Hemodynamic Effects of Glucagon in Patients with Heart Disease

By John F. Williams, Jr., M.D., Richard H. Childress, M.D., Jerold N. Chip, M.D., and John F. Border, M.D.

SUMMARY
The intravenous administration of 3 or 5 mg of glucagon to 13 patients with heart disease resulted in a statistically significant increase in heart rate, cardiac index, stroke power index, mean rate of left ventricular ejection, and maximum rate of rise of left ventricular pressure, whereas systemic vascular resistance declined. A moderate increase in mean stroke volume index and stroke work index and a slight fall in left ventricular end-diastolic pressure also occurred, although these changes were not statistically significant. The increase in cardiac index averaged 19%, with nine of the patients demonstrating an increase exceeding 10% of their respective control value. These effects of glucagon generally reached a maximum within 15 min after drug administration and also were of short duration.

Positive inotropic and chronotropic effects of glucagon were observed in most but not all of these patients. In addition, the magnitude of these effects varied considerably among patients; the variation, however, did not appear to be related to the severity or duration of the heart disease. In eight patients, the infusion of isoproterenol produced greater increases in cardiac index and decreases in left ventricular end-diastolic pressure than glucagon did.

Although the effect of glucagon was short, the frequent improvement in hemodynamics which occurred in the absence of significant side effects, notably arrhythmias, indicates that the inotropic actions of this agent may be useful under certain clinical conditions.

Additional Indexing Words:
Positive inotropism Positive chronotropism Potassium

The effect of glucagon on hepatic glycogenolysis and its therapeutic usefulness in the treatment of hypoglycemia is well recognized. That this agent can exert profound effects on other organ systems, however, is only now being appreciated (Sokal reviews this subject in detail). Recently, interests in the actions of this agent have centered on the cardiovascular changes which it may produce. It has been observed that glucagon produces both positive chronotropic and positive inotropic effects on isolated cardiac muscle, in heart-lung preparations and in the intact animal. In addition, Parmley and associates have reported that glucagon produces similar effects in man. To provide further information regarding this potentially useful action of glucagon in patients with heart disease, the following study was performed.

Methods
Thirteen men with hypertensive cardiovascular disease or primary myocardial disease who were undergoing diagnostic intravascular catheterization constituted the subjects of this study. After diagnostic right heart catheterization, a catheter
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was placed in the right ventricle and a no. 8 NIH catheter was inserted retrogradely into the left ventricle. Brachial arterial pressure and the pressures in the above chambers were measured with Statham P23Db transducers with the mid-thoracic level used as the zero reference point. Cardiac output was determined by the indicator-dilution method with the injection of indocyanine-green dye into the right ventricle and sampling from the brachial artery. The first derivative of left ventricular pressure was determined with an R-C differentiating circuit. The left ventricular systolic ejection time was measured from an indirect carotid arterial tracing or simultaneously measured left ventricular and brachial artery pressure curves recorded at a paper speed of 100 mm/sec. After heart rate, systemic arterial pressure, and left ventricular end-diastolic pressure had remained constant for 15 to 20 min, 3 or 5 mg of glucagon was injected intravenously over approximately 30 sec.* The above variables were then recorded 5, 15, 30 and 60 min after completion of glucagon administration.

Stroke work index (SWI) was calculated from the following formula:

\[
\text{SWI in g-m/m}^2 = \frac{\text{SVI} \times (\text{LVSP} - \text{LVEDP}) \times 1.36}{100}
\]

where SVI equals the stroke volume index in ml/m², LVSP, the mean left ventricular pressure during ejection in mm Hg determined by planimetric integration, and LVEDP, left ventricular end-diastolic pressure in mm Hg. Stroke power index (SPI) in g-m/sec/m² was calculated by dividing SWI by the systolic ejection period in seconds. The mean rate of left ventricular ejection in ml/sec/m² was determined by dividing SVI by the systolic ejection period in seconds. Systemic vascular resistance in dynes sec cm⁻⁵ was calculated according to the standard formula with the exception that right ventricular end-diastolic pressure rather than mean right atrial pressure was subtracted from the mean systemic arterial pressure. All pressures were averaged over at least two complete respiratory cycles.

To compare the effect of glucagon in these patients with that of an agent with known positive inotropic actions, eight patients received a constant infusion of isoproterenol at the end of the 60-min glucagon study period. An attempt was made to obtain as great an inotropic effect as possible with isoproterenol under these conditions by infusing at the maximum rate that the patient would safely tolerate without an inordinate fall in systemic arterial pressure, marked increase in sinus rate, or production of arrhythmia. The infusion rate varied from 3 to 8 μg/min, and when systemic arterial pressure, heart rate, and LVEDP had been constant from 3 to 5 min, hemodynamic measurements were made. Statistical analyses were performed using Student’s t test with paired observations.

The clinical characteristics of each patient are presented in table 1. Each patient had radiographic evidence of cardiomegaly or electrocardiographic changes of left ventricular hypertrophy. The patients ranged in age from 34 to 63 years (average, 48). Nine of the patients had congestive heart failure prior to the study, and eight were receiving a digitalis preparation.

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>BSA (m²)</th>
<th>Diagnosis</th>
<th>History of CHF</th>
<th>Digitalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.W.</td>
<td>46</td>
<td>1.86</td>
<td>PMD</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>D.P.</td>
<td>42</td>
<td>2.18</td>
<td>HCVD</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>H.F.</td>
<td>43</td>
<td>1.80</td>
<td>HCVD</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>B.D.</td>
<td>49</td>
<td>2.29</td>
<td>HCVD</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>R.C.</td>
<td>55</td>
<td>2.16</td>
<td>PMD</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>H.B.</td>
<td>54</td>
<td>2.30</td>
<td>HCVD</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>R.W.</td>
<td>34</td>
<td>1.88</td>
<td>PMD</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>R.K.</td>
<td>47</td>
<td>1.90</td>
<td>PMD</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>V.N.</td>
<td>63</td>
<td>1.62</td>
<td>PMD</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>E.D.</td>
<td>43</td>
<td>1.74</td>
<td>HCVD</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>H.W.</td>
<td>49</td>
<td>2.02</td>
<td>PMD</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>W.G.</td>
<td>56</td>
<td>1.78</td>
<td>PMD</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>E.M.</td>
<td>41</td>
<td>1.70</td>
<td>PMD</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: BSA = body surface area in m²; PMD = primary myocardial disease; HCVD = hypertensive cardiovascular disease; CHF = congestive heart failure.

*Glucagon was kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.
<table>
<thead>
<tr>
<th>Time (min)</th>
<th>PAP (mm Hg)</th>
<th>PVR (dynes/sec/cm^5)</th>
<th>CVP (cm H_2O)</th>
<th>CI (liters/min/m^2)</th>
<th>HR (beats/min)</th>
<th>LVEDP (mm Hg)</th>
<th>LVEF (%)</th>
<th>SVI (liters/min/m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>78</td>
<td>2.1</td>
<td>23/5</td>
<td>3</td>
<td>26</td>
<td>121</td>
<td>114</td>
<td>88</td>
</tr>
<tr>
<td>30</td>
<td>76</td>
<td>1.5</td>
<td>20/3</td>
<td>3</td>
<td>19</td>
<td>17</td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td>60</td>
<td>76</td>
<td>1.7</td>
<td>18/6</td>
<td>5</td>
<td>22</td>
<td>21</td>
<td>-99</td>
<td>105</td>
</tr>
</tbody>
</table>

**V.N.**
- 0: 85
- 5: 104
- 15: 98
- 30: 100
- 60: 102

**E.D.**
- 0: 84
- 5: 96
- 15: 80
- 30: 86
- 60: 90

**H.W.**
- 0: 90
- 5: 96
- 15: 78
- 30: 86
- 60: 90

**W.G.**
- 0: 80
- 5: 81
- 15: 80
- 30: 85
- 60: 90

**E.M.**
- 0: 84
- 5: 84
- 15: 84
- 30: 84
- 60: 90

**Mean ± SEM**
- 0: 83 ± 101 ±
- 5: 90 ± 104 ±
- 15: 86 ± 100 ±
- 30: 86 ± 95 ±
- 60: 88 ± 95 ±

**Abbreviations:**
- Time = time in min after glucagon
- HR = heart rate
- Mean art pr = mean systemic arterial pressure
- CI = cardiac index
- RV pr = right ventricular pressure
- S/D = systolic-end diastolic pressure
- LVEDP = left ventricular-end diastolic pressure
- SVI = stroke volume index
- SWI = stroke work index
- SPI = stroke power index
- MRE = mean rate of left ventricular ejection
- LV dp/dt = maximum rate of rise of left ventricular pressure
- SVR = systemic vascular resistance

*Patients receiving 5 mg of glucagon.
†Values significantly different from control (P < 0.05).
Only two patients, H. F. and E. M., had clinical evidence of heart failure at the time the study was performed. All patients but H. W. were in sinus rhythm, and in this patient with atrial fibrillation, all intravascular pressures were averaged over 10 cardiac cycles.

Results

In four patients, each of whom had received 5 mg of glucagon, nausea without vomiting developed. Otherwise no complications occurred, and specifically, no arrhythmias were observed. Nausea did not appear to affect significantly the results in these patients since it was transient and usually followed the major hemodynamic changes that were observed.

The hemodynamic data before and after glucagon for each individual are presented in Table 2. The study was initially designed to compare the effect of glucagon at two different dosages. However, upon completion of the study, it was discovered that by chance the group which received 5 mg had much greater impairment of resting hemodynamics than did the group receiving 3 mg. Since it was not possible to separate conclusively the effect of different doses from the response of hearts with differing degrees of myocardial dysfunction, all results were combined. A comparison of the effect of these two doses of glucagon and the potential significance of differences in response to these two doses, however, is discussed later.

Cardiac index was reduced at rest (<2.5 L/min/m²) in five patients, whereas LVEDP was elevated at rest (>12 mm Hg) in two of these five and in an additional three patients. Five minutes after the administration of glucagon, there was a modest but statistically significant increase in mean heart rate, cardiac index, and maximum LV dp/dt, whereas no statistically significant differences were observed in any of the other variables. Thereafter, the only statistically significant differences observed were a slight decrease in mean systemic arterial pressure and LVEDP at the 30 and the 60-min periods and in SVI at the 60-min period. Examination of individual results, however, revealed that

<table>
<thead>
<tr>
<th>Hemodynamics Before and at the Time of the Maximum Increase in CI After Glucagon</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
</tr>
<tr>
<td>(beats/min)</td>
</tr>
<tr>
<td>CI</td>
</tr>
<tr>
<td>(L/min/m²)</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
</tr>
<tr>
<td>SVI (ml/m²)</td>
</tr>
<tr>
<td>MRE (ml/sec/m²)</td>
</tr>
<tr>
<td>SRI (g-sec/beat)</td>
</tr>
<tr>
<td>(cm Hg)</td>
</tr>
<tr>
<td>Mean-HR</td>
</tr>
<tr>
<td>Control values: C = After glucagon.</td>
</tr>
<tr>
<td>C = 0.05</td>
</tr>
<tr>
<td>For abbreviations, see Table 2.</td>
</tr>
</tbody>
</table>

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comparison of mean values at the various time periods did not present an accurate picture of the hemodynamic effects of glucagon. Although maximum hemodynamic changes after glucagon did occur in most subjects at the 5-min period, similar but delayed changes occurred in several others, thereby minimizing mean changes when viewed only with respect to time. To provide a clearer understanding of the effects of glucagon, therefore, it became necessary to compare values in a different manner. In nine of the 13 patients, an increase in CI exceeding 10% of the control occurred at some time after injection of glucagon. In seven of these nine patients, LVEDP was reduced or unchanged at the time of the maximum increase in CI. In the remaining four of the 13 patients, CI was essentially unchanged although a slight increase in the calculated value occurred in each, whereas a fall in LVEDP occurred in three. Therefore, it was elected to compare hemodynamic variables existing at the time of the maximum increase in CI in each individual with his respective control values.

The mean values for this comparison are presented in table 3. This reveals that a significant increase in cardiac index, averaging 19%, was accompanied by a significant increase in SPI, mean rate of left ventricular ejection (MRE), and maximum LV dp/dt, as well as a significant decrease in systemic vascular resistance (SVR). Although a slight decrease in LVEDP and an

![Figure 1](image)

**Figure 1**

Comparison of individual changes in stroke power index (SPI), mean rate of left ventricular ejection (MRE), stroke work index (SWI), and stroke volume index (SVI) to changes in left ventricular end-diastolic pressure (LVEDP) after glucagon. Values represent those existing at the time of the maximum increase in cardiac index. Open circles represent values in patients receiving 3 mg, closed circles 5 mg.
increase in SVI and SWI were observed at this time, the changes were not significantly different from their respective controls. To characterize the myocardial effects of glucagon further, the changes in SPI, MRE, SWI, and SVI existing at the time of the maximum increase in CI were compared to the changes in LVEDP at that time for each individual. These results are illustrated in figure 1. An increase in mechanical work or rate or performing work without an accompanying increase in LVEDP or decrease in LVEDP without a reduction in the former variables was taken to indicate a positive inotropic effect. In seven patients, a positive inotropic effect was apparent in the changes which occurred in SVI, in eight by changes in SWI and MRE, and in 10 by changes in SPI. Thus, although a positive inotropic effect of glucagon was apparent in most patients, such an effect could not be demonstrated universally. Furthermore, it must be appreciated that the effect of glucagon was relatively short-lived; the maximum increase in CI being sustained for two successive periods in only one patient.

A comparison of the effect of glucagon and isoproterenol in eight patients, four of whom received 3 mg of glucagon and the other four, 5 mg, is given in table 4. Three and 5 mg of glucagon resulted in an average maximum increase in cardiac output of 13 and 16%, respectively, whereas isoproterenol in doses of 3 and 8 μg/min produced an increase averaging 21% in the former and 23% in the latter group. A greater reduction in LVEDP followed administration of isoproterenol than either of the doses of glucagon. The marked increase in heart rate and decrease in resistance to left ventricular ejection that occurred with isoproterenol, however, prohibits any comparison of the direct inotropic effect of these two agents.

Blood glucose and plasma potassium values 30 min after administration of glucagon were determined in eight patients, four of whom received 3 mg and the other four, 5 mg. Results are given in table 5. As expected, blood glucose increased in each of these patients, and this effect was more pronounced after injection of 5 mg than of 3 mg of glucagon. In addition, a decrease in plasma potassium occurred in each patient, averaging 0.3 mEq/L after 3 mg and 0.8 mEq/L

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**Table 4**

**Comparison of the Hemodynamic Effects of Glucagon and Isoproterenol**

| Abbreviations: GL = glucagon; IS = isoproterenol; C = control; G = at the time of the maximum increase in cardiac index, after glucagon; I = at time of maximal increase in cardiac index after isoproterenol. For other abbreviations, see table 2. Values represent mean ± standard error of the mean. |

| GL | C | 78 ± 6.7 | 92 ± 6.6 | 3.5 ± 0.3 | 9 ± 2.4 |
| 3 mg | G | 84 ± 9.2 | 92 ± 5.7 | 3.9 ± 0.3 | 6 ± 0.8 |
| IS | C | 81 ± 9.1 | 83 ± 8.2 | 3.4 ± 0.2 | 9 ± 2.4 |
| I | 113 ± 10.1 | 58 ± 2.7 | 4.4 ± 0.2 | 5 ± 0.6 |
| GL | C | 85 ± 2.1 | 103 ± 7.6 | 2.0 ± 0.1 | 16 ± 4.7 |
| 5 mg | G | 86 ± 5.0 | 98 ± 5.2 | 2.3 ± 0.1 | 15 ± 3.7 |
| IS | C | 88 ± 5.5 | 94 ± 8.7 | 1.9 ± 0.1 | 13 ± 4.3 |
| I | 112 ± 11.0 | 81 ± 11.0 | 2.5 ± 0.3 | 9 ± 3.9 |

---

**Table 5**

**Effect of Glucagon on Blood Glucose and Plasma K**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time</th>
<th>Blood glucose (mg %)</th>
<th>Plasma K+ (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg</td>
<td>A</td>
<td>110 ± 5.2</td>
<td>3.6 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>170 ± 14.4</td>
<td>3.4 ± 0.2</td>
</tr>
<tr>
<td>5 mg</td>
<td>A</td>
<td>108 ± 3.9</td>
<td>4.5 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>187 ± 13.7</td>
<td>3.7 ± 0.2</td>
</tr>
</tbody>
</table>

A = control period; B = 30 min after glucagon.
after 5 mg of glucagon. The greatest decrease in plasma potassium occurred in patient R. K., in whom a decrease from a control of 4.4 mEq/L to 2.8 mEq/L was observed. Although the results are not presented, both glucose and potassium had returned toward control values in each patient 60 min after glucagon.

Discussion

The magnitude of the hemodynamic changes and the time at which the maximum changes occurred after glucagon varied considerably among patients and was seemingly unrelated to the severity or duration of the heart disease. However, significant hemodynamic improvement occurred in most of these

Figure 2

Comparison of the hemodynamic changes in the group receiving 3 mg (dashed lines) and 5 mg (solid lines) of glucagon. C = control values; G = after glucagon. Values after glucagon represent means calculated from values existing at the time of the maximum increase in cardiac index in each individual. Vertical bars indicate standard error of the mean. For abbreviations, see table 2.
subjects with heart disease. Thus, a significant increase in cardiac output occurred after glucagon in nine patients. Furthermore, in 10 patients, an increase in CI was associated with unchanged or reduced LVEDP, or unchanged CI was accompanied by a fall in LVEDP. This suggests that, at least in these 10 patients, glucagon exerted a positive inotropic effect.

Evidence to support this contention was obtained by comparing the hemodynamic variables existing at the time of the maximum increase in cardiac output in each individual to their respective control values rather than comparing changes only with respect to time after administration of glucagon. Examined in this manner (table 3), the increase in cardiac output was accompanied by a statistically significant increase in those variables reflecting primarily the velocity of myocardial contraction, that is, SPI, MRE, and maximum left ventricular dp/dt without a significant change in heart rate, systemic arterial pressure, or LVEDP. The fact that the increases in SVI and SWI were not statistically significant need not detract from the conclusion that glucagon does produce a positive inotropic effect. Others have demonstrated that changes in the contractile state of the myocardium can occur which will not affect the mechanical work performed by the ventricle but which will alter those variables reflecting the rate with which work is performed.9,10 Furthermore, changes in the relationship of mechanical work performed and the rate of performing work to changes in LVEDP (fig. 2) provide additional evidence that glucagon did produce a positive inotropic effect in most of our patients.

The mechanism responsible for the increase in cardiac output in the patients in whom definitive evidence of a positive inotropic action of glucagon was not observed is unclear. It is possible that changes in the contractile state of the myocardium might have occurred which were not of sufficient magnitude to produce changes in the variables used to assess myocardial function in the present study, as others have demonstrated in animals.10 Also it is possible that glucagon may exert peripheral effects, for example, an effect on capacitance vessels and an increase in venous return, which at present are unrecognized.

Only minor differences are evident between the results of this study and the observations of Parmley and associates on patients receiving similar doses of glucagon.6 These investigators observed positive chronotropic and inotropic effects of glucagon more consistently than they were observed in the present study, although the magnitude and duration of the changes in CI and LVEDP in these two studies generally are comparable. They also reported that systemic arterial pressure was increased and systemic vascular resistance was unchanged after glucagon, whereas in this study systemic vascular resistance was reduced and systemic arterial pressure was essentially unchanged. Their observations also were made in patients with a wider variety of heart diseases than those of this study.

Initially, our study was designed to determine the effect of glucagon at two different dosages. Seven patients were given 3 mg of glucagon and six patients were given 5 mg. For comparative purposes the results in these two groups are illustrated in figure 2. The values represent those existing at the time of the maximum increase in cardiac output. Five milligrams of glucagon did result in a greater increase in cardiac index, averaging 28% above control values as opposed to 12% with 3 mg, and a somewhat greater increase in SVI, SWI, SPI, and MRE. However, as stated earlier, it is apparent that the two groups are not comparable and that the severity of the heart disease as judged by the resting CI and LVEDP was significantly greater in the group receiving 5 mg. Thus, it is not possible to determine precisely whether the greater hemodynamic effect of 5 mg of glucagon represents the effects of a larger dose or the response of the myocardium whose function is more severely impaired. However, the response to glucagon within each group did not appear to be related to
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the severity of the hemodynamic derangement at rest, suggesting that the quantitative differences in response between groups occurred primarily as a result of the administration of different doses.

The ability of glucagon to elevate blood glucose is, of course, well recognized. Its effect on serum potassium, however, appears to be less well recognized. A decrease in serum potassium would be expected in view of its known effect on blood glucose and insulin secretion, and a decrease in plasma potassium at the 30-min period did accompany the increase in blood glucose in each individual in whom it was determined, these effects being more marked after 5 mg than after 3 mg. A similar decrease in plasma potassium was observed by Parmley and associates. These results suggest that the intravenous administration of glucagon to patients receiving digitalis may promote the development of digitalis-induced arrhythmias. Several of the patients in this study were receiving digitalis, including the patient in whom plasma potassium decreased from 4.4 to 2.8 mEq/L; however, no arrhythmias were observed.

The clinical usefulness of glucagon remains to be determined. An increase in cardiac output at a lower filling pressure, as occurred in the majority of these patients, certainly is a desirable goal in the treatment of low output congestive heart failure. However, the ability of glucagon to produce such an effect is not universal, and when this effect does occur, it is relatively short-lived. Furthermore, the development of nausea in four of the six patients receiving 5 mg indicates that this is near the maximum dose which can be tolerated when given over a short period of time. Also the effect of glucagon on cardiac output and filling pressures appears to be significantly less than that of isoproterenol whose positive inotropic action has proved useful under certain clinical conditions. In this regard, however, it must be appreciated that this was a near maximal dose of isoproterenol for these patients, and it is unlikely that this dose could have been administered for an indefinite period of time or that its effect would have been sustained. Since any agent which can produce improvement in myocardial function, albeit short lived, without producing arrhythmias is potentially useful, further studies on patients with different types of heart disease and under different clinical conditions are warranted.

References

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