Hemodynamic Evaluation of Glucagon in Symptomatic Heart Disease

By Paul W. Armstrong, M.D., Herman K. Gold, M.D., Willard M. Daggett, M.D., W. Gerald Austen, M.D., and Charles A. Sanders, M.D.

SUMMARY
Glucagon was administered as a 5 mg intravenous bolus in 26 patients. Studies were performed in the Cardiac Catheterization Laboratory and soon after cardiac surgery. When the response to glucagon was compared on the basis of functional classification, patients with class I and II heart disease had a significantly greater increase in cardiac output (+700 ml) than patients with class III and IV heart disease (+100 ml). Isoproterenol augmented cardiac output by a significantly greater amount (+2500 ml) than glucagon in eight of these patients. It is concluded that glucagon is a less effective inotropic agent than isoproterenol and that glucagon’s usefulness is limited in patients with advanced symptomatic heart disease.

Additional Indexing Words:
Inotropic
Postoperative
Preoperative
Functional classification
Isoproterenol

Glucagon, a polypeptide hormone synthesized by the alpha cells of the pancreas, has been the subject of intensive clinical investigation since it was first reported to have an inotropic effect in man. Early observations on the hemodynamic effects of this agent showed that it was capable of producing a significant increase in myocardial contractility. These observations and the need for a new inotropic agent free of the potential to produce arrhythmias aroused a considerable amount of interest. The subsequent clinical reports, however, did not demonstrate a quantitatively consistent increment in cardiac output in all patients. The basis for this variability remains largely undetermined. There is, however, experimental and clinical evidence to imply that its inotropic efficacy may be limited in chronic congestive heart failure. Accordingly, this study was undertaken to define the clinical conditions in which this drug may be beneficial and to identify possible factors responsible for the variability of the cardiovascular response.

Methods
Thirty hemodynamic studies were performed in 24 patients during the course of diagnostic cardiac catheterization (16 studies) or soon after cardiac surgery (14 studies). Six of the 24 patients had studies pre- and postoperatively. Prior to the study all patients were evaluated by one of the investigators, and their functional classifications determined according to the New York Heart Association classification. Of the total group of 24 patients, 11 patients were in functional class I and II: eight patients had
valvular disease, two patients had coronary artery disease (one of whom had an acute myocardial infarction), and one patient had acute pulmonary embolus. The average duration of symptoms of patients in this group was 1.1 years, and none had previously been in functional class III or IV. None of these patients had the physical findings of congestive heart failure, and only one had cardiomegaly by chest X-ray. Four were receiving diuretics, and all were on digitalis. Thirteen patients were placed in functional class III and IV: nine patients had valvular disease and four patients had coronary artery disease (one of whom had an acute myocardial infarction with a low output syndrome). The average duration of symptoms in this group was 2.7 years. Twelve of these patients had physical findings associated with congestive heart failure: namely, rales, S3 gallop sound, or elevated jugular venous pressure. All had demonstrated cardiomegaly by chest X-ray and were on diuretics and digitalis.

Patients who were studied in the Cardiac Catheterization Laboratory were evaluated in the fasting state either before or at least 30 min following angiography. During a 10-min control period simultaneous determinations of heart rate (HR), systolic arterial (SBP), mean arterial (MAP), and left ventricular (LVP) pressures were recorded.

Cardiac output (CO) measurements were made at least in duplicate by the dye-dilution technique with 1 ml injections (7 mg) of indocyanine green dye into the pulmonary artery followed by a 4 ml saline flush. Sampling was carried out through a Gilford densitometer from the radial or brachial artery with a Harvard constant speed withdrawal pump (30 ml/min). Blood was reinfused into the artery after each output measurement. Dye curves were recorded directly, and the output signal was passed to a Lexington analog computer that provided an integration curve on the recorder for subsequent output determinations. No curve was accepted unless an exponential decay was demonstrated by employing at least three points separated by 0.5-sec intervals. The computer was calibrated with a 1:1000 dilution of dye in the blood, prepared with a Hamilton micro pipette. Ten milliliters of blood

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>CO (liters/min)</th>
<th>CI (liters/min/m²)</th>
<th>SBP (mm Hg)</th>
<th>MAP (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td><strong>Total group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>C</td>
<td>82 ± 3</td>
<td>4.6 ± 0.2</td>
<td>2.6 ± 0.1</td>
<td>129 ± 4</td>
<td>88 ± 3</td>
</tr>
<tr>
<td>G</td>
<td>89 ± 2</td>
<td>5.0 ± 0.2</td>
<td>2.9 ± 0.1</td>
<td>139 ± 6</td>
<td>93 ± 4</td>
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<tr>
<td>P</td>
<td>&lt;0.005</td>
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<tr>
<td><strong>Functional class I and II</strong></td>
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<tr>
<td>C</td>
<td>80 ± 4</td>
<td>4.7 ± 0.3</td>
<td>2.7 ± 0.1</td>
<td>135 ± 7</td>
<td>94 ± 5</td>
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<td>5.4 ± 4</td>
<td>3.1 ± 0.2</td>
<td>152 ± 10</td>
<td>103 ± 7</td>
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<tr>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
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<tr>
<td><strong>Functional class III and IV</strong></td>
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<tr>
<td>C</td>
<td>83 ± 4</td>
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<td>2.6 ± 0.2</td>
<td>124 ± 6</td>
<td>84 ± 3</td>
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<tr>
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<td>2.7 ± 0.2</td>
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<td>NS</td>
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</table>

*These values represent means ± standard errors.

Abbreviations: C = control before glucagon; G = after glucagon; CIs = control before isoproterenol (Isuprel); Is = less than or equal to 10 min after isoproterenol; Δ = difference of measurement between control and G or Is; HR = heart rate; CO = cardiac output; CI = cardiac index; SBP = systolic blood pressure; MAP = mean arterial pressure; LVFP = left ventricular filling pressure; TPR = total peripheral resistance; SV = stroke volume; LVSWI = left ventricular stroke work index; TTI = tension time index; dp/dt = first derivative of left ventricular pressure pulse.
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<table>
<thead>
<tr>
<th>LVFP (mm Hg)</th>
<th>TPR (units)</th>
<th>SV (ml)</th>
<th>LVSWI (g·m/m²)</th>
<th>TTI (mm Hg/min × 10⁻³)</th>
<th>dp/dt (mm Hg/sec)</th>
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<tbody>
<tr>
<td>10 ± 1</td>
<td>20 ± 1</td>
<td>58 ± 3</td>
<td>37 ± 2</td>
<td>1042 ± 44</td>
<td>1295 ± 343</td>
</tr>
<tr>
<td>9 ± 1</td>
<td>20 ± 1</td>
<td>56 ± 2</td>
<td>38 ± 2</td>
<td>1242 ± 71</td>
<td>1467 ± 334</td>
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<tr>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</tbody>
</table>

**Functional class I and II**

| 9 ± 2        | 21 ± 2      | 60 ± 4  | 40 ± 4         | 1080 ± 87               | NS               |
| NS           | NS          | NS      | NS             | <0.01                   | NS               |

| 11 ± 1       | 20 ± 2      | 56 ± 4  | 34 ± 2         | 1014 ± 46               | NS               |
| 10 ± 2       | 21 ± 2      | 54 ± 3  | 34 ± 2         | 1117 ± 61               | NS               |
| NS           | NS          | NS      | NS             | <0.02                   | NS               |

**Glucagon and isoproterenol**

| 9 ± 2        | 20 ± 2      | 52 ± 5  | 29 ± 3         | 991 ± 78                | NS               |
| NS           | NS          | NS      | NS             | NS                      | NS               |

| 10 ± 2       | 18 ± 2      | 52 ± 3  | 28 ± 3         | 999 ± 70                | NS               |
| NS           | NS          | NS      | NS             | 1480 ± 131              | NS               |

| 10 ± 3       | 11 ± 1      | 54 ± 3  | 28 ± 3         | <0.001                  | NS               |
| NS           | NS          | NS      | NS             | <0.001                  | NS               |

were drawn for determination of blood glucose and serum potassium.

After completion of control measurements, a bolus of 5 mg glucagon was infused over 1 min into a central venous site. Simultaneous measurement of pressures and CO were repeated between 5 and 10 min after the infusion and again between 20 and 30 min after glucagon was administered. Another 10-ml sample of blood was withdrawn for the determination of blood glucose and serum potassium between 20 and 30 min after glucagon was given. In four patients after the bolus of glucagon, nausea was produced, and in two of these vomiting occurred. In such circumstances, measurements were made 4 to 5 min after the patient's condition had stabilized.

Thirteen patients were studied soon after aortic or mitral valve replacement and one after a pulmonary embolectomy. Pressures were monitored from radial artery, left atrium, and pulmonary artery through polyethylene catheters in a manner previously described. Pre- and post-glucagon measurements were made in a format identical to those performed in the Cardiac Catheterization Laboratory. Observations in these patients were obtained in the first 8 hr postoperatively at a time when the patient's condition had stabilized.

In addition, isoproterenol was administered in eight of the 24 patients. Five of these eight patients were in functional classes III and IV, and seven of the eight studies were performed postoperatively. Following a second control period, isoproterenol was given as a separate infusion in a dosage (2–4 μg/min) designed to increase heart rate at least 30 beats/min without producing hypotension or arrhythmias. When this had been achieved, simultaneous pressure and output measurements were again recorded.

Pressures were measured with P23db Statham strain gauges from a zero reference level 5 cm below the angle of Louis. The total peripheral resistance (TPR) in units was calculated by the formula: mean arterial pressure/cardiac output. The left ventricular stroke work index (LVSWI) in g·m/m² was calculated by the formula:

\[
LVSWI = \frac{SI \times (MAP - LVFP) \times 13.6}{1000}
\]

where SI = stroke index in ml/min/m², MAP = mean arterial pressure in mm Hg, and LVFP = left ventricular filling pressure measured as left ventricular end-diastolic pressure (LVEDP) during cardiac catheterization and mean left atrial pressure (MLAP) postoperatively. A modified tension time index (TTI) was calculated as the product of peak left ventricular systolic pressure and HR. This was used as an indirect measurement of the myocardial oxygen consumption associated with glucagon, and has been
previously demonstrated by more direct measurements. The maximum rate of rise of the left ventricular pressure (dp/dt) was obtained preoperatively in 10 patients by an electronic differentiator.

Student's t-test for paired and unpaired data was used for all statistical calculations where applicable.

Results

A summary of the hemodynamic data showing the response to glucagon is displayed in table 1. Control hemodynamics were similar in patients with functional class I and II heart disease and those with class III and IV heart disease. Following the administration of glucagon, measurements were made during a 30-min period. Only those values obtained within 10 min after injection are included, since all later measurements confirmed that the peak effect occurred before 10 min. The results were evaluated in the following manner: (a) control measurements were compared with those following glucagon administration in all patients or in the total group, (b) a similar comparison was made in those patients who were in functional class I and II, (c) a similar comparison was made in those patients who were in functional class III and IV, and (d) changes from control values produced by glucagon in patients of functional class I and II were compared with those produced in patients of class III and IV. When the group was considered as a whole, HR rose from 82 to 89 beats/min ($P<0.005$), and there was a small, but significant, rise in CO from 4.6 to 5.0 liters/min ($P<0.001$). There was also a significant increase in SBP (129 to 139 mm Hg; $P<0.005$) and MAP (88 to 93 mm Hg; $P<0.05$). There was, however, no significant change in LVFP. Associated with the increase in SBP and HR there was a significant increase in TTI from 1042 to 1242 mm Hg/min $\times 10^{-1}$; $P<0.001$). No significant

![Graph A](image1.png)

**A**

CARDIAC OUTPUT RESPONSE TO GLUCAGON

![Graph B](image2.png)

**B**

HEART RATE RESPONSE TO GLUCAGON

**Figure 1**

(A) Cardiac output response to glucagon. There is a significant increase in the response of the total group, a greater increase in that of the functional class I and II patients, and no significant change in that of the functional class III and IV patients. (ns signifies $P \geq 0.05$.) (B) Heart rate response to glucagon. A significant increase is seen in the response of the overall group and in that of both functional class I and II and class III and IV patients.
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Figure 2

(A) Comparison of cardiac output response to glucagon and isoproterenol (Isuprel) in eight patients. (B) Comparison of heart rate response to glucagon and isoproterenol in eight patients.

(A and B) No change is seen following glucagon infusion, but a significant increase occurs following isoproterenol infusion.

Changes occurred in stroke volume (SV), TPR, LVSWI, or dp/dt. When the changes in CO are evaluated from the point of view of the functional classification in figure 1A, a distinctive pattern emerges. Although a significant increase in CO of 400 ml (+9%) occurred in the total group, there was a substantially greater rise of 700 ml (+15%) in functional class I and II patients. By contrast there was a small and nonsignificant 100-ml increment (+2%) in functional class III and IV patients. In figure 2B the changes in HR are illustrated in these groups. Although these changes were significant within each group, a statistical comparison between the HR increments in functional class I and II patients and functional class III and IV patients revealed no significant difference. Glucagon produced increases from the control value in SBP (5 mm Hg) and TTI (103 mm Hg/min × 10⁻¹) in class III and IV patients (P < 0.05). When MAP, SV, TPR, and LVSWI were analyzed by separate functional classification groups, there was no significant change.

The hemodynamic data of the eight patients who received a separate infusion of isoproterenol (Isuprel) are summarized in table 1. There was no significant change in CO in these patients following glucagon infusion although an average increase of 2500 ml/min (+56%) followed isoproterenol infusion. Similarly, HR did not change significantly with glucagon but rose 41 beats/min (+46%) after isoproterenol was administered. These changes in CO and HR are illustrated in panels A and B, respectively, of figure 2. Neither group showed a change in MAP, SBP, LVFP, SV, or LVSWI. Concurrent with the increase in CO and HR following isoproterenol infusion, there was a significant fall in
TPR from 18 to 11 units and a significant rise in TTI from 999 to 1480 mm Hg/min × 10⁻¹.

Analysis of the metabolic data revealed that in the total group blood sugar rose from 139 to 190 mg/100 ml and serum potassium fell from 4.1 to 3.9 mEq/liter. These findings are in agreement with those of other observers and were not associated with any untoward effects.¹, ⁴, ⁵

Discussion

On the basis of these observations one can anticipate that a small but significant rise in CO will be seen in most individuals with functional class I and II heart disease after an intravenous bolus of 5 mg glucagon. As this increase in output was not accompanied by changes in either LVFP or TPR, it may be attributed to a positive inotropic response. This appeared to be mediated, at least in part, by an increase in heart rate. Ashley and his coworkers,¹⁶ however, have demonstrated significant increments in resting cardiac index in patients with fixed-rate pacemakers, and there are isolated examples within our own study to show that the inotropic response may occur entirely independently of changes in heart rate.

The similarity in the resting hemodynamics in functional class I and II patients as compared to those of the patients in class III and IV is not surprising. Several factors appear to contribute to this finding: (a) since functional classification is based on the tolerance to exercise, a better separation would undoubtedly have been present had exercise hemodynamics been performed in the 16 preoperative studies, (b) vigorous medical therapy in all patients prior to catheterization and surgery would tend to diminish the differences in LVFP and CO, and (c) surgical correction of the mechanical cardiac defects prior to our measurements in the 14 early postoperative studies would again tend to diminish differences in resting hemodynamics. There were, however, a number of distinguishing features peculiar to patients in functional class III and IV. Their symptoms were more severe, and they had been present for a longer period of time (2.7 years versus 1.1 years for functional class I and II patients). Twelve of 13 patients had physical findings suggestive of congestive heart failure. All of these individuals had radiologically confirmed cardiomegaly. These characteristics attest to the presence of more advanced impairment of cardiac function in the functional class III and IV patients.

Of particular interest is the observation that the magnitude of change in CO in functional class I and II patients is greater than in functional class III and IV patients. The fact that 13 of our studies were performed following cardiac valvular replacement did not appear to alter the observation that there was a limited inotropic responsiveness to glucagon occurring in functional class III and IV patients. Thus it would appear that the preoperative functional classification and the duration of symptoms are important determinants in predicting the responsiveness to glucagon, even in the postoperative setting.

Although the two clinical reports by Parmley and coworkers demonstrated a positive inotropic response following glucagon, the magnitude of change in CO in the initial report was substantially greater than that noted in their more recent study.¹, ⁵ The basis for this difference was not evident at that time. In the light of our observations, this disparity in inotropic response can be explained on the basis of the functional classification of their patients. Williams and his associates attempted to assess the efficacy of glucagon on the basis of the severity of heart disease but were unable to do so.⁴ Greenberg et al. found no significant increase in cardiac index in 11 patients with chronic valvular disease.¹⁰ Another study by Nord and coworkers demonstrated limited effectiveness of glucagon in the treatment of chronic congestive heart failure, but it did not contain definitive hemodynamic measurements to document these changes.⁶ Hence, our study in a variety of patients allows, for the first time, a clear separation of the responsiveness to glucagon on the basis of a clinical functional classification.

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The mechanism for this finding is not clear, but it is interesting to note the experimental findings of Gold and his associates, who observed the failure of glucagon to activate adenyl cyclase in cats with chronic heart failure in contrast to cats with normal hearts or with acute heart failure. Such a mechanism might well explain the variable response we have demonstrated in man.

In eight patients who received isoproterenol as a separate infusion, there was clearly a greater inotropic and chronotropic effect, suggesting that patients who fail to respond to glucagon can retain their capacity to respond to another inotropic agent. The disparity in augmentation of CO between glucagon and isoproterenol seen in our data is substantially greater than that reported by Williams and associates. It should be noted, however, that five of the eight patients who received both drugs were in functional class III and IV, and in the light of the present findings would, therefore, be expected to be less responsive to glucagon.

In conclusion, we believe that the clinical usefulness of glucagon in advanced symptomatic heart disease is limited. Clearly patients who fail to respond to glucagon may still be capable of augmenting their CO following the administration of an alternative inotropic agent such as isoproterenol. Much of the controversy and variability concerning the hemodynamic response of glucagon would appear resolved when one considers it in the light of the functional classification of the patients studied.

Acknowledgment

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References

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