Effects of Glucagon on Myocardial Metabolism in Patients With and Without Coronary Artery Disease

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SUMMARY
The metabolic effects of glucagon on the heart were studied in subjects with and without coronary artery disease. In both groups, a moderate rise in the arterial glucose level occurred with practically unchanged glucose uptake by the myocardium. Myocardial oxygen extraction was also unchanged in both groups of subjects. In individuals with normal coronary arteries, myocardial extraction ratio of lactate was normal before and unchanged after glucagon administration. In patients with significant coronary artery disease, mean extraction ratio of lactate was very low before glucagon and increased markedly following its administration. Seven of 18 patients had production of lactate by the myocardium before glucagon, and this reverted to lactate extraction 5 min after glucagon administration. Left ventricular work index was found to increase more than indices of myocardial contractility and oxygen consumption, and improved aerobic lactate utilization during glucagon action may be partly related to the lower oxygen cost of work performance or improved cardiac efficiency. Arterial serum potassium level decreased in both groups of subjects after glucagon administration, with the appearance of a slightly negative potassium balance across the myocardium. The possible relationship of the cardiac inotropism induced by glucagon to intramyocardial ionic exchanges is discussed.

Additional Indexing Words:
Inotropism  Cyclic AMP  Cardiac efficiency  Lactate extraction ratio
Serum potassium level  Intracellular ionic exchange

IMPORTANT cardiovascular effects of glucagon have recently been demonstrated in experimental preparations1-7 and in man.8-14 The drug was shown to have a significant inotropic and chronotropic cardiac action1-4, 8-13 and to enhance atrioventricular conduction velocity without increasing ventricular automaticity.5-7, 14 It has been found of actual or potential value in the treatment of cardiac failure, cardiogenic shock, and various degrees of atrioventricular block.

These reports have also stressed several advantages of glucagon in these clinical situations. Firstly, glucagon therapy can be effective despite full digitalization5, 8, 11, 12 and does not enhance ventricular irritability.1-12 It acts also after myocardial depletion of catecholamines by previous treatment with reserpine,1, 3, 4 It is not antagonized by beta-receptor blocking agents.3, 4, 6, 7 Duration of action is at least 15 to 20 min.3, 8, 9 and tachyphylaxis does not occur.8 Lastly, glucagon is remarkably free of any serious side effects.8-13

It is not known, however, whether the myocardial oxygen requirements of increased contractility and heart rate, following administration of glucagon, can adversely influence its clinical use. Consequently, some measurable aspects of myocardial metabolism following glucagon administration were investigated, in

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the present study, in subjects with normal coronary arteriograms, and in patients with documented coronary artery disease.

Methods

Following left heart and coronary sinus catheterization, a 5-mg, single intravenous dose of glucagon was administered to 28 selected subjects.

The hemodynamic data were obtained prior to and 2, 5, 10, and 15 min after administration of glucagon. Aortic pressure, left ventricular pressure, first derivative of left ventricular pressure, and lead II of the electrocardiogram were recorded on a multichannel photographic recorder. The zero reference point was placed at the midthoracic level. Cardiac output was determined by the indicator-dilution technic. The first derivative of left ventricular pressure was obtained with an R-C differentiating circuit. Systemic vascular resistance was calculated in dynes sec cm\(^{-5}\) using the standard formula. Systolic ejection rate was calculated in ml/sec/m\(^2\) as the ratio of cardiac index in L/min/m\(^2\) divided by the duration of systolic ejection in seconds and heart rate. Tension-time index was measured in mm Hg/min as the product of mean aortic pressure in mm Hg, duration of systolic ejection in seconds, and heart rate. Left ventricular work index was calculated using the formula:

\[
CI \times (MAP - LVEDP) \times 13.6
\]

1,000

where CI is the cardiac index in L/min/m\(^2\), MAP is the mean aortic pressure in mm Hg, and LVEDP is the left ventricular end-diastolic pressure in mm Hg.

Arterial and coronary sinus blood samples were withdrawn in the control period and 5 min after administration of glucagon. The samples were obtained in the midportion of the main coronary sinus, with the catheter placed approximately 2 cm from the left heart border.

The pH and PO\(_2\) were measured with the pH/gas analyzer, and the oxygen saturation was obtained with a hemoreflector.* Blood glucose and potassium were measured on the Technicon Autoanalyzer. Lactate concentrations were determined by the enzymatic method* and were expressed in millimoles per liter. The extraction ratio of lactate by the myocardium was calculated as A-V/A \times 100 in per cent, where A represents the arterial lactate concentration and V lactate concentration in the midportion of the coronary sinus.

After completion of the study, percutaneous selective cine coronary arteriography\(^{17}\) was performed in all subjects as part of a diagnostic investigation. Ten individuals were shown to have normal coronary arteries (group A), and 18 patients had significant coronary artery disease (group B). The age range, sex, and severity of disease of the patients are presented in table 1.

Coronary artery disease was considered significant when there was more than 50% narrowing of one or more major branches of the coronary arteries.

Results

The hemodynamic data, pH, oxygen, glucose, and potassium measurements were not significantly different in subjects with normal coronary arteriograms (group A) and in patients with significant coronary artery disease (group B).

Hemodynamic Data

Maximum hemodynamic changes occurred between 2 and 5 min after administration of glucagon. The effects of glucagon decreased progressively in 10 to 15 min. There was often a return to or near to control levels at 15 min (table 2).

Heart rate and mean aortic pressure rose 12% in group A and 13% in group B. Cardiac index


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Table 2

Hemodynamic Data Before and After Glucagon*

<table>
<thead>
<tr>
<th>Time</th>
<th>Heart rate (beats/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Cardiac index (L/min/m²)</th>
<th>Systemic vascular resistance (dyne sec cm⁻²)</th>
<th>LVEDP (mm Hg)</th>
<th>Max. LV dp/dt (mm Hg/sec)</th>
<th>Systolic ejection rate (ml/sec/m²)</th>
<th>Tension-time index (mm Hg sec/min)</th>
<th>LVWI (kg-m/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>66 ± 6.4</td>
<td>84 ± 9.9</td>
<td>2.81 ± 0.70</td>
<td>1716 ± 544</td>
<td>8.1 ± 1.3</td>
<td>1071 ± 187</td>
<td>130 ± 34</td>
<td>1848 ± 304</td>
<td>2.90 ± 1.07</td>
</tr>
<tr>
<td>2</td>
<td>74 ± 8.9</td>
<td>94 ± 11.2</td>
<td>3.27 ± 0.90</td>
<td>1685 ± 652</td>
<td>8.6 ± 2.0</td>
<td>1265 ± 282</td>
<td>144 ± 47</td>
<td>2184 ± 391</td>
<td>3.84 ± 1.06</td>
</tr>
<tr>
<td>5</td>
<td>69 ± 7.5</td>
<td>91 ± 12.4</td>
<td>3.33 ± 0.81</td>
<td>1652 ± 540</td>
<td>7.9 ± 1.9</td>
<td>1253 ± 300</td>
<td>150 ± 36</td>
<td>2043 ± 425</td>
<td>3.77 ± 1.16</td>
</tr>
<tr>
<td>10</td>
<td>67 ± 7.9</td>
<td>89 ± 12.0</td>
<td>2.96 ± 0.63</td>
<td>1695 ± 457</td>
<td>7.9 ± 1.9</td>
<td>1209 ± 277</td>
<td>137 ± 34</td>
<td>1910 ± 378</td>
<td>3.26 ± 0.92</td>
</tr>
<tr>
<td>15</td>
<td>66 ± 6.5</td>
<td>85 ± 11.6</td>
<td>2.84 ± 0.57</td>
<td>1730 ± 518</td>
<td>7.3 ± 1.3</td>
<td>1212 ± 313</td>
<td>133 ± 31</td>
<td>1827 ± 267</td>
<td>3.03 ± 0.96</td>
</tr>
</tbody>
</table>

A. Subjects with normal coronary arteries

Maximum change
from control 12%  12%  16%  —  —  18%  11%  18%  32%

B. Subjects with significant coronary artery disease

Maximum change
from control 13%  13%  21%  —  —  20%  15%  24%  39%

*Figures after = = standard deviation from the mean value.
Abbreviations: LVEDP = left ventricular end-diastolic pressure (mm Hg); Max LV dp/dt = maximum left ventricular dp/dt (mm Hg/sec); LVWI = left ventricular work index (kg-m/min/m²).
increased 16% in group A and 21% in group B. There was no significant variation in systemic vascular resistance and left ventricular end-diastolic pressure. Left ventricular dp/dt rose 18% in group A and 20% in group B. Tension-time index increased 18% in group A and 24% in group B. On the other hand, left ventricular work index rose 32% in group A and 39% in group B.

**Metabolic Data**

**Oxygen and pH Measurements**

Arterial and coronary sinus values and arteriovenous difference of oxygen tension and saturation are unchanged after glucagon administration (fig. 1). Blood pH values are also unchanged following glucagon (fig. 1).

**Glucose and Potassium Measurements**

Significant changes occurred in glucose and potassium measurements as shown in figure 2. Arterial and coronary sinus blood glucose rose significantly after glucagon, without change in the narrow coronary arteriovenous difference of glucose. Thus, glucose extraction by the myocardium is not changed significantly.

There is a slight consistent drop in arterial potassium level, whereas the level in the coronary sinus is maintained practically unchanged following administration of glucagon. Although not statistically significant, this was
was low in the control period and was shown to increase significantly after glucagon (fig. 4). Moreover, in seven of the 18 patients the myocardium produced lactate prior to glucagon administration, and in all seven, there was a reversal to lactate extraction within 5 min after glucagon injection.

Symptoms

The injection of glucagon was always given slowly over a period of 1 min. This was followed by transient nausea in approximately one fourth of the subjects. The nausea was usually mild and was rarely accompanied by vomiting. Anginal pain was not observed in any of the patients following glucagon administration.

Discussion

Our hemodynamic findings confirm the previously reported slight chronotropic and moderate inotropic cardiac action of glucagon in the presence or absence of heart disease.8-13

Arterial lactate concentration is unchanged following glucagon administration. All individuals with normal coronary arteries were shown to have a normal positive lactate extraction by the myocardium in the control period. Myocardial extraction ratio of lactate remained normal and practically unchanged following glucagon administration in all these subjects (fig. 3).

In patients with coronary artery disease, mean ratio of myocardial lactate extraction consistently noted in all subjects and probably indicates liberation of potassium by the myocardium during glucagon action on the heart.

Myocardial Extraction Ratio of Lactate

Arterial lactate concentration is unchanged following glucagon administration. All individuals with normal coronary arteries were shown to have a normal positive lactate extraction by the myocardium in the control period. Myocardial extraction ratio of lactate remained normal and practically unchanged following glucagon administration in all these subjects (fig. 3).

In patients with coronary artery disease, mean ratio of myocardial lactate extraction was low in the control period and was shown to increase significantly after glucagon (fig. 4). Moreover, in seven of the 18 patients the myocardium produced lactate prior to glucagon administration, and in all seven, there was a reversal to lactate extraction within 5 min after glucagon injection.

Symptoms

The injection of glucagon was always given slowly over a period of 1 min. This was followed by transient nausea in approximately one fourth of the subjects. The nausea was usually mild and was rarely accompanied by vomiting. Anginal pain was not observed in any of the patients following glucagon administration.
Enhancement of myocardial contractility is shown by a moderate elevation of the cardiac index with an unchanged left ventricular filling pressure and moderate rise in peak left ventricular dp/dt. The increase in myocardial oxygen consumption, based on the tension-time index, is proportional to the rise in contractility indices.

Oxygen extraction by the myocardium remains unchanged following the inotropic action of glucagon, and total coronary blood flow has been shown to rise in proportion to the increase in myocardial oxygen consumption.\(^\text{13, 17, 18}\)

The ability of the left ventricle to perform work, on the other hand, increases more than myocardial oxygen consumption. This, in the presence or absence of coronary heart disease, indicates an improved cardiac efficiency,\(^\text{17, 19}\) which is presumably related to better energy or oxygen utilization by the myocardium following glucagon administration.

A moderate rise in blood glucose level and slight drop in serum potassium level, observed in the present study, have been previously shown.\(^\text{11}\) The hyperglycemia, however, is not responsible for the inotropic effect of glucagon, since the simultaneous administration of insulin in dogs does not alter the positive response.\(^\text{3}\) Moreover, despite higher arterial levels, glucose and free fatty acid uptake by the myocardium are not increased in dogs.\(^\text{18}\)

Glucose uptake by the myocardium was also unchanged in our patients following the moderate hyperglycemia induced by glucagon. This is in agreement with previous observations showing that myocardial extraction of glucose no longer increases after arterial glucose level has reached 110 mg%.\(^\text{20, 21}\) The reduction in serum potassium following administration of glucagon has been attributed to the insulin response to hyperglycemia with subsequent movement of glucose and potassium into cells.

Two very significant observations from our study are (1) a marked improvement of myocardial lactate metabolism in patients with significant or severe coronary artery disease, and (2) the occurrence of a negative potassium balance across the myocardium during glucagon action in both groups of subjects studied.

Unchanged myocardial extraction of lactate following glucagon administration has previously been shown in normal individuals\(^\text{13}\) and also in dogs.\(^\text{18}\) Improved lactate utilization by the myocardium in patients with coronary artery disease, on the other hand, is in marked contrast with the known effects of the catecholamines and emphasizes the important differences in the action of both hormones on the heart.

The beta-receptor stimulation of catecholamines, following activation of the adenylyl cyclase enzyme system, increases cyclic AMP formation from ATP in the myocardial cells.\(^\text{22}\) The elevation of intracellular cyclic AMP can be correlated with the inotropic effect of these hormones.\(^\text{23}\)

Beta-adrenergic stimulation has also been shown to have a direct effect on coronary circulation\(^\text{24, 25}\) and intermediary myocardial metabolism.\(^\text{26}\) Isoproterenol, an agent with exclusive beta-receptor activity, produces an important increase in coronary blood flow usually much greater than the increase in myocardial oxygen consumption resulting from increased contractility.\(^\text{27}\) Moreover, myocardial oxygen consumption is also much in excess of the external cardiac work performed.\(^\text{27}\)

Catecholamines can also result in a direct increase in phosphorylase activity and glycolysis. Glycolysis is enhanced, and it has been shown that, following isoproterenol administration, lactate can accumulate within the myocardium rather than being metabolized.\(^\text{26}\) In patients with significant coronary artery disease, the occurrence of anaerobic metabolism and myocardial lactate accumulation and production has been repeatedly shown during infusions of isoproterenol.\(^\text{28, 29}\)

It has been well established recently that glucagon does not stimulate alpha\(^\text{8}\) or beta-receptors\(^\text{3, 4}\) of the heart and blood vessels and that it has no cholinergic action.\(^\text{3}\) In the intact heart, glucagon probably activates the adenylyl cyclase enzyme system through a mechanism.
not yet identified.\textsuperscript{30} This results in an increase in intracellular cyclic AMP.\textsuperscript{23, 31} The action of glucagon on myocardial contractility and anaerobic metabolism are presumably both secondary to the effects of cyclic AMP in the myocardial cells.\textsuperscript{32, 33}

Increased intracellular levels of cyclic AMP can be related to the inotropic effects of glucagon.\textsuperscript{23} Cyclic AMP also activates phosphorylase to promote glycogenolysis and supply endogenous glucose for substrate utilization. Cyclic AMP also has the ability to enhance glycogen formation in the myocardium in the presence of high arterial glucose level.

It can be postulated that, following interventions on myocardial contractility in patients with restricted coronary circulation, the oxygen cost of work performance or myocardial efficiency directly affects aerobic lactate utilization by the myocardium.

Thus, following glucagon administration, the lower oxygen cost for a given work load of the left ventricle may contribute at least partly to the improved myocardial lactate utilization in patients with coronary artery disease. Previous studies from this laboratory have shown that a similar situation may be obtained during moderate leg exercise.\textsuperscript{34}

On the other hand, beta-receptor stimulation and electrical stimulation\textsuperscript{35} of the heart significantly decrease cardiac efficiency and often result in lactate production by the myocardium in patients with coronary artery disease. This occurs despite a marked increase in total coronary blood flow following these inotropic interventions on the heart.

The present data suggest that, although glucagon increases myocardial contractility only moderately, it is a more suitable inotropic agent than the beta-adrenergic stimulators, especially in patients with acute and chronic ischemic heart disease.

The higher potassium level in coronary sinus blood, compared to arterial level, is probably not an effect of concentration, since it occurs with a presumed increase in coronary blood flow. This negative potassium balance across the myocardium may well represent intracellular replacement of potassium by sodium, like that which follows digitalis administration. It has also been shown that increased cyclic AMP probably influences cardiac inotropism by increasing the intramyocardial calcium pool and cellular membrane permeability.\textsuperscript{23} As is well known, calcium is needed for excitation-contraction coupling and has a major role in increased contractility.

This inotropic mechanism of glucagon, however, appears to differ from that of digitalis glycosides in many respects. Glucagon does not block adenosine triphosphatase (ATPase) activity at the cell membrane and has been shown not to have any competitive effect with digitalis preparations. Also, this potassium loss is not accompanied by increased irritability of the myocardium.

\textbf{References}


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