Experimental Pulmonary Embolism

Effect on Pulmonary Blood Volume and Vascular Compliance

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SUMMARY
Autologous blood clot was used to produce pulmonary macroembolism, and lycopodium spores to produce microembolism in normal mongrel dogs. Pressures were recorded from the pulmonary artery, left atrium and femoral artery; cardiac output and pulmonary blood volume (PBV) were determined using sequential indicator dilution curves from injections into the pulmonary artery and left atrium. Macro- and microembolism caused comparable elevations of pulmonary artery pressure and total pulmonary resistance. Macroembolism with blood clots resulted in marked decreases in PBV and pulmonary vascular compliance. However, microembolism with lycopodium spores caused only small decreases in PBV despite a large reduction in pulmonary vascular compliance. Prostaglandin E₁ infusion after microembolism had no effect on pulmonary hemodynamics, but caused significant systemic hypotension. After macroembolism PGE₁ infusion decreased PBV and decreased systemic arterial pressure.

Additional Indexing Words:
Macroembolism Microembolism

Blood clot Prostaglandin

EXPERIMENTAL PULMONARY EMBOLISM may produce elevation in pulmonary arterial pressure via two mechanisms. Evidence indicates that emboli larger than 100 micra in diameter (macroemboli) cause pulmonary hypertension by mechanical blockade of pulmonary arteries; pulmonary hypertension develops only when more than 50% of these vessels are occluded.¹,²,³ When emboli smaller than 100 micra in diameter (microemboli) lodge in arterioles and capillaries the resultant elevation of pulmonary arterial pressures appears to be the result of vasoconstriction superimposed on mechanical obstruction.²,⁴ The effect of experimental pulmonary embolism on pulmonary blood volume and pulmonary vascular compliance has not been thoroughly investigated.² This is particularly true for microemboli. Moreover, although pulmonary vasodilators have been found to be ineffective in reversing the hemodynamic abnormalities caused by experimental macro-pulmonary embolism, equivalent studies have not been performed involving microemboli.⁵

The present study reports the response of pulmonary blood volume, vascular compliance, and flows to embolization with macro- and micro-pulmonary emboli. In addition, the hemodynamic effects of a known pulmonary vasodilator, Prostaglandin E₁ (PGE₁), were measured following both forms of embolism.⁶,⁷

Material and Methods
Normal mongrel dogs (16–24 kg) were lightly anesthetized with pentobarbital, 32 mg/kg intraperitoneally, and were placed in the supine position on a fluoroscopic table. Additional small doses of pentobarbital were given intraperitoneally as needed during each experiment, but these administrations were always separated from experimental maneuvers by at least a 30 min delay. The dogs breathed room air spontaneously. Periodic "spot checks" of femoral arterial pO₂, pCO₂, and pH were obtained and analyzed on an IL pH/gas analyzer, model 113 to insure that the animal was ventilating adequately.

Standard USCI #8 Courand catheters were positioned under fluoroscopic control in the right atrium, main pulmonary artery and through the mitral valve into the left atrium via the aorta and left ventricle. A polyethylene cannula (internal diameter 2 mm) was inserted into one femoral artery. Phasic and mean pressures were monitored by means of P23db Statham strain-gauge manometers and were recorded along with

Footnotes:
¹ From the Cardiovascular Laboratory and the Department of Medicine, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Massachusetts.
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³ Address for reprints: Joseph S. Alpert, M.D., Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts 02115.
⁴ Received June 4, 1973; revision accepted for publication August 16, 1973.
lead II of the electrocardiogram by a Sanborn recorder. The strain-gauges were placed at the mid-chest level. The position of all catheters was verified fluoroscopically and with pressure control during each experiment. Cardiac output and pulmonary blood volume (PBV) were determined using sequential, rapid, hand injections of freshly prepared cardiogreen (2.5 mg/ml) into the main pulmonary artery and left atrium. Blood was withdrawn from the femoral artery through a Gilford densitometer at 24.7 ml/min by a Harvard Withdrawal Pump. Mean transit time (MTT) and cardiac output (CO) were calculated using the method of Hamilton. Pulmonary blood volume was calculated employing the mean transit time from the two sequential dye curves as described by Yu. The reproducibility of this method when performed in duplicate varies from 3.2 to 7%. Cardiac output was expressed as an average of the two values obtained from the pulmonary arterial and left atrial injections. Total pulmonary and total systemic resistances (TPR, TSR) were calculated in dynes-sec-cm⁻⁵ using the formulae: Total Pulmonary Resistance = Mean Pulmonary Arterial Pressure/Cardiac Output × 80, and Total Systemic Resistance = Mean Femoral Arterial Pressure/Cardiac Output × 80. Relative pulmonary compliance was calculated in ml/mm Hg using the formula: Compliance = Pulmonary Blood Volume/Mean Pulmonary Arterial Pressure.

Eight dogs were emboлизed with macroemboli utilizing autologous blood clot produced by a modification of the technique of Dalaen et al. Ten ml of femoral arterial blood were mixed thoroughly with 0.5 ml of CaCl₂ and 0.5 ml of thromboplastin® and immediately placed in glass tubes with an internal diameter of 4 mm for 60 to 120 min at room temperature. Four to 6 ml of the resultant firm clot were repeatedly injected into the right atrium via a #8 Courand catheter. This injection technique results in emboli approximately 1.4 mm in diameter. It has previously been documented that these emboli lodge mainly in first and second order pulmonary arteries.

Macroembolism was produced in eight dogs using lycopodium spores in saline suspension. This type of embolism occludes arterioles and the arteriolar entrance of pulmonary capillaries. Injections of the emboli were continued until the mean pulmonary arterial pressure rose 20–30 mm Hg. Occasionally, pulmonary arterial pressure fell rapidly towards normal soon after embolization. In these cases, an additional 4 to 8 cc of clot or lycopodium suspension were injected to sustain the desired level of pulmonary arterial pressure.

PGE₁ was first dissolved in 95% ethanol (10 mg/ml). This prostaglandin and ethanol solution was then mixed with 0.2% (Na)₂CO₃ buffer solution, using 0.9 ml of the buffer solution per 0.1 ml of the prostaglandin and ethanol solution. This buffered prostaglandin stock solution was stored at 0°C between experiments. At the time of its use, varying doses of PGE₁ were diluted in 50 ml of 0.9% NaCl solution and were infused into the right atrium by a Harvard Continuous Infusion Pump at a rate of 3.82 ml/min.

Pressure, flow, and volume measurements were made immediately after blood clot or spore injections had been completed. Then PGE₁, in varying doses (0.04–6.0 mcg/kg/min) was infused and hemodynamic measurements were repeated. Another set of measurements was made approximately 30 min after the termination of the PGE₁ infusion at a time when pulmonary arterial pressure had returned to near normal. Dogs receiving macroemboli were given the same doses of PGE₁ as those receiving microemboli. Measurements were made after pressures and heart rate had maintained a stable value for three to four minutes. This generally occurred after five to seven minutes of the infusion. The pressure values reported below were taken at the time of the dye curves.

Total pulmonary resistance (TPR) was used rather than pulmonary vascular resistance (PVR) because it was difficult to obtain acceptable left atrial pressure in nine of the seventeen dogs, presumably because of the damping secondary to catheter impingement on the left atrial wall. Acceptable left atrial pressure was obtained in eight of seventeen dogs. At no time did left atrial pressure change by more than 1 mm Hg, and even these changes occurred unpredictably, both in direction and in time. It was therefore felt that mean pulmonary arterial pressure adequately reflected the distending pressure in the pulmonary circuit and that total pulmonary resistance thus demonstrated the changes in pulmonary vascular resistance.

Means, standard deviations and Student's t-tests for paired variables were calculated using standard formulae. All mean values are reported ± one standard deviation.

Results

Hemodynamic Response to Macroembolism (Autologous Blood Clot)

Macroembolism with autologous blood clot caused marked and sustained decreases in pulmonary blood volume (152 ± 32 to 79 ± 17 ml) and in pulmonary vascular compliance (9.6 ± 2.7 to 2.0 ± 0.4 ml/mm Hg) (table 1, fig. 1). Mean pulmonary arterial pressure (17.1 ± 2.8 to 37.8 ± 4.1 mm Hg) and total pulmonary resistance (845 ± 349 to 1796 ± 680 dynes-sec-cm⁻⁵) increased significantly. Cardiac output, heart rate, mean femoral arterial pressure and total systemic resistance did not change significantly (table 1).

Hemodynamic Response to Microembolism (Lycopodium Spores)

Microembolism with lycopodium spores resulted in a decrease in pulmonary blood volume that was not statistically significant (162 ± 48 to 128 ± 23 ml) (table 2, fig. 1). However, mean pulmonary arterial pressures rose significantly (13.0 ± 1.3 to 36.6 ± 10.9 mm Hg). Total pulmonary resistance was...
increased significantly (551 ± 76 to 1329 ± 687 dynes-sec-cm⁻⁵) as did cardiac output (1.9 ± 0.3 to 2.4 ± 0.5 L/min). Total systemic resistance decreased significantly while mean femoral arterial pressure decreased only slightly and heart rate was essentially unchanged (table 2). There was a marked decrease in pulmonary vascular compliance in response to microembolism (12.4 ± 3.3 to 3.7 ± 1.0 mm Hg).

Thirty minutes after both macro- and microembolism, hemodynamic measurements showed some return towards the normal pre-embolic values. However, in no case did the hemodynamic measurements entirely return to pre-embolic levels by thirty minutes (tables 1 and 2).

### Hemodynamic Response to PGE₁ Infusion

Since PGE₁ doses were similar in the two groups of dogs, values of the hemodynamic measurements in each group have been combined despite small dose-related differences in individual animals. Intravenous PGE₁ infusion immediately following macroembolism resulted in a deterioration of the hemodynamic situation (table 3). That is, both mean femoral arterial pressure (128 ± 20 to 88 ± 26 mm Hg) and mean pulmonary arterial pressure (31 ± 5.0 to 25.9 ± 4.2 mm Hg) decreased significantly. Pulmonary blood volume also tended to fall (76 ± 16 to 60 ± 13 ml) but pulmonary vascular compliance remained unchanged. Cardiac output, heart rate and total pulmonary resistance were essentially unchanged while total systemic resistance decreased significantly (table 3).

After microembolism, the only significant hemodynamic effect of PGE₁ infusion was systemic hypotension. Mean femoral arterial pressure was significantly decreased (124 ± 35 to 91 ± 28 mm Hg) as was total systemic resistance while mean pulmonary arterial pressure did not change significantly. There was no significant change in pulmo-

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Immediately post-embolism</th>
<th>30 minute recovery</th>
<th>P values* (control vs post-embolism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, (beats/min)</td>
<td>157 ± 26</td>
<td>152 ± 21</td>
<td>158 ± 32</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary blood volume, (ml)</td>
<td>152 ± 32</td>
<td>79 ± 17</td>
<td>89 ± 20</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Cardiac output, (L/min)</td>
<td>1.8 ± 0.5</td>
<td>1.9 ± 0.4</td>
<td>1.7 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean transit time (PA), (secs)</td>
<td>13.4 ± 1.7</td>
<td>10.8 ± 1.4</td>
<td>11.9 ± 1.7</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Mean transit time (LA), (secs)</td>
<td>8.0 ± 0.9</td>
<td>8.3 ± 0.9</td>
<td>8.5 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Mean femoral arterial pressure, (mm Hg)</td>
<td>125 ± 22</td>
<td>119 ± 22</td>
<td>125 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure, (mm Hg)</td>
<td>17.1 ± 2.8</td>
<td>37.8 ± 4.1</td>
<td>27.1 ± 3.9</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Total pulmonary resistance, (dynes-sec-cm⁻⁵)</td>
<td>845 ± 349</td>
<td>1796 ± 680</td>
<td>1481 ± 532</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Compliance, (ml/mm Hg)</td>
<td>9.6 ± 2.7</td>
<td>2.0 ± 0.4</td>
<td>3.3 ± 0.7</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Total systemic resistance (dynes-sec-cm⁻⁵)</td>
<td>6201 ± 3154</td>
<td>5717 ± 2419</td>
<td>6763 ± 2375</td>
<td>NS</td>
</tr>
</tbody>
</table>

The values given above are the means ± one standard deviation from 9 separate experiments.

*NS = difference not significant, P > .05.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Immediately post-embolism</th>
<th>30 minute recovery</th>
<th>P values* (control vs post-embolism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, (beats/min)</td>
<td>143 ± 23</td>
<td>140 ± 18</td>
<td>141 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary blood volume, (ml)</td>
<td>162 ± 48</td>
<td>128 ± 23</td>
<td>130 ± 25</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output, (L/min)</td>
<td>1.9 ± 0.3</td>
<td>2.4 ± 0.5</td>
<td>1.8 ± 0.2</td>
<td>P &lt; .05</td>
</tr>
<tr>
<td>Mean transit time (PA), (secs)</td>
<td>13.3 ± 2.7</td>
<td>10.4 ± 1.9</td>
<td>12.6 ± 2.3</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Mean transit time (LA), (secs)</td>
<td>8.1 ± 1.4</td>
<td>7.1 ± 1.6</td>
<td>8.2 ± 1.9</td>
<td>P &lt; .05</td>
</tr>
<tr>
<td>Mean femoral arterial pressure, (mm Hg)</td>
<td>131 ± 30</td>
<td>119 ± 37</td>
<td>117 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure, (mm Hg)</td>
<td>13.0 ± 1.3</td>
<td>36.6 ± 10.9</td>
<td>17.7 ± 2.7</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Total pulmonary resistance, (dynes-sec-cm⁻⁵)</td>
<td>551 ± 76</td>
<td>1329 ± 687</td>
<td>793 ± 122</td>
<td>P &lt; .05</td>
</tr>
<tr>
<td>Compliance, (ml/mm Hg)</td>
<td>12.4 ± 3.3</td>
<td>3.7 ± 1.0</td>
<td>7.5 ± 1.3</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Total systemic resistance, (dynes-sec-cm⁻⁵)</td>
<td>5565 ± 1400</td>
<td>3891 ± 1139</td>
<td>5504 ± 890</td>
<td>P &lt; .002</td>
</tr>
</tbody>
</table>

The values given above are means ± one standard deviation from 8 separate experiments.

*NS = difference not significant, P > .05.

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EXPERIMENTAL PULMONARY EMBOLISM

Pulmonary blood volume (PBV) in milliliters plotted against mean pulmonary artery pressure in mm Hg for all control, macroemboli and microemboli experimental periods.

Discussion

The pulmonary vascular bed is vulnerable to extensive passive as well as active hemodynamic alterations. Yu and his associates have shown that in order to determine to what extent a particular intervention causes active or passive vasomotion in the pulmonary circuit, pulmonary pressure and vascular volume must be determined simultaneously. Thus, parallel increases in pulmonary distending pressure and pulmonary blood volume represent passive vascular distention whereas decreases in both measurements indicate vascular shrinkage usually secondary to major changes in cardiac or peripheral vascular hemodynamics. Changes in pressure and volume parameters in opposite directions are indicative of active pulmonary vasomotion. For example, in the normal pulmonary vascular bed, increasing pulmonary distending pressure in the face of decreasing pulmonary blood volume, nor in cardiac output, total pulmonary resistance or heart rate.

Table 3

<table>
<thead>
<tr>
<th>PGE1 infusion in Dogs with Macro- and Micro-Pulmonary Embolism</th>
<th>CO (l/min)</th>
<th>PBF (ml)</th>
<th>MTT (s)</th>
<th>MPAP (mm Hg)</th>
<th>TPR (dyn-s-cm⁻²)</th>
<th>CVM (ml/min/mm Hg)</th>
<th>ThSP (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>76 ± 16</td>
<td>10.9 ± 0.4</td>
<td>10.0 ± 0.4</td>
<td>10.7 ± 1.0</td>
<td>8.2 ± 1.0</td>
<td>P &lt; 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Macroemboli immediately before 140 ± 18</td>
<td>60 ± 3.3</td>
<td>10.4 ± 1.9</td>
<td>7.1 ± 1.6</td>
<td>124 ± 8.1</td>
<td>7 ± 2</td>
<td>P &lt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Microemboli immediately before 140 ± 18</td>
<td>128 ± 3.8</td>
<td>2.4 ± 0.5</td>
<td>10.4 ± 1.9</td>
<td>7.1 ± 2</td>
<td>110 ± 2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>PGE1 infusion n = 8</td>
<td>140 ± 21</td>
<td>138 ± 37</td>
<td>2.1 ± 0.4</td>
<td>11.0 ± 2.1</td>
<td>110 ± 2</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

The values given are the means ± one standard deviation and the P values for the number of experiments performed. HR = heart rate; PBV = pulmonary blood volume; CO = cardiac output; MTT (IA) = mean transit time of indicator dilution curve from pulmonary arterial injection; MPAP = mean pulmonary arterial pressure; TPR = total pulmonary resistance; CVM = pulmonary vascular compliance.
volume signifies active vasoconstriction and vice versa. In the face of pulmonary embolism, increasing pulmonary arterial pressure together with decreasing pulmonary blood volume reflect the blockage and separation from the normal circulation of certain segments of the pulmonary vascular bed.

Studies of the effects of experimental pulmonary embolism have resulted in extensive data on pulmonary hemodynamics during and following embolism. However, relatively few observations have been made on the effects of pulmonary embolism on pulmonary blood volume and pulmonary vascular compliance. Hyman, Myers and Meyer employed pulmonary artery injections of cardiogreen and sampled from the left atrium to obtain pulmonary mean transit time and pulmonary blood volume. This technique is open to criticism because of questionable mixing of dye. These authors did demonstrate a decrease in pulmonary blood volume following embolization with autologous blood clot. Yu reported several patients with pulmonary embolism in whom pulmonary blood volume and vascular compliance were reduced.

The present study reports markedly reduced pulmonary blood volume and vascular compliance following macroembolism with autologous blood clot, but only slightly reduced pulmonary blood volume with markedly decreased pulmonary vascular compliance in response to microembolism. Changes in pulmonary artery to femoral artery mean transit time (MTT-PA) paralleled the changes in pulmonary blood volume with significant reductions in both macro- and microemboli groups. These post-embolic decreases in MTT-PA reflect the decreased functional pulmonary vascular volume in which the green dye is distributed after pulmonary macroembolism. Left atrial to femoral arterial mean transit time (MTT-LA) was unchanged after macroemboli but significantly reduced after microemboli. This undoubtedly reflects the unchanged cardiac output after macroembolism and the significantly increased cardiac output after microemboli.

Pulmonary blood volume was reduced to approximately one-half the control value following macroembolism. This agrees with previous semi-quantitative estimates in patients of the amount of pulmonary vascular obstruction necessary to produce a similar degree of pulmonary hypertension.

Even though microembolism resulted in pulmonary hypertension of the same magnitude as macroembolism, the decrease in pulmonary blood volume was much less after microembolism. This minimal decrease in pulmonary blood volume after microembolism reflects the fact that a much smaller cross-sectional area of the pulmonary vasculature was compromised by occlusion and/or vasoconstriction of pulmonary arterioles.

Pulmonary vasodilators such as isoproterenol and aminophylline have found some limited clinical use in patients with pulmonary embolism. However, these agents have significant effects on the peripheral circulation and they frequently cause ventricular arrhythmias. PGE1 was selected for testing as a therapeutic agent in experimental pulmonary embolism because it is an active pulmonary vasodilator free of arrhythmogenic properties.

PGE1 infusions following microembolism produced little or no change in pulmonary blood volume and pulmonary vascular compliance despite the fact that mean femoral arterial pressure and total systemic resistance decreased. This lack of change in pulmonary blood volume despite considerable peripheral circulatory vasodilatation would seem to reflect the end result of two opposing hemodynamic processes induced by PGE1 infusion: some active pulmonary vasodilatation occurring in pulmonary arterioles put into vasospasm by lycopodium microemboli together with passive pulmonary vascular shrinkage secondary to a redistribution of blood from the lungs to the periphery. This explanation is supported by previous observations that PGE1 causes marked active vasodilatation of the peripheral circulation and mild active vasodilatation of the pulmonary circulation.

In dogs embolized with autologous blood clot, PGE1 caused a further reduction in pulmonary blood volume, indicating passive shrinkage of the pulmonary vascular bed. These observations can be explained solely by a redistribution of blood from pulmonary to systemic circulatory beds during PGE1 infusion. The fact that PGE1 increases pulmonary blood volume in the undisturbed canine lung but decreases pulmonary blood volume in the macroembolized pulmonary circulation suggests that the pulmonary vascular bed is not vasoconstricted following macroembolism. These observations lend further support to the concept that macroembolism produces hemodynamic alterations primarily through mechanical blockage of the pulmonary arterial circuit.

Since pulmonary embolism in man is primarily macroembolism, it seems quite unlikely that the prostaglandin, PGE1, would have a beneficial
hemodynamic effect in patients with pulmonary embolism.

References
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