The Effect of Glucagon on the Pulmonary Transvascular Fluid Filtration Rate*

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Administration of glucagon has been shown to decrease pulmonary vascular resistance, but its primary site of action is undetermined. Whether this is on the arterial or venous side of the capillary would be reflected in the microvascular hydrostatic pressure. We used the pulmonary flow of lymph, a sensitive index of the transvascular fluid filtration rate, to monitor the microvascular hydrostatic pressure. Eight unanesthetized sheep with a surgically created long-term fistula for monitoring pulmonary lymph were given a 3-mg bolus of glucagon after a baseline period. We found no change in pulmonary arterial or left atrial pressures but noted a significant increase in cardiac output and a decrease in pulmonary resistance. The flow of pulmonary lymph increased by 50 percent for 30 minutes after administration of glucagon, and the protein content of the lymph decreased by 15 percent, indicating a large increase in the microvascular hydrostatic pressure. From these data, we calculated a decrease in arterial resistance from 60 percent to 30 percent of the total and, subsequently, an increase of 6 cm H2O in the microvascular hydrostatic pressure. Administration of glucagon, therefore, decreases the arterial resistance while increasing microvascular pressure in the process.

Glucagon has been found to significantly decrease the pulmonary vascular resistance, besides having positively inotropic and chronotropic effects on the myocardium. Because of this effect on vascular resistance, therapy with glucagon has been recommended for the treatment of various forms of pulmonary hypertension; however, the results of clinical trials have been conflicting. Both improvement and deterioration have been reported. Although total resistance is decreased, it has not been determined whether the arterial or venous resistance is primarily affected. This information is necessary to determine which forms of pulmonary vascular disease can be treated effectively with glucagon. The pulmonary transvascular fluid filtration rate would clearly reflect on which side of the capillary resistance has changed. Microvascular hydrostatic pressure would either increase toward pulmonary arterial pressure or decrease toward left atrial pressure with decreases in arterial or venous resistance, respectively. The flow of pulmonary lymph in the surgically created experimental pulmonary fistula described by Staub has been shown to be an excellent indicator of the fluid filtration rate across the microcirculation. We used this experimental preparation to better define the mechanism of action of glucagon.

Materials and Methods

Long-Term Experimental Pulmonary Fistula

We prepared eight adult sheep (weighing 60 to 80 kg [132 to 176 lb]) for collection of pulmonary lymph according to the method of Staub et al. Briefly, this entailed three sequential procedures performed over a period of two weeks. First, we made a small thoracotomy through the ninth right intercostal space, identified the caudal mediastinal lymph node, which drains approximately two-thirds of the pulmonary lymph, and resected its posterior portion. This eliminated any systemic contribution to this lymph node. One week later, catheters were placed in the pulmonary artery and left atrium through a thoracotomy on the left side. The third procedure, performed one week after that, consisted of making a thoracotomy through the sixth right intercostal space and identifying and cannulating the efferent duct of the caudal mediastinal node with a small Silastic catheter. This was tunneled through the wall of the chest and secured externally. All procedures were done with minimal manipulation of the lung. Animals were allowed to recuperate for five days prior to any studies, in order to allow for a steady-state flow of lymph. All studies were performed with the sheep in the unanesthetized state and resting comfortably in a metabolic cage, with free access to food and water.

Baseline Measurements

The flow of lymph was measured for ten-minute periods over the course of two hours or until a steady state was reached. Lymph was collected in heparin-treated graduated
Table 1—Response of Flow of Lymph and Pulmonary Vascular Hemodynamic Data to Administration of Glucagon

<table>
<thead>
<tr>
<th>Time after Injection of Glucagon</th>
<th>Flow of Lymph, ml/10 min</th>
<th>Mean Pressure, cm H₂O</th>
<th>Cardiac Output, L/min</th>
<th>Total Pulmonary Resistance, cgs units (dyne-sec/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.2 ± 0.9</td>
<td>21 ± 8</td>
<td>1 ± 1</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>10 min</td>
<td>3.2 ± 1.1*</td>
<td>19 ± 9</td>
<td>1 ± 1</td>
<td>7 ± 1*</td>
</tr>
<tr>
<td>30 min</td>
<td>2.7 ± 1.1</td>
<td>20 ± 8</td>
<td>0 ± 1</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>2.6 ± 1.1</td>
<td>19 ± 7</td>
<td>1 ± 1</td>
<td>6 ± 1*</td>
</tr>
<tr>
<td>90 min</td>
<td>2.6 ± 1.0</td>
<td>20 ± 7</td>
<td>1 ± 2</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>120 min</td>
<td>2.3 ± 0.9</td>
<td>20 ± 5</td>
<td>1 ± 1</td>
<td></td>
</tr>
</tbody>
</table>

*Significantly different from baseline.

cylinders. A sample of plasma was collected every hour. The total protein level (biuret) and the albumin concentration of the lymph and plasma were determined. Pulmonary arterial and left atrial pressures were continuously measured using calibrated pressure transducers (Statham P23-10) and a four-channel recorder (Gilson Polygraph 1CT-58). The point of reference was the front of the shoulder, which is considered to be at the level of the left atrium. Cardiac output was measured in duplicate using the dye dilution technique (indocyanine green) and a linear densitometer (Gilson).

Glucagon

After the baseline period, glucagon (Lilly) was dissolved in saline solution (1 mg/ml) and was administered as a 3-mg bolus into a central vein over one minute. Pulmonary vascular pressures, the flow of lymph, and the protein levels of the lymph and plasma were measured for two hours or until values returned to baseline. Cardiac output was measured at 10, 60, and 90 minutes after administration of glucagon. Statistical significance was considered as P < 0.05, using the paired t-test.

RESULTS

Our data are tabulated in Table 1. Pulmonary arterial and left atrial pressures after administration of glucagon were not significantly different from baseline values. There was a significant decrease in pulmonary vascular resistance and an increase in cardiac output ten minutes after injection of

![Flow of pulmonary lymph, levels of total protein and albumin in lymph, and pulmonary vascular pressures are shown before and after intravenous injection of 3 mg of glucagon. Vascular pressures remained constant. Flow of pulmonary lymph increased rapidly, with maximum level at ten minutes after injection. Level of proteins in plasma remained constant. Level of protein in lymph varied inversely with flow of pulmonary lymph, indicating "sieving effect" of microvascular membrane as fluid filtration rate increased. PA, Mean pulmonary arterial pressure; and LA, mean left atrial pressure.](Image)
glucagon. Both values returned to baseline at the 90-minute period. The flow of pulmonary lymph increased in all animals by nearly 50 percent in the 10-minute period after injection of glucagon. The flow of lymph was still elevated at 30 minutes, with a return to baseline by 120 minutes. In three of the studies, pulmonary lymph became tinged with blood immediately after injection of glucagon, with gradual clearing as the flow of lymph returned to baseline.

Baseline values for the concentrations of total protein and albumin in the plasma were 6.0 ± 0.5 and 2.8 ± 0.7 gm/100 ml, respectively. There was no change after injection of glucagon. Baseline levels for the concentrations of total protein and albumin in the lymph were 4.0 ± 1.1 and 2.2 ± 1.1 gm/100 ml, respectively. The levels of total protein and albumin in the lymph decreased as the flow of pulmonary lymph increased (Fig 1), with the maximum decrease occurring within 30 minutes after injection of glucagon. The decreases from baseline values were 15 percent and 22 percent for the total protein level and the albumin level, respectively. Values returned to baseline with the flow of pulmonary lymph.

**DISCUSSION**

The fluid transport equation for the lung is \( Q_t = K_t(P_{mv}-P_{pmv})-\sigma(\pi_{mv}-\pi_{pmv}) \), where \( Q_t \) is the net transvascular fluid rate, \( P_{mv} \) and \( P_{pmv} \) are the pulmonary microvascular and interstitial hydrostatic pressures, respectively, \( \sigma \) is the coefficient of fluid reflection (measuring the relative leakiness of the membrane to protein compared to water, and being nearly equal to one for protein and zero for small molecules), and \( \pi_{mv} \) and \( \pi_{pmv} \) are the microvascular and interstitial protein osmotic pressures, respectively. The increase in the flow of pulmonary lymph or \( Q_t \) after injection of glucagon could be explained by (1) an increase in \( K_t \), a product of the conductivity of the membrane and the total area for filtering, (2) an increase in microvascular hydrostatic pressure, or (3) a decrease in the lymph-to-plasma oncotic gradient.

Since the protein level of the lymph decreased and that of the plasma remained constant, the lymph-to-plasma gradient actually increased. Since vascular pressures remained constant, it is unlikely that \( K_t \) could be increased. An increase in the flow of pulmonary lymph with a decreased protein content is the response which is characteristic of an increase in microvascular hydrostatic pressure, as described by Erdmann and associates,7 and shown in Figure 2. As more fluid than protein is filtered, the protein content of the lymph decreases. An increase in the number of small pores along the endothelial membrane, still restrictive to the flow of protein, would also increase fluid relative to protein in pulmonary lymph; however, this effect of therapy with glucagon would be very unlikely because of the immediate and short-term course of the response in the flow of lymph.

The increase in the red blood cell content of the lymph that we noted has been described with increased hydrostatic pressure in this experimental preparation.8 Extrapolating from the data of Erdmann and associates,7 a 50 percent increase in the flow of pulmonary lymph requires about an increase of 6 cm H2O in the hydrostatic pressure. Since the pulmonary arterial and left atrial pressures remained constant, a large decrease in arterial resistance would have had to have occurred.

Pulmonary microvascular pressure can be calculated by the formula, \( P_{mv} = Rv(P_{pa}-P_{pla}) + P_{pla} \), where \( P_{mv} \) is the pulmonary microvascular pressure, \( Rv \) is the fraction of venous resistance, \( P_{pa} \) is the pulmonary arterial pressure, and \( P_{pla} \) is the left atrial pressure. Under baseline conditions, \( Rv \) is 0.4, with 60 percent of the resistance being arterial.1,9 An increase of 6 cm H2O in the pulmonary microvascular pressure with the constant vascular pressures noted in our study would require \( Rv \) to equal 0.7, decreasing the arterial resistance to 30 percent of the total at the peak of the effect of glucagon. Using the data in Table 1, the baseline value for the

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**Figure 2.** Flow of pulmonary lymph, level of protein in lymph and plasma, and pulmonary vascular pressures are shown before, during, and after elevation of hydrostatic pressure by inflation of left atrial balloon. As pressure increases, flow of lymph increases, and level of protein in lymph decreases. Values return to baseline with deflation of balloon.

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mean total pulmonary resistance was 520 (dyne-sec/cm²), making arterial resistance 60 percent or 312 and venous resistance 40 percent or 208. Total pulmonary resistance ten minutes after injection of glucagon was 360. Arterial and venous resistances would now be 30 percent or 108 and 70 percent or 252, respectively. This would mean not only a marked decrease in arterial resistance but a 20 percent increase in venous resistance compared to baseline. It is possible that this small increase is due to error introduced when summary data from two sources were used; however, a small reflex increase in venous resistance could occur in response to the sudden increase in microvascular pressure caused by the administration of glucagon. Further studies are necessary to better define this response.

If, as our data indicate, the arterial resistance is the principal site of action, we can suggest more precise clinical indications for the use of therapy with glucagon. Patients with disease such as hypoxic-induced or primary pulmonary hypertension, where arterial resistance is markedly increased, may benefit from the use of therapy with glucagon. The increased pulmonary vascular resistance after hemorrhagic or septic shock is primarily due to increased venous resistance. Therapy with glucagon would probably be of less benefit. The increase in microvascular pressure which occurs may also be very important in determining indications for the use of therapy with glucagon.

This increase in microvascular pressure may help to explain the conflicting results noted with the clinical use of therapy with glucagon in heart failure. Kones and Phillips noted that the condition of patients with acute heart failure was improved, while the condition of those with chronic heart failure and associated pulmonary hypertension was made worse. This could be due to a further increase in pulmonary water as the high arterial resistance decreased. More studies are necessary to adequately define the uses of glucagon for the treatment of diseases with increased pulmonary vascular resistance.

ACKNOWLEDGMENT: We thank Ms. Susan Retzlaff and Mr. Gordon Johnson for technical assistance.

REFERENCES