Experimental Myocardial Infarction

X. Efficacy of Glucagon in Acute and Healing Phase in Intact Conscious Dogs: Effects on Hemodynamics and Myocardial Oxygen Consumption

By Raj Kumar, M.D., G.V.R.K. Sharma, M.D., Farouk A. Molokhia, M.D., John C. Norman, M.D., A.N. Inamdar, Ph.D., Joseph V. Messer, M.D., Walter H. Abelmann, M.D., and William B. Hood, Jr., M.D.

SUMMARY

This study was designed to test the efficacy of glucagon in the treatment of hemodynamic abnormalities of acute and healing experimental canine myocardial infarction. Myocardial infarction was produced in intact, conscious dogs by gradual inflation of a balloon cuff device implanted around the left anterior descending coronary artery 1 to 2 weeks prior to the study. Hemodynamic and metabolic effects of 50 μg/kg of glucagon were assessed serially in the control state, 1 hour after myocardial infarction and again 1 week later. In the control state glucagon improved cardiac performance and increased myocardial oxygen consumption. One hour after acute myocardial infarction glucagon improved cardiac performance and reduced the degree of left ventricular failure, without any increase in myocardial oxygen consumption. Similar effects of glucagon were noted in the healing phase of myocardial infarction. It is postulated that in this animal model in the presence of heart failure due to myocardial infarction there are reciprocal changes in the factors that increase myocardial oxygen consumption (glucagon-induced inotropy) and decrease oxygen consumption (fall in ventricular end-diastolic volume and wall stress), resulting in no net change in oxygen requirement.

Additional Indexing Words: Coronary occlusion  Coronary blood flow  Left ventricular failure

The positive inotropic effects of glucagon have been established in the isolated heart,1 papillary muscle,2 and in intact animal preparations.3-4 However, opinions as to its usefulness in the treatment of clinical heart failure of various etiologies have been divided.5-8 Like other positive inotropic agents, glucagon may increase myocardial oxygen consumption, and this may potentially limit its clinical usefulness. This might apply particularly to acute myocardial ischemia, in which oxygen supply is compromised.

The present study was designed to answer the following questions: (1) Does glucagon ameliorate the left ventricular failure of acute and healing myocardial infarction in an intact

From the Thorndike Memorial and Sears Surgical Laboratories, Harvard Medical and Surgical Units, the Tufts Circulation Laboratory, Boston City Hospital, the Departments of Medicine and Surgery, Harvard Medical School, and the Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts.

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Address for reprints: Dr. William B. Hood, Jr., Thorndike Memorial Laboratory, Boston City Hospital, 818 Harrison Avenue, Boston, Massachusetts 02118.

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conscious canine preparation? (2) Is the glucagon-induced augmentation of cardiac function accompanied by increased metabolic demands?

Methods

Eight mongrel dogs, weighing 22.0 ± 1.3 kg, were used for the study. Effects of glucagon were assessed before and 1 hour after acute myocardial infarction in all animals, and five of these animals were restudied 1 week later in the healing phase of myocardial infarction. The remaining three animals died 12 to 36 hours after acute myocardial infarction, presumably as a consequence of ventricular arrhythmias.

The technique of producing myocardial infarction in intact conscious dogs has been described in detail.9, 10 One to two weeks prior to the study thoracotomy was performed under 30 mg/kg pentobarbital anesthesia, and a balloon catheter was implanted around the left anterior descending coronary artery. Myocardial infarction was produced by manual inflation of the balloon catheter over a period of 10 to 15 min. This represents a modification of the original method of balloon inflation,9 in which a microflow pump was employed.

Experimental Design

Beginning 1 to 2 weeks after thoracotomy, animals underwent three studies (A, B, and C) on two separate occasions. In study A after the control measurements were made, the effects of glucagon were assessed before myocardial infarction. For study B myocardial infarction was produced 50 min after administration of glucagon in study A. One hour after the infarction, measurements were repeated; glucagon was reinflated, and its effects were reassessed. In study C the five animals which survived for 7 days were again studied in the healing phase of myocardial infarction, before and after administration of glucagon.

In each of these three studies the same protocol

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Table 1
Summary of the Hemodynamic and Metabolic Data in the Control State, and after Acute and Healing Myocardial infarction: before (B) and 5, 13, and 25 Min after Glucagon (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>5</th>
<th>13</th>
<th>25</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>97 ± 3</td>
<td>145 ± 8*</td>
<td>142 ± 9*</td>
<td>137 ± 3*</td>
<td>107 ± 8†</td>
</tr>
<tr>
<td>Cardiac output (liters/min)</td>
<td>3.72 ± 0.24</td>
<td>4.86 ± 0.27*</td>
<td>4.34 ± 0.36†</td>
<td>4.63 ± 0.32*</td>
<td>3.08 ± 0.27†</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>38.3 ± 2.2</td>
<td>33.8 ± 1.7*</td>
<td>30.8 ± 2.0*</td>
<td>33.7 ± 2.0†</td>
<td>28.1 ± 1.5*</td>
</tr>
<tr>
<td>Aortic mean pressure (mm Hg)</td>
<td>109 ± 2</td>
<td>101 ± 2*</td>
<td>103 ± 2*</td>
<td>111 ± 2</td>
<td>111 ± 2</td>
</tr>
<tr>
<td>Pulmonary arterial mean pressure (mm Hg)</td>
<td>13.5 ± 1.1</td>
<td>16.6 ± 2.1*</td>
<td>14.2 ± 1.1</td>
<td>13.0 ± 1.1</td>
<td>13.6 ± 0.9</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>6.0 ± 1.6</td>
<td>4.1 ± 1.3*</td>
<td>3.7 ± 1.1*</td>
<td>5.9 ± 1.3</td>
<td>13.2 ± 0.9*</td>
</tr>
<tr>
<td>Left atrial mean pressure (mm Hg)</td>
<td>4.7 ± 1.1</td>
<td>4.1 ± 1.0</td>
<td>4.2 ± 0.9</td>
<td>4.6 ± 0.9</td>
<td>6.6 ± 1.0*</td>
</tr>
<tr>
<td>Total systemic resistance (dyne·sec/cm²)</td>
<td>2417 ± 160</td>
<td>1716 ± 128*</td>
<td>2033 ± 176*</td>
<td>2029 ± 159*</td>
<td>3047 ± 257</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyne·sec/cm²)</td>
<td>198 ± 33</td>
<td>208 ± 36</td>
<td>189 ± 29</td>
<td>151 ± 25*</td>
<td>182 ± 22</td>
</tr>
<tr>
<td>Coronary arteriovenous O₂ difference (vol %)</td>
<td>11.8 ± 0.3</td>
<td>11.9 ± 0.5</td>
<td>11.8 ± 0.5</td>
<td>11.8 ± 0.5</td>
<td>11.8 ± 0.5</td>
</tr>
<tr>
<td>Myocardial oxygen extraction (vol %)</td>
<td>67 ± 2.4</td>
<td>67 ± 2.2</td>
<td>67 ± 2.2</td>
<td>67 ± 2.2</td>
<td>67 ± 2.2</td>
</tr>
<tr>
<td>Coronary blood flow (ml/100 g of LV/min)</td>
<td>99 ± 8.3</td>
<td>129 ± 12.4*</td>
<td>107 ± 9.8</td>
<td>107 ± 9.8</td>
<td>107 ± 9.8</td>
</tr>
</tbody>
</table>

*†Compared to control before glucagon: *P < 0.05; †0.05 < P < 0.10.
‡§Compared to acute myocardial infarction before glucagon: ‡P < 0.05; §0.05 < P < 0.10.
**††Compared to healing myocardial infarction before glucagon: **P < 0.05; ††0.05 < P < 0.10.

Note: Figures in parentheses are coefficients of variation calculated as s/s·r·m·ean.
**Acute myocardial infarction** (8 dogs)  
<table>
<thead>
<tr>
<th>After glucagon (min)</th>
<th>5</th>
<th>13</th>
<th>25</th>
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</thead>
<tbody>
<tr>
<td>145 ± 11†</td>
<td>133 ± 10†</td>
<td>128 ± 10†</td>
<td>102 ± 10†</td>
</tr>
<tr>
<td>(0.08)</td>
<td>(0.07)</td>
<td>(0.07)</td>
<td>(0.10)</td>
</tr>
<tr>
<td>4.26 ± 0.29†</td>
<td>3.72 ± 0.28†</td>
<td>3.66 ± 0.25†</td>
<td>3.41 ± 0.45</td>
</tr>
<tr>
<td>(0.07)</td>
<td>(0.08)</td>
<td>(0.07)</td>
<td>(0.13)</td>
</tr>
<tr>
<td>30.2 ± 2.6</td>
<td>28.4 ± 2.2</td>
<td>27.9 ± 1.6</td>
<td>33.9 ± 3.6</td>
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<tr>
<td>(0.09)</td>
<td>(0.08)</td>
<td>(0.06)</td>
<td>(0.11)</td>
</tr>
<tr>
<td>97 ± 2†</td>
<td>102 ± 1†</td>
<td>106 ± 3</td>
<td>115 ± 5</td>
</tr>
<tr>
<td>(0.02)</td>
<td>(0.01)</td>
<td>(0.03)</td>
<td>(0.04)</td>
</tr>
<tr>
<td>14.3 ± 0.9§</td>
<td>13.1 ± 0.7§</td>
<td>14.1 ± 0.9</td>
<td>13.6 ± 1.6</td>
</tr>
<tr>
<td>(0.06)</td>
<td>(0.05)</td>
<td>(0.06)</td>
<td>(0.12)</td>
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<tr>
<td>6.1 ± 1.1†</td>
<td>6.3 ± 0.9†</td>
<td>8.0 ± 1.3†</td>
<td>11.4 ± 2.7†</td>
</tr>
<tr>
<td>(0.07)</td>
<td>(0.05)</td>
<td>(0.06)</td>
<td>(0.12)</td>
</tr>
<tr>
<td>3.3 ± 0.6‡</td>
<td>3.1 ± 0.6‡</td>
<td>3.7 ± 0.6</td>
<td>6.7 ± 1.3</td>
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<tr>
<td>(0.07)</td>
<td>(0.07)</td>
<td>(0.07)</td>
<td>(0.13)</td>
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<tr>
<td>1879 ± 130‡</td>
<td>2278 ± 162‡</td>
<td>2386 ± 172‡</td>
<td>2911 ± 380</td>
</tr>
<tr>
<td>(0.07)</td>
<td>(0.07)</td>
<td>(0.07)</td>
<td>(0.11)</td>
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<tr>
<td>216 ± 20</td>
<td>228 ± 17</td>
<td>230 ± 15</td>
<td>165 ± 10</td>
</tr>
<tr>
<td>(0.09)</td>
<td>(0.07)</td>
<td>(0.07)</td>
<td>(0.06)</td>
</tr>
<tr>
<td>12.3 ± 0.6</td>
<td>10.6 ± 0.8</td>
<td>13.1 ± 0.8</td>
<td>10.6 ± 0.8</td>
</tr>
<tr>
<td>(0.05)</td>
<td>(0.05)</td>
<td>(0.06)</td>
<td>(0.05)</td>
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<tr>
<td>73 ± 3.3</td>
<td>72 ± 2.2</td>
<td>79 ± 2.9</td>
<td>72 ± 2.2</td>
</tr>
<tr>
<td>(0.05)</td>
<td>(0.03)</td>
<td>(0.04)</td>
<td>(0.03)</td>
</tr>
<tr>
<td>115 ± 9.5</td>
<td>109 ± 9.4</td>
<td>101 ± 8.6</td>
<td>109 ± 9.4</td>
</tr>
<tr>
<td>(0.9)</td>
<td>(0.09)</td>
<td>(0.09)</td>
<td>(0.09)</td>
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</table>

**Healing myocardial infarction** (5 dogs)  
<table>
<thead>
<tr>
<th>After glucagon (min)</th>
<th>5</th>
<th>13</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 ± 25**</td>
<td>143 ± 23**</td>
<td>124 ± 10**</td>
<td></td>
</tr>
<tr>
<td>(0.10)</td>
<td>(0.16)</td>
<td>(0.08)</td>
<td></td>
</tr>
<tr>
<td>4.62 ± 0.59**</td>
<td>3.55 ± 0.60**</td>
<td>4.13 ± 0.40**</td>
<td></td>
</tr>
<tr>
<td>(0.13)</td>
<td>(0.14)</td>
<td>(0.10)</td>
<td></td>
</tr>
<tr>
<td>31.3 ± 1.4</td>
<td>30.8 ± 2.6</td>
<td>33.4 ± 2.1</td>
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<tr>
<td>(0.04)</td>
<td>(0.08)</td>
<td>(0.06)</td>
<td></td>
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<tr>
<td>102 ± 5**</td>
<td>106 ± 4**</td>
<td>116 ± 6</td>
<td></td>
</tr>
<tr>
<td>(0.05)</td>
<td>(0.04)</td>
<td>(0.05)</td>
<td></td>
</tr>
<tr>
<td>16.6 ± 1.5**</td>
<td>14.6 ± 1.7</td>
<td>14.4 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>(0.09)</td>
<td>(0.09)</td>
<td>(0.12)</td>
<td></td>
</tr>
<tr>
<td>5.6 ± 1.3**</td>
<td>6.4 ± 1.1**</td>
<td>9.0 ± 2.7**</td>
<td></td>
</tr>
<tr>
<td>(0.10)</td>
<td>(0.12)</td>
<td>(0.17)</td>
<td></td>
</tr>
<tr>
<td>4.2 ± 0.9††</td>
<td>5.5 ± 1.3</td>
<td></td>
<td></td>
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<tr>
<td>(0.10)</td>
<td>(0.09)</td>
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<tr>
<td>1961 ± 206**</td>
<td>2067 ± 218**</td>
<td>2300 ± 190**</td>
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<tr>
<td>(0.11)</td>
<td>(0.10)</td>
<td>(0.09)</td>
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<tr>
<td>198 ± 10**</td>
<td>200 ± 24††</td>
<td>200 ± 17††</td>
<td></td>
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<tr>
<td>(0.06)</td>
<td>(0.12)</td>
<td>(0.17)</td>
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</tr>
</tbody>
</table>

was followed. After control measurements, glucagon 50 μg/kg (Glucagon for Injection U.S.P.*) was injected into the pulmonary artery over a period of 1 minute. Continuous measurements were made of heart rate, and aortic, left ventricular, left atrial, and pulmonary arterial pressures. Cardiac outputs were measured 5, 13, and 25 min after the midpoint of glucagon injection. Between the 9th and 13th min after the injection arterial and coronary sinus blood samples were drawn for oxygen analysis, and estimation of coronary blood flow followed. Animals were sacrificed at the end of the study, and all showed infarction of the anterior wall of the left ventricle. Although infarct size was not quantified, the extent of infarction was comparable to previous studies of the same type of preparation, in which infarcts ranged from 22 to 49% (mean 34%) of the left ventricular mass.

**Procedure**

Animals were lightly sedated with morphine sulfate, 15 mg given intramuscularly, at least 3 hours before the first measurements were made. Animals lay on their right sides. Under local anesthesia a femoral artery and vein were isolated. Under fluoroscopic control, a no. 7 Goodale-Lubin catheter was passed retrogradely through the femoral artery into the left atrium, and a no. 7 Courand catheter was passed through the femoral vein into the pulmonary artery. In addition a polyethylene catheter (I.D., 0.045 in) was inserted into the femoral artery and positioned in the aorta. Through an external jugular vein cutdown, another Goodale-Lubin catheter was introduced in the coronary sinus and was positioned beyond the posterolateral coronary vein. The position of the catheter in the coronary sinus was confirmed by injection of radiopaque dye. By using the Seldinger technic, a polyethylene catheter (I.D., 0.045 in) was inserted percutaneously in the left ventricle. After studies A and B the arteriotomy was repaired and the animals were returned to the kennel until study C was performed 7 days later.

All recordings were made on direct-writer recorders.† Statham P 23 Db transducers were used for pressure measurements. The zero for

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*Eli Lilly and Company, Indianapolis, Indiana.

†Hewlett-Packard Co., Palo Alto, California.
Myocardial oxygen extraction was calculated from:

\[
\text{Coronary A-VO}_2\text{ difference (in vol\%)} \times 100
\]

\[
\text{Arterial O}_2\text{ content (in vol\%)}
\]

Myocardial oxygen consumption/100 g of LV/min was calculated from:

- coronary blood flow (in ml/100 g LV/min) ×
- coronary A-VO₂ difference (in vol\%) × 10⁻²

Total systemic resistance in dyne-sec/cm² was calculated as:

\[
\frac{\text{Aortic mean pressure (in mm Hg) × 80}}{\text{Cardiac output (in liters/min)}}
\]

Pulmonary vascular resistance in dyne-sec/cm² was calculated as:

\[
\frac{(\text{PA}_m\text{ pressure} - \text{LA}_m\text{ pressure}) \times 80}{\text{Cardiac output}}
\]

where PA₀ pressure is pulmonary artery mean pressure and LA₀ pressure is left atrial mean pressure (both in mm Hg) and cardiac output was measured in liters/min.

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**Figure 1**

Effects of infusion of 50 μg/kg of glucagon 1 hour following acute myocardial infarction. Note decrease in aortic mean, left ventricular (LV) end-diastolic, and left atrial (LA) mean pressures and increase in heart rate and cardiac output after glucagon injection. There is also a slight increase in pulmonary artery (PA) pressure. The PA tracing is briefly interrupted during glucagon injection. Also, shortly after glucagon injection, the aortic and PA mean pressure tracings are interrupted by 15 sec of phasic tracing.

Cardiac output was measured by the indicator-dilution technic using indocyanine green dye.²

Coronary blood flow was measured by the K₂ krypton method with injection of indicator into the left ventricle (LV) and sampling of coronary venous blood to obtain a myocardial clearance curve, as described by Cohen and co-workers.¹¹ Coronary arterial and venous oxygen contents were analyzed by the micro Van Slyke method.¹²

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²The indocyanine dye was kindly supplied by Hynson, Westcott, and Dunning, Baltimore, Maryland.

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**Figure 2**

Effects of infusion of 50 μg/kg of glucagon 1 week after myocardial infarction. Changes are similar to those in figure 1.
Changes in left ventricular end-diastolic pressure (LVEDP) and myocardial oxygen consumption 13 min after glucagon infusion in control study (study A), acute myocardial infarction (study B), and healing myocardial infarction (study C). Bars show mean ± SEM. LVEDP fell significantly in all three states; however, myocardial O₂ consumption rose significantly only in the control state.

The data were analyzed in the following manner: (1) For each of the three studies, the data before glucagon were compared with the data at 5, 13, and 15 min after glucagon. (2) The control observations (before myocardial infarction) were compared to those of acute myocardial infarction and healing myocardial infarction. All comparisons were made by paired t-test and the data presented as mean ± standard error of the mean (SEM). A coefficient of variation for each set of measurements was calculated as SEM/mean, to permit ready comparison with percentage changes presented in the "Results" section.

Results

All data are summarized in table 1. Figures 1 and 2 show representative pressure tracings obtained in animals during glucagon administration both at 1 hour and 1 week after acute myocardial infarction. Figure 3 depicts changes in left ventricular end-diastolic pressure and myocardial oxygen consumption at all three phases of the study.

Study A: Effects of Glucagon in the Control State

Changes were noted within 3 min after injection of glucagon and lasted for more than 20 min, but disappeared by 40 min, as measured from continuous pressure tracings. Heart rate and cardiac output increased, and stroke volume, aortic mean pressure, left ventricular end-diastolic pressure, and total systemic resistance decreased as a result of infusion of glucagon. These changes were most marked in the period 5 to 13 min after the injection of glucagon with a maximal
increase in heart rate of 49% and in cardiac output of 31%, and a maximal decrease in stroke volume of 20%, in aortic mean pressure of 7%, and in total systemic resistance of 29%. Left ventricular end-diastolic pressure decreased from 6.0 to 3.7 mm Hg (table 1, fig. 3). Five minutes after the glucagon infusion a significant (23%) increase in pulmonary artery mean pressure was observed in every animal. This was not associated with any significant change in pulmonary vascular resistance (table 1).

Coronary blood flow increased 30% after glucagon administration (table 1), and myocardial oxygen consumption increased from 11.7 to 15.4 ml/100 g of left ventricle/min (fig. 3), without any significant change in coronary arteriovenous oxygen difference or oxygen extraction (table 1). These increases in coronary blood flow and myocardial oxygen consumption were observed in seven of the eight animals studied.

**Study B: Acute Myocardial Infarction**

One hour after myocardial infarction a 10% increase in heart rate and a 27% decrease in stroke volume occurred which resulted in a 17% decrease in cardiac output. Aortic mean pressure remained at control levels, and no animal developed cardiogenic shock. Left ventricular end-diastolic pressure increased from 6.0 to 13.2 mm Hg, and left atrial mean pressure, from 4.7 to 6.6 mm Hg. A 26% increase in total systemic vascular resistance was noted, but this was not statistically significant. Coronary blood flow increased 8% and myocardial oxygen consumption 9%; however, these changes were not significant. After the injection of glucagon, the time course of changes from the continuous pressure measurements was similar to the control state, with appearance of changes in 3 min and disappearance by 40 min; however, left ventricular end-diastolic pressure appeared to remain at a lower level than before glucagon infusion even after 50 min in some animals.

As in study A, a maximal increase in heart rate (35%) and cardiac output (38%), and a decrease in aortic mean pressure (13%) and total systemic resistance (38%) occurred between 5 and 13 min after administration of glucagon. Left ventricular end-diastolic pressure decreased from 13.2 to 6.1 mm Hg, and left atrial mean pressure from 6.6 to 3.1 mm Hg (table 1, figs. 1 and 3). In contrast to the control state (study A) stroke volume, which was already decreased as a result of acute infarction, did not further decrease and was maintained. Similar to the control state, the trend toward maintenance of pulmonary artery pressure and unchanging pulmonary vascular resistance was again noted (table 1).

It is noteworthy that, despite the presence of sinus tachycardia due to infarction, the heart rate was lower 13 and 25 min after glucagon infusion than in the control state (study A). Compared with a heart rate increase of 42% at 25 min after glucagon in the control state, the value after infarction was only 20% (0.05 < P < 0.10). There were no instances of ventricular premature beats or other ectopic arrhythmias resulting from glucagon administration in these dogs with acute myocardial infarction.

In contrast to the control state (study A) the 7% increase in coronary blood flow and 8% increase (from 12.8 to 13.9 ml/100 g of left ventricle/min) in myocardial oxygen consumption after glucagon administration were not statistically significant (table 1, fig. 3). Moreover, there was no consistent directional change in these two measurements, which increased slightly in five animals and decreased slightly in the other three.

**Study C: Healing Myocardial Infarction**

Seven days after myocardial infarction heart rate, cardiac output, and stroke volume returned toward the control level noted in study A. However, left ventricular end-diastolic pressure remained borderline elevated at 11.4 mm Hg, indicating persistence of left ventricular failure (table 1). No significant changes were observed in oxygen metabolism compared to either of the previous baseline measurements (table 1, fig. 3). The time course of changes after glucagon injection was similar to that observed in
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studies A and B. The fall in left ventricular end-diastolic pressure was maintained for more than 50 min in three of the five animals. As in study A and B, between 5 and 13 min after glucagon injection a maximal increase in heart rate (47%) and cardiac output (35%) and a decrease in aortic mean pressure (11%) and total systemic resistance (36%) occurred. Left ventricular end-diastolic pressure decreased from 11.4 to 5.6 mm Hg, and left atrial mean pressure was maintained for more than 11.4 to 5.6 mm Hg, and left atrial mean pressure was maintained for more than 6.7 to 4.2 mm Hg (table I, figs. 2 and 3). As in study B, stroke volume was maintained. As noted in study A, a significant increase in pulmonary artery pressure was observed; this was 22% in this study. In contrast to both studies A and B, a 20% increase in pulmonary vascular resistance was also seen. As in study B, arrhythmias were absent. However, the increase in heart rate (47%) like that in study A (49%) was more marked than in study B (table 1). Similar to study B, no changes in oxygen metabolism were seen. The slight (14%) increase (from 11.7 to 13.3 ml/100 g of LV/min) in myocardial oxygen consumption was not significant (fig. 3).

Discussion

That glucagon has a positive inotropic effect in normal cardiac muscle has been clearly established. The usefulness of this agent in acute or chronic clinical congestive heart failure remains controversial, however, and there is evidence that myocardium from experimental preparations with chronic heart failure may be unresponsive to the drug. The action of the drug in heart failure of shorter duration is also uncertain. Both beneficial and insignificant effects have been reported in cardiogenic shock. There is some evidence that the drug is useful in postoperative low cardiac output states. The discrepancies noted in these clinical reports may well be due to inclusion of a heterogeneous population of patients.

The role of glucagon therapy in left ventricular failure of myocardial infarction unaccompanied by shock has not been clearly established. Recent reports have shown improvement in cardiac performance in patients with myocardial infarction and left ventricular failure and in open-chest experimental animal preparations. Still, it is not known whether this improved cardiac performance is associated with increased myocardial metabolic demands. It has been demonstrated that glucagon increases myocardial oxygen requirement in the normal canine heart. It is also important to determine whether this efficacy persists in the recovery period following myocardial infarction, when long-term therapy with glucagon may be feasible.

In the present study the hemodynamic and metabolic effects of glucagon were assessed serially in intact conscious dogs. In the control state before myocardial infarction glucagon increased the cardiac output. This was mediated primarily by increase in heart rate, since stroke volume decreased. Left ventricular end-diastolic pressure decreased, while left atrial pressure did not change significantly. Pulmonary artery pressure increased in the early phase after glucagon administration and gradually returned to control values. In contrast to systemic vasodilatation, this increase in pulmonary artery pressure and the unchanged pulmonary vascular resistance in the presence of a modest increase in cardiac output suggest relative pulmonary vasoconstriction. These changes in hemodynamic parameters are similar to those reported in man. The enhanced cardiac performance was accompanied by a 32% increase in myocardial oxygen consumption. This increase in myocardial oxygen consumption was achieved entirely by an increase in coronary flow, there being no change in coronary arteriovenous oxygen difference. Similar results have been obtained in anesthetized dogs, though in one study coronary sinus oxygen content declined significantly with administration of glucagon.

The hemodynamic effects of acute myocardial infarction, that is, sinus tachycardia, decreased stroke volume, and increased left ventricular filling pressure are identical to those previously described in this preparation in other studies from this laboratory.
Administration of glucagon in acute myocardial infarction reduced the degree of left ventricular failure and improved cardiac performance. In contrast to the control study, stroke volume was maintained and contributed to the increase in cardiac output along with the increase in heart rate. The increase in heart rate tended to be less than in the control state. In contrast to the systemic peripheral vasodilatation, vasoconstriction was seen in the lesser circulation, as is also seen in patients. Also of interest is the lack of ventricular premature beats in the presence of increased inotropy induced by glucagon, despite the lowered threshold for ectopic stimuli in the postinfarction period.

The most noteworthy finding of this study was that the improved cardiac performance after infarction was achieved without a significant increase in coronary blood flow or myocardial oxygen consumption, indicating relative improvement in cardiac efficiency. The reasons for this are not well understood at present. It is possible that an increase in myocardial oxygen consumption due to enhanced inotropic state was compensated for by a comparable decrease due to reduction in the ventricular size and wall stress. A similar result has been reported from digitalis administration in an isolated supported canine heart-failure preparation. Decrease in ventricular end-diastolic volume has been reported in patients with coronary artery disease after glucagon administration. Also the improved cardiac performance was accompanied by an unchanged flow work (stroke volume) and reduction rather than increase in pressure work. This may be important since changes in oxygen consumption are more directly related to alterations in pressure work.

In the healing phase of myocardial infarction elevation of left ventricular end-diastolic pressure persisted, but the other parameters had returned toward normal, as in previous studies. Again administration of glucagon reduced the degree of left ventricular failure. As in the acute phase of infarction, stroke volume did not change, and the increase in cardiac output was mediated by an increase in heart rate. Pulmonary vasoconstriction was noted early and persisted for more than 25 min. Again the improved cardiac performance was achieved without any significant increase in coronary blood flow or myocardial oxygen consumption. It is noteworthy that the glucagon-induced reduction of left ventricular end-diastolic pressure was present for at least 50 min in both the acute and healing phases of myocardial infarction. This suggests that the effects of glucagon may persist longer in the presence of heart failure than in the compensated state.

It is important to realize that the improvement in cardiac performance caused by glucagon is probably due in part to the sinus tachycardia caused by this agent. It has been shown in this conscious-dog preparation that increasing the heart rate by rapid atrial pacing will substantially lower the left ventricular end-diastolic pressure in both acute and healing myocardial infarction. In the healing phase, cardiac output is also increased by pacing. With glucagon administration there is a similar lowering of left ventricular end-diastolic pressure, but also an increase in cardiac output in both acute and healing myocardial infarction. In contrast to effects of pacing, stroke volume is maintained after glucagon administration. This observation suggests that glucagon has an additional direct inotropic effect upon the myocardium in acute infarction, quite apart from changes in heart rate induced by the agent.

The hemodynamic effects of glucagon are similar in some respects to those of beta-receptive catecholamines; these effects include both positive chronotropic and inotropic actions. From the therapeutic standpoint, glucagon seems to offer certain advantages over catecholamines in the treatment of cardiac failure due to myocardial infarction. Decreased threshold to ventricular arrhythmias from catecholamines is well known. Puri and Bing have reported that the increased paradoxical bulging of the ischemic myocardium noted with catecholamines was not seen with glucagon. In patients with acute myocardial infarction a comparable
improvement in cardiac function with norepinephrine was accompanied by relatively higher pressure load (and presumably myocardial oxygen requirement) compared to glucagon.  

Clinical Implications

In the animal model used in the present study the hemodynamic profile of left ventricular failure of myocardial infarction is quite similar to that observed in man.  

Also, the effect of glucagon on hemodynamics and myocardial oxygen consumption in normal awake animals resembles that observed in man.  

Although caution must be used in extrapolating the results of this experiment to the clinical situation, the present study does have certain implications. In left ventricular failure of myocardial infarction not associated with shock, glucagon may be a useful therapeutic agent. Glucagon not only ameliorates left ventricular failure and enhances cardiac performance in experimental myocardial infarction, but also achieves this without increasing myocardial oxygen consumption.

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