Glucagon in Congestive Heart Failure*

Richard J. Kones, M.D., and John H. Phillips, M.D., F.C.C.P.

Nineteen patients with congestive heart failure were given a continuous infusion of glucagon 3 to 5 mg/hour. Those with acute processes improved, while only 1 of 12 with chronic CHF benefited. Urine output increased 495 ml/24 hours, BUN rose 4.9 mg percent, serum glucose increased 22.1 mg percent, and serum potassium decreased 0.35 mEq/liter. No induced arrhythmias were noted, even in the presence of digitalis toxicity. Evidence of increased “ischemia” (angina, depressed ST segments and inverted T waves) during the infusion were seen in four patients. In chronic congestive failure associated with coexisting manifest chronic obstructive pulmonary disease or pulmonary heart disease, the response to glucagon was uniformly unfavorable. Glucagon should be reserved for acute CHF and then only after other modes of therapy, especially digitalization, are unsuccessful.

Glucagon has been intensively investigated with respect to its demonstrated inotropic actions in experimental preparations and in man. Attention was further stimulated by recognition of desirable properties of glucagon as compared with other inotropic agents: these include lack of arrhythmogenicity, additive inotropic effect with digitalis, failure of propranolol to block inotropy, and absence of tachyphylaxis. Although glucagon is in relatively wide use for its inotropic actions (and chronotropic in cardiac arrest as well), reported experience with this agent in continuous intravenous infusion is limited and conflicting. While uniform improvement in congestive heart failure has been reported by Brogan, Kozonis, and Overy, others have noted a more variable response in congestive heart failure (CHF) of longer duration. The purpose of this study was to provide additional data in an effort to determine the efficacy of glucagon in CHF of varying duration.

METHODS

Nineteen patients with CHF of diverse etiology were selected and permission obtained to infuse glucagon intravenously at a rate of 3 to 5 mg/hour over a 24-hour period. Glucagon was diluted with a 5 percent dextrose solution in water and not with the supplied diluent to eliminate possible direct cardiac effects of the preservative. In addition to clinical markers, the following studies were performed immediately prior to beginning and discontinuing the infusion:

- 24-hour urine volume, glucose, sodium, potassium, creatinine;
- serum sodium, potassium, chlorides, CO2 combining power, glucose, urea nitrogen, lactate dehydrogenase, bilirubin, calcium, phosphorus, alkaline phosphatase, creatinine, serum glutamic-oxalacetic transaminase (SGOT), albumin;
- arterial pH, pCO2, pO2, bicarbonate;
- venous pressure;
- electrocardiography and lead I1 oscilloscope monitoring. Hence the 24-hour urine collected during the actual infusion was compared with the 24-hour urine collected during the prior noninfusion 24-hour period. The above were performed as previously established standard laboratory techniques. Maintenance drugs were continued in unaltered dose and schedule and an attempt was made to continue exercise at the level established prior to glucagon infusion. Care was taken not to begin an infusion during a period of response to a previously administered drug.

RESULTS

Retrospectively the patients were segregated into three groups: I, acute CHF with initial episode being treated; II, recurrent CHF (“chronic”); and III, patients with moderately advanced chronic obstructive pulmonary disease as well as chronic CHF. The relevant data are tabulated in Table 1 in order of decreasing responsiveness. Blood pressure followed no characteristic group pattern; sustained rises in both systolic and diastolic values occurred in patients 16 and 17. A minimal fall in both pressures appeared more likely to occur if the patient was previously hypertensive. These changes were unaccompanied by significant pulse rate differences with the exception of patient 4. Urinary output (Fig 1) mean increased 583 ml/24 hours in

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Glucagon produced an increased urine output which attended clinical improvement.

Group I, 815 ml/24 hours in group II, and 86 ml/24 hours in group III. Error variance in groups I and II was great; therefore, intergroup comparison was not possible. However, the increase in urinary output in group III was clearly less than in either group I or II. Overall improvement in the clinical status was attended by a proportional diuresis. Venous pressure (Fig 2) decreased a mean of 2.2 cm H₂O in group I, 1.8 cm H₂O in group II, and increased a mean of 0.4 cm H₂O in group III. Blood glucose (Fig 3) mean rose 22.1 mg percent for all groups taken together (p < 0.05, using Student's paired T test, excluding patient 17). Patient 10 was a diabetic to whom additional insulin (+ 15 units/24 hours) was given, hence his decrease in peripheral glucose. Patients 3, 5, and 7 were stress diabetics; patient 17 was probably an overt diabetic but time did not permit further investigation as he died postinfusion. Serum potassium (Fig 4) decreased a mean of 0.35 mEq/liter for all groups (p < 0.05, Student's T test), excluding three patients to whom potassium supplements were given orally. These patients were receiving 45 mEq potassium/24 hours prior to the infusion and thus were maintained on the same dose schedule (indicated on Fig 4 beneath the respective lines). Two of these patients' serum potassium levels rose (0.9, 0.2 mEq/liter), while the third's fell (0.4 mEq/liter). In the absence of potassium supplements, however, two values rose, one from 3.8 to 4.6 mEq/liter. Variation in blood urea nitrogen (Fig 5) was remarkably wide and heterogeneous. Quality control in the clinical laboratories was maintained throughout the period of the study. The mean change in BUN for groups I, II, and III taken together was +4.9 mg percent (p < 0.05). Moreover, no correlation was found between clinical response and direction of BUN change (6 rose, 12 fell). Serum calcium uniformly fell during the infusion, with no change in phosphorus, alkaline phosphatase, or albumin. Arterial gases and acid-base balance change during infusion was diverse and appeared solely dependent on the preceding values and basic disease process, rather than on glucagon administration. These data should, however, be interpreted in the light of the small sample size and lack of a control group.

The electrocardiogram showed a minimal increase in rate in a majority of instances, except for patient 4, in whom there was an increase in rate...
Glucagon has been reported to have both a positive inotropic and positive chronotropic action, the latter being only moderate in man. Group I patients with acute pathology improved clinically, with the exception of patient 5, in whom angina, ST depression and inversion of the T waves were noted. These results agree with those of

**Discussion**

Nausea occurred in nine of the patients (Table 1, column entitled “N”) but in only one was the infusion stopped on this basis alone. In patient 2 (with infarction) there was deepening of the inverted T waves which reversed after the infusion was discontinued. More frequent and severe anginal episodes were noted in patient 5, with depressed ST segments and inverted T waves in the precordial leads noted simultaneously, also alleviated when glucagon was stopped. During the infusion, patient 15 experienced a prolonged period of chest pain unaccompanied by ECG changes, but during which the total serum lactic dehydrogenase rose from 140 to 201 units. Additionally, depression of ST segments in the precordial leads during the infusion was documented in patient 16, whose cardiac index (RISA method) decreased from 2.8 liter/min/M² to 2.4 liter/min/M² measured during the same period.

**Side Effects**

Figure 3. Glucagon produced a mean increase in blood glucose but variation was great.

With alternating bundle branch blocks and supraventricular bradyarrhythmias. A prolonged P-R interval (patient 8) shortened. There was a decrease in premature ventricular complexes (VPC) in four patients (1, 3, 13, 15); in patient 17, salvos of ventricular tachycardia of 6 to 8 complexes each were immediately obliterated by a bolus of 5 mg glucagon intravenously followed by an infusion. In no instance was there noted an increase in VPC’s or change to an undesirable rhythm.

Figure 4. Glucagon caused an overall decrease in serum potassium, although individual responses were unpredictable (three patients receiving 45 mEq oral potassium supplementation are so represented above).
Table 1—Summary of data during glucagon infusion intravenously.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Function Class</th>
<th>Diagnosis</th>
<th>Prior Drugs</th>
<th>Blood, Glucose</th>
<th>K+</th>
<th>Urinary Output</th>
<th>BP</th>
<th>Clinical Eval.</th>
<th>N</th>
<th>Comment</th>
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</thead>
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<tr>
<td>GROUP I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1 53 4 3</td>
<td></td>
<td>Cardiomyopathy</td>
<td>Digoxin, Furosemide</td>
<td>13 29</td>
<td>106</td>
<td>100</td>
<td>3.4, 3.7</td>
<td>2050</td>
<td>2900</td>
<td>13 7</td>
</tr>
<tr>
<td>2 77 4 3</td>
<td></td>
<td>Myocardial Infarction + HHD</td>
<td>Digoxin, Reserpine, Hydrochlorothiazide</td>
<td>46 56</td>
<td>104</td>
<td>110</td>
<td>4.8, 4.2</td>
<td>450</td>
<td>580</td>
<td>16 15</td>
</tr>
<tr>
<td>3 52 4 5</td>
<td></td>
<td>Myocardial Infarction + HHD</td>
<td>Diazepam</td>
<td>23 34</td>
<td>164</td>
<td>166</td>
<td>4.4, 4.0</td>
<td>530</td>
<td>955</td>
<td>14 15</td>
</tr>
<tr>
<td>4 86 4 3</td>
<td></td>
<td>Complete Heart Block + HHD</td>
<td></td>
<td>47 54</td>
<td>110</td>
<td>140</td>
<td>3.9, 3.4</td>
<td>1550</td>
<td>2200</td>
<td>21 18</td>
</tr>
<tr>
<td>5 75 3 4</td>
<td></td>
<td>Angina Syndrome CHF + HHD</td>
<td>Digoxin, Furosemide</td>
<td>34 44</td>
<td>164</td>
<td>210</td>
<td>3.8, 4.7</td>
<td>1200 1125</td>
<td>17</td>
<td>—</td>
</tr>
<tr>
<td>6 57 4 3</td>
<td></td>
<td>Myocardial Infarction + HHD</td>
<td>Digoxin, Hydrochlorothiazide</td>
<td>13 18</td>
<td>96</td>
<td>108</td>
<td>4.1, 3.8</td>
<td>1100</td>
<td>2250</td>
<td>10 8</td>
</tr>
<tr>
<td>7 78 3 3</td>
<td></td>
<td>Ischemic Myocardiospathy</td>
<td>Digoxin, Furosemide</td>
<td>22 24</td>
<td>180</td>
<td>170</td>
<td>4.4, 4.0</td>
<td>960</td>
<td>2350</td>
<td>12 12</td>
</tr>
</tbody>
</table>

GROUP II

| 8 73 3 3    |                | Recurrent CHF ASHD | Digoxin, Furosemide | 8 7 | 94 | 119 | 3.8, 3.5 | 920 | 2080 | 16 14 | 150 90 | 150 90 | ++ O JHT Size on X Ray; Correction of ↑1AV Block |
| 9 51 4 3    |                | Recurrent CHF ASHD | Digoxin, Warfarin | 12 21 | 84 | 126 | 4.6, 4.2 | 1300 | 2790 | 22 17 | 190 46 | 178 90 | ++ N |
| 10 71 3 3   |                | Pulmonary Emboli Angina ASHD | | 24 30 | 254 | 228 | 5.7, 5.0 | 1200 | 1080 | 18 16 | 130 90 | 140 88 | ≈ O Effusions Cleared |
| 11 77 3 3   |                | Recurrent CHF ASHD | Digitalis Leaf, Hydrochlorothiazide | 24 18 | 108 | 82 | 4.6, 4.6 | 475 | 990 | 14 13 | 130 80 | 120 78 | ≈ O |
| 12 76 3 3   |                | Recurrent CHF HHD + ASHD | Alphamethyldopa, Digitalis | 41 36 | 134 | 124 | 4.2, 4.2 | 830 | 1275 | 11 8 | 130 80 | 134 80 | + N |
| 13 45 3 3   |                | Recurrent CHF ASHD | Digitalis | 10 22 | 138 | 126 | 4.3, 4.5 | 730 | 1800 | 13 12 | 120 82 | 100 80 | + N ↓ VPC'S |

GROUP III

| 14 59 3 3   |                | ASHD CHF COPD | Digitalis, Aminophylline Supp. | 43 34 | 92 | 129 | 4.6, 4.1 | 1290 | 1340 | 18 16 | 128 84 | 100 88 | — N |
| 15 70 3 3   |                | Angina: COPD CHF | | 31 23 | 108 | 134 | 4.4, 3.5 | 880 | 880 | 18 17 | 152 80 | 138 94 | — O ↑ VPC'S Angina LDH Rise 140-201 |
| 16 89 4 3   |                | PHD, COPD, CHF | Digitalis Leaf, Bunocon® | 148 | — | 86 | 3.7 | — | 790 | 27 28 | 90 62 | 132 80 | ST ↓ PT Died CT 2.8-3.4 |
| 17 77 4 3   |                | PHD, COPD, CHF | Digitalis Toxic | 22 36 | 82 | 248 | 3.8, 4.6 | 900 | 1000 | 26 26 | 90 60 | 109 74 | — O Salves of VT Eliminated; Died |
| 18 78 4 3   |                | PHD + ASHD, Lactic AI, CHF, COPD | Furosemide | 19 25 | 102 | 122 | 5.4, 4.2 | 1170 | 1120 | 9 11 | 140 94 | 110 70 | — O |
| 19 80 3 4   |                | CHF, COPD | Digitalis Leaf | 21 15 | 82 | 102 | 5.1, 4.5 | 580 | 830 | 14 13 | 150 82 | 180 90 | — N |

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VanderArk and Reynolds,2 Linhart and co-workers,11 and Parmley, Matloff, and Sonnenblick14 and indicated greater glucagon responsiveness in acute CHF.

Demonstration in the dog of increased contractility in noninfarcted cardiac muscle15 after glucagon administration implies a possible role of glucagon in the treatment of myocardial infarction in man. Indeed, hemodynamic studies in man13 confirm increased cardiac output and stroke volume during glucagon therapy postinfarction.

Patients in groups II and III were disappointing in their response to glucagon. Only one of six in group II unequivocally benefited from the infusion. Thus in contrast to the uniform improvement reported by Brogan, Kozonia, and Overy,1 our data suggest the response to glucagon in chronic CHF is unacceptably variable. While not strictly comparable because of differences in administration, such was also the experience of Greenberg and associates16 and Amsterdam and colleagues,17 using a single bolus of glucagon during cardiac catheterization. Failure of glucagon to increase contractility and induce adenyl cyclase activity in chronic experimental CHF with subsequent demonstration of preservation of response to norepinephrine in the same preparation18 may provide a more fundamental explanation for these observations.

Patients with obstructive lung disease and chronic CHF (group III) appeared to respond negative-

ly to glucagon (Table 1); patients 16 and 17 with pulmonary heart disease (and "cardiogenic shock") initially improved with a stable increase in both systolic and diastolic pressures. However, increased ST depression in the precordial leads during glucagon infusion was noted in patient 16 with a decrease in cardiac index, followed by death at the termination of the infusion. In patient 17, although salvos of ventricular tachycardia disappeared after a 5 mg bolus of glucagon, the patient died several hours after discontinuing glucagon the following day. While the reason for the apparent detrimental effect of glucagon in this group is unclear, elevation of the pulmonary artery pressure by glucagon may be contributory. Modest elevations of pulmonary artery pressure have been reported10-13 during catheterization following single doses of glucagon. The exact variation in pulmonary artery dynamics during continuous infusion of glucagon remains to be investigated.

Blood glucose was noted to fall in some patients (comparing the value before discontinuing the infusion to the initial value). An explanation for this apparent inconsistency with the well-known hyperglycemic effect may be found in the probable invocation of compensatory hypoglycemic mechanisms during continuous glucagon administration rather than after a single dose, including release of insulin and growth hormone.20 and "resetting" of central nervous system glucose-sensitive receptors.

Serum potassium fell more commonly, but an unpredictable rise in potassium in the absence of potassium supplementation was noted in two patients, a phenomenon previously reported.2 The observed fall in serum calcium is consistent with that previously noted22 and postulated to be the result of increased thyrocalcitonin release.23 Gross calcium influx into the myocardium from the extracellular space is currently thought not to be responsible for glucagon's cardiotonic property.24

Increase in frequency and severity of angina during the infusion in two patients (the first with depressed ST segments and inverted T waves, the second with increased LDH), as well as a deepening of T wave inversion in a third patient, and depression of ST segments associated with decreased cardiac index in a fourth deserves special comment. Inotropic agents have been held potentially responsible for increased ischemia by increasing contractility in the face of relatively fixed oxygen supply.18 Evidence has been presented12,20,21 however, indicating a proportional increase in oxygen consumption in relation to left ventricular work after a single dose of glucagon. Resolution of this problem awaits investigation.
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CONCLUSION

Glucagon in continuous infusion would be expected to be of maximum benefit in acute congestive heart failure. From the data presented, its use does not seem justified in chronic CHF unless all other therapeutic maneuvers are exhausted. Serum glucose and potassium must be determined frequently. Caution is advised in the patient with severe ischemic heart disease (angina, "preinfarction angina") and in the patient with coexistent obstructive pulmonary disease and frank pulmonary heart disease or both. No "toxic" arrhythmias developed in the present study; a decrease in ventricular tachycardia in another may in fact reflect an independent antiarrhythmogenic property of glucagon. Although reported beneficial by other investigators, the use of glucagon in postoperative prosthetic valve replacement and in propranolol-induced congestive heart failure was not studied in this series.

REFERENCES

19 Braunwald E: Factors regulating the oxygen consumption of the heart: (Lecture) Opening Plenary Session, Nineteenth Annual Scientific Session, American College Cardiology, 1970

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