). Infusions were continued for 1–7 days depending on the response. In the absence of a clinical response, the dosage was increased to 10 mg/hour, and in one patient to 15 mg/hour. In six patients, the dosage had to be reduced from 5 mg/hour because of persistent nausea and vomiting. In all, 60 infusions were given to the 50 patients.

Serum electrolytes, blood urea, and liver function tests were estimated before and after, and sometimes during, the glucagon infusions. The blood sugar was estimated randomly and also in the presence of symptoms suggestive of hypoglycemia. Blood pressure, pulse rate, respiratory rate, body weight, and fluid balance were recorded throughout, and all patients with intractable heart failure (group 1) were given heparin (5000 units every 4 hours) during infusions. The 40 patients in groups 1, 2, and 3 were all nursed in an intensive care unit and had continuous electrocardiographic monitoring. Where possible, chest X-rays were obtained before and after glucagon.

Patients were classified as either responding or showing no improvement to treatment with glucagon. Minor or transient improvement not significant in the management of the case was not recorded as improvement. Patients in group 1 (intractable cardiac failure) were recorded as responding if glucagon treatment resulted in a large diuresis accompanied by rapid resolution in the signs of heart failure with correction of the abnormal serum electrolytes, blood urea, and liver function tests. Group 2 patients (acute myocardial infarction) with cardiogenic shock were recorded as responding if there was a sustained increase in blood pressure of at least 15 mm Hg, which was accompanied by a reversal of the signs of shock. Glucagon was commenced and isoproterenol was continued for varying periods depending upon the response. Those patients with severe heart failure with major arrhythmias were recorded as responding if there was reversal of the heart failure and a reduced incidence of major arrhythmias. Group 3 patients (postoperative myocardial depression) were assessed as responding if there was a reversal of the signs of shock as outlined for group 2 patients, or if there was a reversal of acute heart failure resistant to conventional therapy. Group 4 patients with controlled heart failure were recorded as responding if, after glucagon, the transverse diameter of the heart was reduced substantially (more than 2.0 cm measured from standardized chest X-rays).

Results

The results are summarized in table 1.

Group 1

Figure 1 shows the urine volumes and weight loss which occurred during an infusion
Table 1
Results of Glucagon Treatment in Each Group

<table>
<thead>
<tr>
<th>Condition</th>
<th>No.</th>
<th>Improved</th>
<th>No improvement</th>
<th>Discharged</th>
<th>Late deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intractable heart failure</td>
<td>12</td>
<td>8 (3)*</td>
<td>4 (4)*</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Acute myocardial infarction:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With cardiogenic shock</td>
<td>15</td>
<td>6 (1)*</td>
<td>9 (9)*</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>With severe CHF and major arrhythmias</td>
<td>2</td>
<td>2 (0)*</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative myocardial depression</td>
<td>11</td>
<td>6 (2)*</td>
<td>5 (3)*</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>10</td>
<td>2 (0)*</td>
<td>8 (0)*</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>50</td>
<td>24</td>
<td>26</td>
<td>28</td>
<td>3</td>
</tr>
</tbody>
</table>

*Hospital deaths in each group.
Abbreviation: CHF = congestive heart failure.

in a 38-year-old man with long-standing ischemic heart disease. He had remained cyanosed and icteric with generalized edema, ascites, and the auscultatory signs of mitral and tricuspid incompetence despite intensive treatment for heart failure. A diuresis began 2 hours after glucagon was added to his therapy and continued after the infusion was stopped. He died at home 4 months later of pulmonary edema.

Eight patients of the 12 in group 1 responded, although three of these died in the hospital and a further one died at home 4 months after discharge. Three of the eight had cardiogenic shock in addition to intractable heart failure and two of these were hospital deaths; the other, who has ischemic heart disease, remains alive 19 months after the first of three separate episodes of resistant heart failure complicated by the development of left bundle-branch block and cardiogenic shock. Each episode responded to a glucagon infusion with first an increase in blood pressure and reversal of the signs of shock, and then a change from left bundle-branch block to normal intraventricular conduction. Another patient with ischemic heart disease also had left bundle-branch block of recent onset which reverted to normal intraventricular conduction during an infusion. He died of resistant ventricular fibrillation 2 days after completing the second of two successful glucagon infusions over a 3-month period. The four patients in group 1 who did not respond to glucagon all died in the hospital (see table 1).

Group 2

Figure 2 shows the changes in heart rate and blood pressure which occurred with the onset of chest pain in a 56-year-old woman with known ischemic heart disease and angina pectoris who had been digitalized previously. This episode occurred in the hospital. When seen a few minutes after the onset of pain, she had a loud pansystolic murmur, grade III/VI, audible at the apex and a third heart sound, neither of which had been present an hour before. An isoproterenol infusion did not increase the blood pressure or influence the intensity of the apical systolic murmur. Within an hour of adding glucagon, the systolic blood pressure increased from 70 to 100 mm Hg and the apical systolic murmur became softer. The glucagon dosage was then reduced from 5 to 2.5 mg/hour because of nausea, but a satisfactory blood pressure was maintained and the isoproterenol could be reduced and finally stopped. The apical systolic murmur became inaudible 6 hours after starting glucagon, which was stopped 24 hours later. Her further recovery was uncomplicated. The murmur was thought to be due to acute mitral
incompetence resulting from papillary muscle dysfunction produced by acute myocardial ischemia.\textsuperscript{12} This patient has angina pectoris but remains otherwise well 10 months later.

Of the 17 patients with myocardial infarction, 15 had cardiogenic shock (group 2A, table 1); six of these responded. One, a 65-year-old diabetic who had not responded to isoproterenol and metaraminol (Aramine) obtained an impressive response to glucagon but developed asystole 18 hours later and could not be resuscitated; there was no necropsy. The other five all recovered. In one, the glucagon infusion was given for a week at a dosage of 10 mg/hour but with short periods at 15 mg/hour. The nine patients who did not respond all died in the hospital. At autopsy, two of these had ruptured ventricles and one a perforated interventricular septum. The two patients in group 2B (see table 1) with severe congestive cardiac failure and major arrhythmias (recurrent ventricular tachycardia and ventricular fibrillation and transient heart block) both improved and were discharged. In one of these, left bundle-branch block reverted to normal intraventricular conduction during the period of the infusion.

**Group 3**

Of the 11 patients in group 3 with postoperative myocardial depression, six responded to treatment. Two of those who responded died in the hospital, one of progressive hepatorenal failure and one of acute myocardial infarction. There has been one late death 4 months after aortic valve replacement of heart failure aggravated by perivalvular incompetence, so that, of the six who responded, three remain alive and well at 6, 5, and 3 months after operation, respectively.

Two of the five patients who did not respond survived. One improved after peritoneal dialysis. The other was underdigitalized and overloaded with intravenous fluid; correction of these factors led to recovery. One other patient developed bradycardia (heart rate 50 beats/min) and hypotension (systolic blood pressure 55 mm Hg) immediately after an intravenous injection of a beta-adrenergic blocking drug (Sandoz LB46, 0.08 mg) given for a supraventricular tachyarrhythmia which had occurred after an episode of ventricular fibrillation in the immediate postoperative period. A bolus injection of 5 mg of glucagon was given and within 2 min the heart rate increased to 95 beats/min and the systolic blood pressure to 105 mm Hg. A glucagon
infusion (5 mg/hour) was begun later because of continuing myocardial depression. There was some initial improvement, but he arrested 12 hours later and could not be resuscitated.

Thus, 22 of the 40 patients with severe heart failure (groups 1, 2, and 3) responded to glucagon treatment and 18 left the hospital; three late deaths occurred during a follow-up period of from 2 to 19 months. Eighteen patients did not respond; 16 of these died in the hospital.

**Group 4**

There were 10 patients in group 4 (miscellaneous) with less advanced heart disease and only two of these responded. The first was a 64-year-old woman with a history of ischemic heart disease and congestive heart failure who was taking digoxin and furosemide, in addition to propranolol (Inderal) 240 mg/day because of incapacitating angina. On admission, she had bradycardia and was in severe heart failure with generalized edema. The electrocardiogram showed atrial fibrillation at a ventricular rate of 35 beats/min and widespread S-T-segment depression and T-wave inversion. An isoproterenol infusion was begun but produced multiple ventricular ectopic beats and was suspended. A bolus injection of glucagon, 1 mg intravenously, was then given and within 3 min the ventricular rate increased from 35 to 60 beats/min and the rhythm changed to sinus rhythm with frequent nodal ectopic beats. A glucagon infusion (5 mg/hour) was then commenced; an hour later there was sinus rhythm at a rate of 100 beats/min and no ectopic beats. This was maintained, and a substantial diuresis with clinical improvement ensued. No further propranolol was given. We concluded that propranolol had aggravated the heart failure and that glucagon had reversed this effect.

Two weeks later and while still hospitalized, she again developed bradycardia and became
hypotensive (systolic blood pressure 60 mm Hg). The electrocardiogram showed nodal rhythm at a rate of 38 beats/min. A bolus injection of 5 mg of glucagon intravenously was given and then repeated but there was no increase in heart rate and she remained hypotensive. An isoproterenol infusion at an initial rate of 250 \( \mu \)g/hour was then begun. An increase in heart rate and blood pressure immediately followed; the infusion was continued at a reduced rate for 36 hours and she made a satisfactory recovery. Serum digoxin levels on the morning of the attack (before it occurred) and on the evening of the same day were both in the toxic range at 3.5 ng/ml. We concluded that this second episode of bradycardia was due to digitalis intoxication and that glucagon had been ineffective in reversing its effects. One other patient in this group also had nodal rhythm with bradycardia due to digitalis intoxication. Glucagon (5 mg/hour) did not influence the heart rate or the rhythm.

The only other patient in this group to respond was one of the six patients with controlled heart failure and cardiomegaly. After glucagon, the chest X-ray showed a reduction in heart diameter of 2.6 and 2.4 cm on the posteroanterior and lateral projections, respectively.

Two of the 10 patients had complete heart block of recent onset. In one, a 21-year-old man, it was associated with an idiopathic peripheral neuropathy and in the other, a 70-year-old woman, it was presumed to be due to localized fibrosis in the region of the A-V bundle; there was no evidence of recent myocardial infarction. In neither case did 24-hour infusions (5 mg/hour) restore normal conduction, but the 70-year-old patient reverted spontaneously to sinus rhythm with first-degree heart block a week later; the other patient has required a permanent pacemaker.

**Discussion**

All 40 patients in groups 1, 2, and 3 of our series were gravely ill and 26 were in cardiogenic shock when glucagon was given. The assessment of the efficacy of glucagon treatment in these patients was clinical. Hemodynamic studies were not performed. Nonetheless, in those patients recorded as responding to treatment, the improvement was clear-cut and dramatic. A number of patients had only transient or very slight improvement. However, these were not recorded as responding, as they did not derive any overall benefit from the treatment. Twenty-two of these 40 patients showed marked improvement. Of these, four subsequently died so that it was possible to discharge 18 (45%) from the hospital. The longest survivor is one patient from group 1 who had his first of three glucagon infusions 19 months ago.

The side effects seen in this series were nausea and vomiting, hypokalemia, and hypoglycemia. Nausea occurred in all except the postoperative patients and, together with vomiting, was the most serious drawback to the use of glucagon in the doses we employed. However, this could usually be controlled by intramuscular prochlorperazine, and this was given routinely before the infusion was commenced and repeated as required. In six patients, the nausea and vomiting could only be controlled by reducing the dosage to less than 5 mg/hour. Significant hypokalemia occurred in only one patient previously reported; however, all patients except four in group 4 were having potassium supplements, and the patients in group 1 in whom the largest diureses occurred were receiving spironolactone.

Hypoglycemia developed in two patients, and this was easily controlled. One was a postoperative patient who also had cirrhosis of the liver. In the remaining patients, blood sugar levels were usually maintained at about 120 mg%. The fact that hypoglycemia did occur in these two patients and that hyperglycemia was not a problem presumably reflects the direct insulin-releasing effect of glucagon. Since insulin release is impaired in severe heart failure and cardiogenic shock, a glucagon-induced increase in circulating insulin could be important therapeutically in these clinical situations. In the one diabetic patient in the series who had cardiogenic...
shock following myocardial infarction, glucagon produced marked hyperglycemia which required frequent adjustments in insulin dosage.

In patients receiving a coumarin type of anticoagulant, glucagon causes a further fall of the prothrombin level. In three patients who were receiving a drug of this type, the drug was withdrawn and heparin substituted. In no patient did a bleeding complication occur.

The data obtained during continuous electrocardiographic monitoring in the 17 patients with complicated myocardial infarction show that glucagon, when used according to the regime described, does not increase the tendency to ventricular ectopic beats or major arrhythmias. Before glucagon, ventricular ectopic beats were occurring in all patients, and in no case did they increase during the infusion. In the two patients with recurrent ventricular tachycardia and ventricular fibrillation, the frequency of these arrhythmias was not increased during the glucagon; in fact, the reverse occurred. These findings support the conclusion that glucagon does not increase the “electrical instability” of the heart after acute myocardial infarction in man. The effects found on pacemaker tissue and the conducting system of the heart associated with the administration of glucagon in this series raise several points of interest. It is known from experimental work in dogs and cats that the inotropic and chronotropic effects of glucagon are not blocked by pretreatment with beta-adrenergic blocking drugs. The application of these findings to clinical situations was demonstrated by the results obtained in the two patients of this series in whom these drugs had produced a profound bradycardia and a worsening of heart failure. Both responded to glucagon with an increase in heart rate and marked clinical improvement. In one patient this could be contrasted with the effect of glucagon on a bradyarrhythmia due to digitalis intoxication. As glucagon facilitates atrioventricular conduction in the dog it might have been expected to increase heart rate. However, it did not, nor did it in the one other patient treated who had atrioventricular block due to digitalis.

These latter findings are not in accord with the experimental results of Cohn, Agmon, and Gamble. They found that glucagon abolished over 70% of arrhythmias due to digitalis intoxication in dogs and that the production of sinus tachycardia with a 1:1 ventricular response appeared to be the principal mechanism involved. Since it is relatively effective that the chronotropic effect of glucagon is much less in man than in the dog, a conclusion which the findings of the present study would support, glucagon might be expected on theoretical grounds to be less effective in the control of digitalis-induced bradyarrhythmias in man. Such was our experience in the two patients we studied.

In three patients of the series with recently developed left bundle-branch block, this reverted to normal intraventricular conduction during glucagon infusions. In one patient, this occurred on three separate occasions. The contributions of myocardial electrolyte disturbances, digoxin levels, regional ischemia, and cardiac dilatation in causing the left bundle-branch block cannot be evaluated in these patients so that it is impossible to define the role of glucagon, if any, in restoring conduction. However, these observations prompted us to use glucagon in the two patients with recently developed complete heart block unrelated to acute myocardial infarction. In neither did glucagon reverse the block. Nevertheless the findings as a whole suggest that the effects of glucagon on conduction disturbances in the heart should be further evaluated, particularly after acute myocardial infarction where the presence of conduction defects carries a high mortality and the mechanisms involved are often reversible.

Recent experiments with isolated papillary muscles have shown that while glucagon has a positive inotropic action and increases cyclic AMP in nonfailing heart muscle, it does not produce these effects in preparations obtained from failing hearts, either in the cat or in man. These results are not in accordance with the findings of the present study. Though...
the mechanism of action of the drug was not investigated, the patients in cardiogenic shock responded with a rise in blood pressure and, as glucagon reduces systemic resistance, it seems very likely that a glucagon-mediated increase in cardiac output was responsible. Indeed, this has been found to be so by others. In apparent conflict with the results of Gold and of Epstein and their associates, Strauer more recently has found that glucagon does exert a positive inotropic effect on papillary muscles obtained from patients with chronic congestive heart failure. Further, there is as yet no convincing evidence that cyclic AMP alterations are necessary for changes in contractility although they may accompany the phenomenon. Thus, it is possible that the inotropic action of glucagon may be mediated at least in part by mechanisms unrelated to cyclic AMP.

Glucagon, like digitalis, augments the movement of calcium ions into myocardial cells and this may be the mechanism underlying its inotropic effect—there is no evidence that the inotropic action of digitalis is accompanied by changes in cyclic AMP. The calcium ions accumulate within the cell at sites different from those involved in digitalis-induced movement of calcium ions. Thus, the inotropic effects of glucagon and digitalis could be additive, and Parmley and Glick and their associates have found this to be so. This was borne out clinically in our series; all patients who responded to glucagon were digitalized.

There are several possible explanations for the differences between the experimental and the clinical findings. The function of the excised papillary muscle may not be representative of the function of the whole of the failing myocardium; these hearts may still retain sufficient cells capable of responding to glucagon for the drug to improve contractility significantly. Also, the results obtained in the isolated preparation are not influenced by the metabolic and renal effects of the drug, and both of these may be important in producing a clinical response.

Several groups have reported unsatisfactory results with glucagon treatment in patients with chronic heart failure, and possible reasons for these differences have been reviewed recently. The results of different series are hard to compare when dose regimes and methods of administration vary. We have used prolonged continuous infusions because of the short duration of action of glucagon, and this may be more effective than intermittent administration. In support of this are the findings of Vander Ark and Reynolds who obtained clinical improvement in patients with low cardiac output states treated by continuous glucagon infusions. A further difference may be that we have used measures to counteract nausea and vomiting before starting, as well as during, infusions and have in general used higher doses than other workers.

The results of the present study show that glucagon has a definite place in the management of patients in intractable heart failure and in postoperative myocardial depression when used as an adjunct to conventional therapy. It is effective clinically in reversing bradycardia and myocardial depression due to beta-adrenergic blocking drugs. There is no evidence from this series that it initiates or aggravates a tendency to arrhythmias after myocardial infarction when used as a constant infusion. Glucagon is useful in the treatment of severe heart failure after myocardial infarction when major arrhythmias are occurring and may occasionally be effective in the treatment of cardiogenic shock. It has no place at present in the routine management of patients with congestive heart failure, in our view, because of the nausea an effective dose commonly produces and the necessity for parenteral administration.

Acknowledgments

We are grateful to Drs. D. Brender and R. M. McGredie for reviewing the manuscript and to Dr. D. Gengos, Medical Director of Eli Lilly (Australia) for supplies of glucagon. We thank Mrs. P. Giles and P. Barrett for clinical and Mrs. D. Wilde for secretarial assistance.
References

27. Strauer BE: Influence of glucagon on myocardial mechanics of papillary muscles obtained from patients with chronic congestive heart failure. Naunyn Schmiedeberg Arch Pharm 270: 90, 1971

Circulation, Volume XLV, March 1972
Glucagon in Heart Failure and in Cardiogenic Shock: Experience in 50 Patients
ROBERT LVOFF and DAVID E. L. WILCKEN

Circulation. 1972;45:534-542
doi: 10.1161/01.CIR.45.3.534

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1972 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/45/3/534

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/