The Effect of Glucagon on the Coronary Circulation in Man

By Nora Goldschlager, M.D., Erwin Robin, M.D., Charles M. Cowan, M.D., Georg Leb, M.D., and Richard J. Bing, M.D.

SUMMARY

Glucagon, 300 µg/minute, was infused intravenously over 15 minutes in 27 subjects. The patients were divided into three groups: group I, patients without heart disease; group II, patients with arteriosclerotic heart disease; and group III, patients with congestive heart failure. Hemodynamic measurements included observations on myocardial blood flow using bolus injections of 84 rubidium and a coincidence counting technique. Myocardial oxygen consumption was determined after coronary sinus introduction in nine of the 27 patients. Significant increases were noted in heart rate, mean arterial pressure, tension-time index/minute and left ventricular work. Myocardial blood flow increased significantly while myocardial oxygen extraction remained constant suggesting that the augmentation in blood flow was sufficient to meet the increased myocardial demands for oxygen. The effects of glucagon on the coronary circulation resemble that of isoproterenol rather than norepinephrine without, however, leading to the production of arrhythmias seen with these catecholamines.

Additional Indexing Words:
Myocardial blood flow  Coincidence counting system  84-Rubidium
Myocardial oxygen consumption  Left ventricular work

The action of glucagon on the human myocardium has recently been the subject of intensive investigation.1-5 Glucagon has been shown to increase mean arterial pressure, cardiac index, and maximum rate of ventricular pressure development. In view of the inotropic effects of the hormone, its use has been suggested in cardiogenic shock and congestive heart failure.1,8,4 Enhancement of cardiac performance by glucagon would be expected to be associated with an increase in myocardial oxygen requirements.6 To date, however, it has not been shown to what extent this occurs, nor whether there is an increase in myocardial blood flow sufficient to meet the increased oxygen demands of the heart.

It is the purpose of this report to relate changes in cardiac dynamics to myocardial oxygen consumption and nutritional myocardial blood flow in subjects with and without heart disease after infusion of glucagon.

Methods

Twenty-seven unanesthetized patients were studied in the postabsorptive state. Six were found to be free of heart disease after subsequent diagnostic studies (group I); 14 had arteriosclerotic heart disease manifested by angina pectoris or prior myocardial infarction or both (group II); and seven had clinical evidence of congestive heart failure of various etiologies (group III; table I). Three patients who experienced nausea and vomiting toward the end of the procedure were excluded from the study. Observations on hemodynamics and myocardial blood flow were made under control conditions and at 15 min

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### Hemodynamic Effects of Glucagon

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<th>Age (yr)</th>
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<th>Heart rate (beats/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Cardiac index (L/min/m²)</th>
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**Group I. No heart disease**

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**Group IIIA. Arteriosclerotic heart disease**

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**Group IIIB. Acute myocardial infarction**

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**Group III. Congestive heart failure**

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**Average ± standard error**

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<th>Standard Error</th>
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<th>Mean % change</th>
<th>Significance (P)</th>
<th>Number of patients</th>
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<td>85 ± 3</td>
<td>91.9 ± 3.0</td>
<td>100.6 ± 3.5</td>
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<td>2.7 ± 0.7</td>
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<td>Mean arterial pressure (mm Hg)</td>
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<td>8.7 ± 1.5</td>
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**Abbreviations:** B = before infusion of glucagon (300 µg/min); A = after infusion of glucagon (300 µg/min).

* Arteriosclerotic heart disease; † rheumatic heart disease; ‡ cardiomyopathy.

* *, †, ‡ Etiology.
Table 1 (Continued)

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<tr>
<th>Case</th>
<th>Tension-time index (mm Hg sec/min)</th>
<th>Peripheral vascular resistance (dyne sec cm⁻²/m²)</th>
<th>Left ventricular work (kg·m/min/m²)</th>
<th>Myocardial blood flow (cc/min/whole heart)</th>
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<td></td>
<td>B</td>
<td>A</td>
<td>% Change</td>
<td>B</td>
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</table>

**Group I. No heart disease**

1  | 2584 | 2736 | 5.9 | 853 | 939 | 10.1 | 4.0 | 4.0 | 0.0 | 458 | 557 | 12.2 |
2  | 2229 | 2484 | 11.4 | 836 | 751 | -10.2 | 3.7 | 4.2 | 13.5 | 367 | 581 | 58.7 |
3  | 2513 | 2788 | 10.9 | 889 | 949 | 6.7 | 4.3 | 4.4 | 2.3 | 389 | 415 | 6.6 |
4  | 2076 | 2496 | 20.2 | 2125 | 2447 | 15.2 | 2.5 | 2.7 | 8.0 | 219 | 305 | 39.3 |
5  | 2580 | 3192 | 12.0 | 1328 | 1110 | -16.4 | 3.9 | 3.9 | 0.0 | 351 | 457 | 30.2 |
6  | 3678 | 3948 | 7.3 | 2200 | 1923 | -12.6 | 4.5 | 5.8 | 28.9 | 319 | 416 | 30.0 |

**Group II. Arteriosclerotic heart disease**

7  | 3379 | 3643 | 7.8 | 1484 | 1529 | 3.0 | 7.7 | 7.3 | -5.2 | 420 | 378 | -11.2 |
8  | 2508 | 2693 | 7.4 | 1354 | 1333 | -1.6 | 4.0 | 4.6 | 15.0 | 313 | 415 | 32.3 |
9  | 2918 | 3672 | 25.8 | 1481 | 1458 | -1.6 | 4.7 | 5.9 | 25.5 | 353 | 396 | 12.2 |
10 | 2470 | 2561 | 3.7 | 1022 | 1187 | 16.1 | 4.7 | 4.6 | -2.1 | 554 | 493 | -11.0 |
11 | 2253 | 2647 | 17.5 | 1077 | 1296 | 20.3 | 3.2 | 3.6 | 12.5 | 244 | 276 | 13.1 |
12 | 2955 | 3890 | 31.6 | 1086 | 1318 | 21.4 | 5.1 | 6.0 | 17.6 | 378 | 317 | -16.1 |
13 | 2273 | 2682 | 18.0 | 1265 | 1278 | 1.0 | 4.5 | 5.5 | 22.2 | 393 | 451 | 14.8 |
14 | 2298 | 2441 | 6.2 | 1667 | 1508 | -9.5 | 4.3 | 4.6 | 7.0 | 174 | 207 | 19.0 |
15 | 3006 | 4088 | 13.4 | 2379 | 2778 | 16.8 | 4.8 | 5.0 | 4.2 | 179 | 244 | 36.5 |
16 | 3639 | 3590 | 1.3 | 1076 | 1108 | 3.0 | 7.2 | 7.2 | 0.0 | 357 | 417 | 17.1 |
17 | 2817 | 3985 | 41.5 | 1365 | 1560 | 14.3 | 4.0 | 6.0 | 50.0 | 193 | 203 | 4.7 |

**Group II. Acute myocardial infarction**

18 | 2032 | 2196 | 8.0 | 1031 | 1091 | 5.8 | 2.6 | 3.1 | 19.2 | 196 | 217 | 10.7 |
19 | 2683 | 3003 | 11.9 | 1427 | 1724 | 20.8 | 5.5 | 5.6 | 1.8 | 186 | 147 | -21.1 |
20 | 2441 | 2772 | 13.6 | 1238 | 1352 | 9.2 | 5.2 | 4.4 | -15.4 | 244 | 216 | -11.5 |

**Group III. Congestive heart failure**

21 | 1753 | 1833 | 4.6 | 2097 | 2000 | -4.6 | 1.6 | 1.7 | 6.3 | 217 | 311 | 43.3 |
22 | 2006 | 2138 | 6.6 | 4059 | 3840 | -17.6 | 1.3 | 1.5 | 15.4 | 259 | 259 | 0.0 |
23 | 2490 | 3120 | 25.3 | 2086 | 2400 | 15.0 | 1.7 | 2.0 | 17.6 | 247 | 263 | 6.5 |
24 | 2214 | 2673 | 20.7 | 5050 | 4400 | -12.9 | 1.7 | 2.2 | 29.4 | 137 | 171 | 24.8 |
25 | 3065 | 3709 | 21.0 | 4190 | 4322 | 7.9 | 1.8 | 2.3 | 27.7 | 192 | 215 | 12.0 |
26 | 1541 | 1405 | -3.0 | 2601 | 1867 | -30.6 | 1.5 | 2.5 | 66.7 | 148 | 242 | 63.5 |
27 | 3100 | 3262 | 5.2 | 1400 | 1887 | 34.8 | 3.9 | 3.5 | -10.3 | 1323 | 314 | -2.8 |

Average ± standard error  
B  | A  | B  | A  | B  | A  | B  | A  |
2604 ± 2953 ± 1828 ± 1816 ± 3.9 ± 4.3 ± 0.3 ± 0.3
107 | 132 | 217 | 194 | 13.2 | 3.8 | 13.3 | 3.8 |
Mean change ± standard error  
B  | A  | B  | A  | B  | A  |
349.1 ± 54.5 ± -11.5 ± 64.1 ± 0.4 ± 0.1
Mean % change  
NS  | NS  | NS  | 6  | 14  | 7  |
Significance (P)  
<0.001 | <0.01 | <0.01 | NS  | NS  |
Number of patients  
27  | 27  | 27  | 27  | 27  |

Group I  | Group II  | Group III
after the onset of an intravenous infusion of glucagon* (300 μg/min).

The principle of myocardial blood flow measurement using a double coincidence counting system and a bolus injection of 84rubidium has been previously reported from this and other laboratories.7-11

The double coincidence counting system consists of two pairs of radiation detectors placed anteriorly and posteriorly to the supine patient. One pair of detectors is positioned anteriorly and posteriorly to the heart, the outline of which is drawn on the chest during fluoroscopy; the other pair of detectors is placed anteriorly and posteriorly to the right chest. The difference in counts between the heart and chest is electronically subtracted and represents myocardial uptake of the tracer. The major advantage of this system consists in the separation of myocardial radioactivity from that of surrounding tissue structures.

84Rubidium is lipid-insoluble, highly diffusible positron emitter. Myocardial blood flow, as measured by myocardial 84rubidium uptake, reflects only that portion of total coronary flow which is effective in blood-tissue exchange; blood flow passing through nonnutritional channels is not measured by rubidium uptake. On the basis of previous work,10 it has been demonstrated that myocardial blood flow (MBF) may be calculated from the formula:

\[
MBF \text{ (cc/min/whole heart)} = \frac{U_H(t)}{\int_0^\infty A_1(t) \, dt}
\]

where \(U_H(t)\) = total uptake of 84rubidium by the heart following injection (counts/min), and

\[
\int_0^\infty A_1(t) \, dt = \text{integrated counts of 84rubidium activity in arterial blood during the primary arterial circulation (counts/sec).}
\]

As 84rubidium is exchanged with myocardial tissue only through capillaries, its uptake by the myocardium is an index of nutritional capillary flow.

Myocardial blood flow was determined in the following manner: With the patient in a supine position, a 6-inch polyethylene cannula was introduced into the left antecubital vein for the purpose of drug administration. After infiltration of the right antecubital fossa with 1% lidocaine (Xylocaine), a no. 18 Courmand needle was placed in the brachial artery. Phasic and mean arterial pressures were detected through a Statham P23D strain gauge and recorded on an Electronics for Medicine DR-8 recorder. Arterial blood was then withdrawn at 40 cc/min by a Harvard withdrawal pump and circulated through a radion which had been placed in a well counter. After withdrawal of blood was begun, a single bolus of 84rubidium (0.2 μc/lb) was administered intravenously through the indwelling cannula. Myocardial and arterial counts were recorded until appearance of recirculation of the isotope, and myocardial uptake of the tracer became constant.12

Myocardial blood flow was calculated from the above formula. \(U_H(t)\) represents the average of the constant precordial radiation counts registered in the period of 90 to 270 sec after 84rubidium injection. \(\int_0^\infty A_1(t) \, dt\) was obtained as the area under the arterial curve plotted on semilogarithmic paper with the straight-line downslope extrapolated to background radioactivity. Cardiac output was calculated from the Stewart-Hamilton formula,13 the total amount of injected 84rubidium serving as the numerator.

Mean arterial pressures were electronically integrated. Tension-time index was calculated according to the method of Sarnoff and associates.14

The following formulae were used:

\[
\text{Left ventricular work (kg-m/min/m}^2\) = \frac{\text{MSAP} \times 13.6 \times \text{CI}}{1000}
\]

and

\[
\text{Peripheral vascular resistance (dynes sec cm}^{-5}/\text{m}^2\) = \frac{\text{MAP} \times 80}{\text{CI}}
\]

where MSAP is the mean systolic aortic pressure (mm Hg); 13.6 is the mercury conversion factor; CI is the cardiac index (L/min/m^2); and MAP is the mean arterial pressure (mm Hg).

In addition to the above determinations myocardial oxygen consumption was studied after intubation of the coronary sinus in nine patients selected at random. Four of the patients were subsequently found to be free of heart disease (group I); two had arteriosclerotic heart disease (group II); and three were in congestive heart failure (group III; table 2). As seen in table 1, the hemodynamic responses to glucagon in these nine patients are similar to those of the total group. Simultaneous arterial (A) and coronary sinus (V) blood samples were obtained from oxygen analysis, performed according to the

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*Eli Lilly and Company, lyophilized preparation supplied as the hydrochloride.
Table 2

Effects of Glucagon upon Myocardial Oxygen Extraction and Consumption

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<th>Myocardial oxygen consumption (cc/min)</th>
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Group I. No heart disease

Group II. Arteriosclerotic heart disease

Group III. Congestive heart failure

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<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Myocardial oxygen extraction (vol %)</th>
<th>Myocardial oxygen consumption (cc/min)</th>
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</tbody>
</table>

Average ± standard error

Mean change ± standard error

Mean % change

Significance (P)

Number of patients

* Etiology: Arteriosclerotic heart disease.
† Etiology: Cardiomyopathy.

Abbreviations: B = before infusion of glucagon (300 µg/min); A = after infusion of glucagon (300 µg/min).
method of Van Slyke and Neill. Myocardial oxygen extraction (A-V) O₂ (vol%) was obtained as the difference in oxygen content between brachial artery (A) and coronary sinus (V) blood. Myocardial oxygen consumption (cc/min) was calculated as the product of myocardial blood flow (cc/min/whole heart) and myocardial oxygen extraction (A-V) O₂ (vol%). Blood samples were obtained before and 15 min after beginning the glucagon infusion. The total dose of the hormone did not exceed 6 mg in any of the 27 patients and usually ranged between 4 and 5 mg for the 15 to 20-min period of study.

Results

Hemodynamic data obtained in six normal persons (group I), 14 arteriosclerotic subjects (group II), and seven patients with congestive heart failure (group III) are presented in table 1 and figure 1. They were tabulated for the three groups individually and subjected to statistical analysis using the t-test and nonpaired data. In addition, data from group II were statistically analyzed, including or omitting the three patients with acute myocardial infarcts. Changes of significance for the group were not altered by including these three subjects. Data on myocardial oxygen consumption were not statistically evaluated for the different patient groups in view of the small number of patients studied but were evaluated for the group as a whole (table 2). With the exception of myocardial blood flow, the hemodynamic response to glucagon infusion did not differ among the different groups.

After glucagon infusion significant increases in heart rate (average, 5.1%; P < 0.005), mean arterial pressure (average, 9.6%; P < 0.001), tension-time index per minute (average, 13.2%; P < 0.001), and left ventricular work (average, 13.3%; P < 0.01) were observed. On the other hand, there were no significant changes in cardiac and stroke indices and peripheral vascular resistance (table 1; fig. 1).

In contrast to a significant rise in normal subjects (average, 29.5%; P < 0.01) there was no significant change in myocardial blood flow in patients with arteriosclerotic heart disease and congestive heart failure (table 1; fig. 1).

In six patients (table 1; cases 7, 10, 12, 19, 20, and 27), myocardial blood flow declined. In four, this was accompanied by a decrease in left ventricular work although the degrees of change in these parameters were not of the same magnitude (table 1; cases 7, 10, 20, and 27).

Glucagon infusion resulted in a significant rise in myocardial oxygen consumption (average, 35.7%; P < 0.01) as myocardial oxygen extraction remained fairly constant (table 2; fig. 1).

In eight of the nine patients both myocardial oxygen consumption and blood flow increased. In one subject coronary blood flow did not change as myocardial oxygen consumption remained at control levels (tables 1 and 2; case 22).

Discussion

The purpose of this study was to investigate the relation of cardiac dynamics with nutritional myocardial blood flow and myocardial oxygen consumption in man during glucagon infusion. The cardiotonic action of glucagon observed by us confirms the work of others in both man1-5 and animals.6-21 Most patients exhibit a positive response to the hormone. In agreement with previous reports,3 the lack of...
response observed in some subjects did not seem to be related to the presence or absence of cardiac disease or to the duration or severity of the disease.

The mechanism of action of glucagon on the myocardium has not been elucidated as yet. It is known that the hormone, like the catecholamines, is an enzyme activator of the adenyl cyclase system, yielding 3', 5'-monophosphate (cyclic AMP) from adenosine triphosphate. It is thought that cyclic AMP may be the mediator of various hormones on cardiac tissue. Levine and co-workers have shown that infusion of cyclic AMP results in increased cardiac output and blood pressure, the inotropic response persisting despite beta-receptor blockade with propranolol. These findings suggest that cyclic AMP may be part of the biochemical basis for myocardial response to catecholamines and glucagon.

Myocardial cyclic AMP levels after glucagon have not been consistently elevated. Furthermore, beta-blockade does not prevent the rise in myocardial cyclic AMP after glucagon in contrast to catecholamines. A recent study has indicated that these findings suggest that cyclic AMP may be part of the biochemical basis for myocardial response to catecholamines and glucagon.

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This concept would explain why beta-receptor blockade prevents both adenyl cyclase activation and inotropic action by catecholamines, but not by glucagon. It would also explain the observation that concomitant administration of glucagon and catecholamines does not produce greater adenyl cyclase activation than administration of either agent alone.

The cardiotonic effects of glucagon in man are well known and have included increases in cardiac output, aortic pressure, heart rate, maximal rate of rise of ventricular pressure (dp/dt), and stroke work. Variable changes in peripheral vascular resistance and ventricular end-diastolic pressure occur. Significant arrhythmias have not been reported in congestive heart failure and cardiogenic shock; its failure to produce arrhythmias in the digitalized patient has been cited as a major advantage. In the present study, all patients in congestive heart failure were fully digitalized and arrhythmias were not seen.

Three patients with recent acute myocardial infarction (at 1, 3, and 4 days, respectively) were included in group II. Neither shock nor congestive heart failure was observed. While the hemodynamic response to hormone infusion followed the general trend exhibited by other subjects in this series, myocardial blood flow declined in two and was accompanied by a slight fall in cardiac index and left ventricular work (table 1; cases 19 and 20).

In all, four of our patients exhibited a decline in left ventricular work, and a concomitant decline in myocardial blood flow after glucagon infusion (table 1; cases 7, 10, 20, and 27). Three patients who did not show a change in left ventricular work had a rise in myocardial blood flow (table 1; cases 1, 5, and 16). Two patients with arteriosclerotic heart disease had a fall in myocardial blood flow that was not associated with a fall in left ventricular work; (table 1; cases 12 and 19). In general, the data reveal that the change in left ventricular work is accompanied by the same directional change in myocardial blood flow, although the degrees of change are not correlative.

When the results pertaining to coronary flow are treated statistically according to groups, it may be seen that only normal individuals respond to the drug with an increase in myocardial blood flow (table 1). This difference in response of the coronary circulation to glucagon, in the presence or absence of coronary artery disease, is similar to that observed with nitroglycerin and nicotine. It should be emphasized, however, that most patients with congestive heart failure have arteriosclerotic heart disease. Thus, the lack of response in group III may be related more to the presence of coronary artery disease than to that of congestive heart failure.

Studies on myocardial oxygen consumption revealed a significant increase in the majority of patients after glucagon infusion (table 2; fig. 1). The absence of an increase in myocardial oxygen extraction suggests that the
concomitant increase in myocardial blood flow is sufficient to meet the increase in oxygen demands of the heart produced by glucagon. This is in contradistinction to norepinephrine which, despite an augmentation in coronary blood flow, results in a rise in myocardial oxygen extraction when oxygen consumption is increased.26 The administration of isoproterenol, on the other hand, results in an augmentation of myocardial blood flow which is adequate to meet oxygen demands, as oxygen extraction is unchanged or even diminished.26 Thus, glucagon resembles isoproterenol rather than norepinephrine in its action on the coronary circulation.

The ability of glucagon to augment myocardial blood flow without increasing myocardial oxygen extraction constitutes another physiologic advantage for the use of this hormone in the treatment of certain patients with cardiac disease.

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The Effect of Glucagon on the Coronary Circulation in Man
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