Pulmonary Vasodilator Activity of Prostacyclin (PGI₂) in the Cat

ALBERT L. HYMAN AND PHILIP J. KADOWITZ

SUMMARY We studied the pulmonary vascular effects of prostacyclin, PGI₂, in the cat with intact chest under conditions of controlled blood flow. Intralobar injections of PGI₂, 0.03–1 μg, decreased arterial pressure in the perfused lobe in a dose-dependent manner. Inasmuch as lobar blood flow was held constant and left atrial pressure was unchanged, the fall in lobar arterial pressure reflects a decrease in lobar vascular resistance. Prostaglandin E₁ (PGE₁) and nitroglycerin also decreased lobar arterial pressure; however, PGI₂ had greater vasodilator activity than did these substances. Vasodilator responses to PGI₁, PGE₁, and nitroglycerin in absolute terms were dependent on the baseline level of tone in the pulmonary vascular bed. Prostacyclin reversed the hypertensive and platelet aggregating responses to ADP in the lobar vascular bed. These data indicate that PGI₂ has significant vasodilator activity in the feline pulmonary lobar vascular bed.

IN the lung, arachidonic acid is transformed into the cyclic endoperoxide intermediates, PGG₂ and PGH₂, by a microsomal cyclooxygenase (Nugteren and Hazeldel, 1973; Hamberg and Samuelsson, 1974). The endoperoxide intermediates then are converted by specific terminal enzymes into prostaglandins (PG), thromboxane A₂, and a newly discovered bicyclic prostaglandin, prostanoyl, or PGI₂ (Nugteren and Hazeldel, 1973; Hamberg and Samuelsson, 1974; Gryglewski et al., 1976). PGI₂ is the major metabolic product formed from arachidonic acid and endoperoxide intermediates in vascular tissue and, since PGI₂ is a potent inhibitor of platelet aggregation, it has been postulated that it may serve to protect vessel endothelium from the adverse effects of intravascular platelet aggregation and thrombus formation (Bunting et al., 1976; Gryglewski et al., 1976; Dusting et al., 1977). PGI₂ relaxes strips of mesenteric and celiac arteries but not strips from aorta and vena cava (Bunting et al., 1976). Prostacyclin decreases systemic arterial pressure in all species in which it has been studied, and a PGI₂ analog has been shown to have marked vasodilator activity in the feline pulmonary and mesenteric vascular beds (Hyman et al., 1977; Paustian et al., 1977; Armstrong et al., 1978; Fitzpatrick et al., 1978; Lefer et al., 1978). Although PGI₂ is formed in blood vessels, “PGI₂-like” substances are released from the lung, and the metabolite, 6-keto-PGF₁α, is released from the lung after immunological challenge, the direct effects of PGI₂ on the pulmonary vascular bed are uncertain (Dawson et al., 1976; Gryglewski et al., 1976; Gryglewski et al., 1978). In a recent study in the anesthetized dog, PGI₂, in a dose of 0.5 μg/kg, iv, caused a 1.4% decrease in pulmonary arterial pressure (Fitzpatrick et al., 1978). However, in that study in the open-chest dog, the effects of PGI₂ on cardiac output and left atrial pressure were not assessed. In another recent study, PGI₂ has been shown to decrease pulmonary arterial pressure in the dog; however, cardiac output was changed (Kadowitz et al., 1978).
so that the direct effects of prostacyclin on the pulmonary circulation are unclear. The present study was undertaken to investigate the direct effects of PGI₂ on the feline pulmonary lobar vascular bed under conditions of controlled lobar blood flow in the spontaneously breathing cat with intact chest. The effects of PGI₂ were studied under resting conditions and when lobar vascular resistance was increased actively by infusion of a prostaglandin endoperoxide analog and PGD₂. In addition, the effects of PGI₂ on the lobar hypertensive response to ADP, a substance that aggregates platelets in the lung, were investigated (Hyman et al., 1971).

Methods

The pulmonary vascular actions of PGI₂ were investigated in 34 adult cats of either sex, weighing 2.4–3.7 kg. The cats were anesthetized with pentobarbital sodium, 35 mg/kg, iv, and were strapped in the supine position to a Philip's fluoroscopic table. The cats spontaneously breathed room air, or room air enriched with oxygen, through a cuffed endotracheal tube. In experiments in which the effects of PGI₂, PGE₁, nitroglycerin, and 6-keto-PGF₁α on the lobar vascular bed were investigated, a specially designed 5 or 6F triple lumen balloon perfusion catheter was passed, under fluoroscopic guidance, from an external jugular vein into the arterial branch to the left lower lung lobe. After the lobar artery had been vascularly isolated by distension of the balloon cuff on the catheter and the cat heparinized (1000 U/kg, iv), the lobe was perfused with blood withdrawn from the femoral artery or vein through the catheter lumen immediately beyond the balloon cuff. Perfusion pressure in the lobar artery was measured through the third lumen, 5 mm distal to the perfusion port. The lobe was perfused with a Harvard model 1210 peristaltic pump, and the perfusion rate was adjusted so that the decrease averaged 1.3 ± 0.3 mm Hg. The PGI₂ concentration in the perfused lobe approximated mean pressure in the main pulmonary artery and was not changed during an experiment. Flow rates in the left lower lobe averaged 45 ± 3 ml/min. Left atrial pressure was measured with a transseptally placed 3 or 4F Teflon catheter. Aortic pressure was measured with a 3 or 4F catheter, inserted into the aorta by way of a femoral artery. These procedures have been described recently (Hyman et al., 1977). All vascular pressures were measured with Statham P23Db transducers zeroed at the right atrial level, and mean pressures, obtained by electronic integration, were recorded on an Electronics for Medicine recorder, model DR-12. During the control period, mean pressures were 14.8 ± 0.4 mm Hg in the perfused lobar artery, 5.2 ± 0.3 mm Hg in the left atrium, and 166 ± 4 mm Hg in the aorta. In these experiments, the effects of the vasoactive substances were evaluated under resting conditions and when lobar vascular resistance was elevated by infusions of the PGI₂ analog, (1S)-hydroxy-11a,9α-epoxymethano prosta-5Z,13E-dienoic acid, or PGD₂. Responses are represented as both the absolute decrease in pressure in mm Hg and as percent decrease in pressure.

In experiments in which the effects of ADP and PGI₂ were investigated, lobar arterial pressure was increased by continuous intralobar infusions of ADP, 250–500 μg/min for 2–5 minutes. After a stable hypertensive response was obtained, PGI₂, 50–150 ng/min, also was infused for 1–2 minutes. In one cat, the trachea and bronchi were flooded rapidly with a cold 3% gluteraldehyde solution at the peak of the pressor response to ADP, and sections of the perfused lobe were obtained for light and electron microscopy. In another cat, sections for light and electron microscopy were obtained during the infusion of both ADP and PGI₂.

Blood gases and pH were measured with an Instrumentation Laboratory Model micro 13 blood gas analyzer. In cats in which the arterial Po₂ fell below 70 mm Hg, the inspired air was enriched with oxygen. Arterial pH was maintained in the normal range with sodium bicarbonate and dilute lactic acid solutions. In the control period, pH, Po₂, and Pco₂ averaged 7.38, 89 mm Hg, and 35 mm Hg.

PGI₂ (Upjohn) was supplied as the sodium salt and was dissolved in 20 mL Tris buffer, pH 9.0, under nitrogen gas in brown bottles. PGI₂ solutions were stored frozen and kept on crushed ice during an experiment. No apparent loss in activity was seen, as estimated by the magnitude of aortic depressor responses over the 3-week period experiments were carried out. Injection of the Tris buffer vehicle into the left lower lobe in the largest volume used (0.3 ml) decreased lobar arterial pressure in four of seven cats, had no effect in two of seven cats, and increased lobar arterial pressure in one of seven cats. In the four cats in which pressure fell, the decrease averaged 1.3 ± 0.3 mm Hg. The PGI₂ metabolite, 6-keto-PGF₁α (Upjohn), was prepared under the same conditions as PGI₂. PGE₁ (Upjohn) was dissolved in 100% ethyl alcohol at a concentration of 5 mg/ml and stored in a freezer. Stock solutions were prepared in 0.9% saline on a frequent basis. Nitroglycerin (Lilly) was prepared as 10 and 100 μg/ml solutions in 0.9% saline on a daily basis. The saline vehicle for nitroglycerin and the 0.2% ethanol and saline vehicle for PGE₁ had transient inconsistent effects on pressure in the perfused lobar artery. All vasoactive substances were injected on a straight gravimetric basis, and doses were not normalized for body weight, organ weight, or blood flow. All hemodynamic data were analyzed by the methods of Snedecor and Cochran (1967) for paired and group data. All values represent peak changes and are expressed as mean ± SEM. A P value of less than 0.05 was used as the criterion for significance.

Results

The effects of PGI₂ on mean vascular pressures in the left lower lobe are summarized in Table 1. In the control period during which lobar vascular re-
sistance was at resting levels (0.029–0.035 mm Hg/ml per min), bolus injections of the prostacyclin, 0.03–1.0 µg, into the lobar artery produced dose-related decreases in mean lobar arterial pressure (Table 1). PGI₂ had no significant effect on mean left atrial pressure but decreased mean systemic arterial pressure at the 0.3- and 1-µg doses. The effects of PGI₂ also were investigated in this same group of cats when vasoconstrictor tone had been elevated by infusion of the prostaglandin endoperoxide analog, (15S)-hydroxy-11α,9α-epoxymethano prosta-5Z,13E-dienoic acid. Intralobar infusions of the analog, 50–100 ng/min, increased lobar arterial pressure and lobar vascular resistance to 0.825–1.010 mm Hg/ml per min. When lobar vascular resistance was actively increased, the reductions in lobar arterial pressure in response to intralobar injections of PGI₂ (0.03–1.0 µg) were significantly greater than observed when lobar arterial pressure was at resting levels (Table 1). However, when expressed as percent decrease, which takes into account the elevation in baseline pressure, the reductions in lobar arterial pressure were not significantly different in the control period and during infusion of the endoperoxide analog (Table 1). The effects of 6-keto-PGF₁α on the left lower lobe also were investigated, and intralobar injections of the breakdown product in doses of 0.3, 1, 3, and 10 µg increased lobar arterial pressure by 2.4 ± 0.6, 5.5 ± 0.6, 9.0 ± 1.1, and 14.5 ± 2.0 mm Hg, respectively (n = 7).

We investigated the effects of PGE₁ and nitroglycerin in two other groups of cats, using a similar experimental design. Nitroglycerin and PGE₁, 3 µg, produced small but significant reductions in lobar arterial pressure when injected into the perfused lobar artery (Table 2). The reductions in lobar arterial pressure were increased significantly during infusion of the endoperoxide analog; however, at the 3-µg dose when responses were compared on a percent basis, depressor responses to PGE₁ and nitroglycerin did not differ significantly in the control period and during infusion of the endoperoxide analog (Table 2).

The effects of PGI₂ on the response of the left lower lobe to infusions of ADP were investigated in another group. The effects of ADP infusions are illustrated in Figure 1; in four cats, intrapulmonary infusion of ADP, 250–500 µg/min, increased lobar arterial pressure from 16.5 ± 4 mm Hg to 36.4 ± 7 mm Hg (P < 0.05) without affecting left atrial pressure. These concentrations of ADP had minimal effects on systemic arterial pressure (Fig. 1). Once a steady state in lobar arterial pressure was attained (2–4 minutes), intralobar infusion of PGI₂, 50–150 ng/min, decreased lobar arterial pressure to 17.4 ± 6 mm Hg in 60–90 seconds (Fig. 1). Electron micrographs of lung sections obtained from a cat at the peak of the pulmonary pressor response to intralobar infusion of ADP, 500 µg/min, show that ADP produced widespread platelet aggregation in small intralobar vessels and capillaries (Fig. 2A). In contrast, electron micrographs from lung sections from a cat in which ADP, 500...
TABLE 2 Effects on Nitroglycerin and PGE\textsubscript{1} on Mean Vascular Pressure in the Left Lower Lobe of the Cat

<table>
<thead>
<tr>
<th></th>
<th>Lobar artery (mm Hg)</th>
<th>Left atrium (mm Hg)</th>
<th>Lobar arterial left atrial gradient (mm Hg)</th>
<th>Gradient decrease (mm Hg)</th>
<th>Gradient decrease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12.8 ± 0.5</td>
<td>5.6 ± 0.4</td>
<td>7.2 ± 0.9</td>
<td>2.4 ± 0.3</td>
<td>33.3 ± 4.8</td>
</tr>
<tr>
<td>GTN, 3.0 \textmu g</td>
<td>10.3 ± 0.9*</td>
<td>5.7 ± 0.4</td>
<td>4.8 ± 0.6*</td>
<td>2.9 ± 0.5</td>
<td>44.9 ± 2.8</td>
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During infusion of endoperoxide analog

<table>
<thead>
<tr>
<th></th>
<th>Lobar artery (mm Hg)</th>
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<th>Lobar arterial left atrial gradient (mm Hg)</th>
<th>Gradient decrease (mm Hg)</th>
<th>Gradient decrease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>39.7 ± 2.4</td>
<td>5.4 ± 0.7</td>
<td>34.3 ± 3.2</td>
<td>6.0 ± 0.5</td>
<td>17.5 ± 2.4</td>
</tr>
<tr>
<td>GTN, 0.3 \textmu g</td>
<td>33.5 ± 3.2*</td>
<td>5.2 ± 0.4</td>
<td>28.3 ± 2.9*</td>
<td>6.0 ± 0.5</td>
<td>17.5 ± 2.4</td>
</tr>
<tr>
<td>Control</td>
<td>32.4 ± 3.2*</td>
<td>5.2 ± 0.2</td>
<td>27.1 ± 3.1*</td>
<td>5.0 ± 1.2</td>
<td>25.9 ± 2.3</td>
</tr>
<tr>
<td>GTN, 1.0 \textmu g</td>
<td>32.4 ± 3.2*</td>
<td>5.2 ± 0.2</td>
<td>27.1 ± 3.1*</td>
<td>5.0 ± 1.2</td>
<td>25.9 ± 2.3</td>
</tr>
<tr>
<td>Control</td>
<td>39.7 ± 4.8</td>
<td>5.7 ± 0.2</td>
<td>34.7 ± 3.1*</td>
<td>9.0 ± 1.2</td>
<td>29.3 ± 2.3</td>
</tr>
<tr>
<td>GTN, 3.0 \textmu g</td>
<td>29.7 ± 4.5*</td>
<td>5.5 ± 0.3</td>
<td>24.2 ± 2.8*</td>
<td>13.0 ± 1.9</td>
<td>34.9 ± 4.1</td>
</tr>
</tbody>
</table>

\( n = 5 \)

<table>
<thead>
<tr>
<th></th>
<th>Lobar artery (mm Hg)</th>
<th>Left atrium (mm Hg)</th>
<th>Lobar arterial left atrial gradient (mm Hg)</th>
<th>Gradient decrease (mm Hg)</th>
<th>Gradient decrease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>14.8 ± 1.0</td>
<td>5.1 ± 0.3</td>
<td>9.7 ± 0.8</td>
<td>2.5 ± 0.2</td>
<td>25.8 ± 2.9</td>
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<tr>
<td>PGE\textsubscript{1}, 3.0 \textmu g</td>
<td>12.3 ± 0.6*</td>
<td>5.1 ± 0.4</td>
<td>7.2 ± 0.4*</td>
<td>2.5 ± 0.2</td>
<td>25.8 ± 2.9</td>
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During infusion of endoperoxide analog

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<tr>
<th></th>
<th>Lobar artery (mm Hg)</th>
<th>Left atrium (mm Hg)</th>
<th>Lobar arterial left atrial gradient (mm Hg)</th>
<th>Gradient decrease (mm Hg)</th>
<th>Gradient decrease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>39.0 ± 2.8</td>
<td>4.9 ± 0.4</td>
<td>34.1 ± 2.1</td>
<td>5.6 ± 0.3</td>
<td>16.4 ± 2.3</td>
</tr>
<tr>
<td>PGE\textsubscript{1}, 0.3 \textmu g</td>
<td>33.7 ± 2.1*</td>
<td>5.1 ± 0.4</td>
<td>28.5 ± 2.4*</td>
<td>5.6 ± 0.3</td>
<td>16.4 ± 2.3</td>
</tr>
<tr>
<td>Control</td>
<td>36.4 ± 3.2*</td>
<td>5.2 ± 0.8</td>
<td>30.2 ± 2.7*</td>
<td>7.9 ± 1.3</td>
<td>20.7 ± 1.9</td>
</tr>
<tr>
<td>PGE\textsubscript{1}, 1.0 \textmu g</td>
<td>36.4 ± 3.2*</td>
<td>5.2 ± 0.8</td>
<td>30.2 ± 2.7*</td>
<td>7.9 ± 1.3</td>
<td>20.7 ± 1.9</td>
</tr>
<tr>
<td>Control</td>
<td>32.2 ± 3.1</td>
<td>5.1 ± 0.6</td>
<td>27.1 ± 2.9</td>
<td>10.2 ± 1.7</td>
<td>27.3 ± 2.3</td>
</tr>
<tr>
<td>PGE\textsubscript{1}, 3.0 \textmu g</td>
<td>32.2 ± 3.4*</td>
<td>5.0 ± 0.4</td>
<td>27.2 ± 2.7*</td>
<td>10.2 ± 1.7</td>
<td>27.3 ± 2.3</td>
</tr>
</tbody>
</table>

\( n = 6 \)

* \( P < 0.05 \) when compared to corresponding control, paired comparison.

\( \mu \text{g/min}, \text{and PGI}_2, 150 \text{ ng/min}, \) were infused at the same time reveal few, if any, platelet aggregates in small intrapulmonary vessels and capillaries (Fig. 2B).

Since PGI\textsubscript{2} inhibits platelet aggregation in the pulmonary vascular bed, it is possible that the decrease in lobar arterial pressure in response to prostacyclin may be due in part to disaggregation of trapped platelets. To evaluate this possibility, the effects of PGI\textsubscript{2} were investigated in a group of seven cats in which PGD\textsubscript{2}, a potent inhibitor of platelet aggregation, was infused. In the control period, intrapulmonary injections of PGI\textsubscript{2}, 1 \textmu g, decreased lobar arterial pressure from 13.8 ± 0.5 to 9.4 ± 0.2 mm Hg without affecting left atrial pressure. Intrapulmonary infusion of PGD\textsubscript{2}, 0.6 \mu g/min, increased lobar arterial pressure from 13.8 ± 0.5 to 32.0 ± 1.8 mm Hg \((P < 0.05)\) without changing left atrial pressure. When lobar arterial pressure was elevated during the PGD\textsubscript{2} infusion, bolus injections of PGI\textsubscript{2}, 1 \textmu g, decreased lobar pressure from 32.0 ± 1.8 to 20.1 ± 0.3 mm Hg \((P < 0.05)\). The reductions in lobar arterial pressure in response to PGI\textsubscript{2}, 1 \textmu g, were 31.9 ± 3.5% in the control period and 36.6 ± 4.8% during the PGD\textsubscript{2} infusion. The percent reductions in lobar arterial pressure in the control period and during the PGD\textsubscript{2} infusion were not significantly different.

**Discussion**

Results of the present study show that PGI\textsubscript{2} decreased lobar arterial perfusion pressure in a
dose-dependent manner in the cat with intact chest. Inasmuch as blood flow to the lobe was held constant with a pump and left atrial pressure was unchanged, the fall in lobar arterial pressure reflects a decrease in lobar vascular resistance. The reductions in lobar arterial pressure in response to PG\textsubscript{I\(_2\)} were enhanced when vasoconstrictor tone was actively increased by infusions of a PG\textsubscript{H\(_2\)} analog or PG\textsubscript{D\(_2\)}. However, when compared on a percent basis, which would take the elevation in baseline pressure into account, reductions in lobar arterial pressure and lobar vascular resistance were not significantly different in the control period and during infusion of pressor substances. PGE\(_1\) and nitroglycerin also decreased lobar arterial pressure, and this effect was enhanced when lobar arterial pressure was elevated. These data indicate that the absolute magnitude of the dilator responses is dependent on the resting level of tone in the pulmonary vascular bed. PG\textsubscript{I\(_2\)} had greater vasodilator activity than PGE\(_1\) or nitroglycerin under resting conditions and when lobar arterial pressure was elevated. The dilator effects of PG\textsubscript{I\(_2\)} in the lobe were not due to conversion of the prostacyclin to its stable breakdown product, since 6-keto-PGF\textsubscript{1\(_a\)} was found to increase lobar arterial pressure in the cat. In this regard, the effects of 6-keto-PGF\textsubscript{1\(_a\)} and PGF\textsubscript{1\(_a\)} were similar in that both substances had pressor activity in the lung (Hyman et al., 1978).

The vasodilator response to PG\textsubscript{I\(_2\)} in the lung of the cat with intact chest probably was not due to reversal of platelet aggregation since the response was not decreased during infusion of PG\textsubscript{D\(_2\)}, a substance which inhibits platelet aggregation (Oelz et al., 1977). However, intralobar infusion of ADP produced a marked elevation in lobar vascular resistance, which was associated with widespread aggregation of platelets in small pulmonary arteries and capillaries. The present studies show that the pulmonary hypertensive response to ADP in the cat with intact chest is reversed rapidly by infusion of small amounts of PG\textsubscript{I\(_2\)}. These data, along with the observation that significant numbers of platelet emboli are not present in small pulmonary vessels as demonstrated by electron microscopy, suggest that PG\textsubscript{I\(_2\)} has the ability to reverse the aggregation process in vivo in the pulmonary vascular bed. The present results are in agreement with in vitro studies with the aggregometer in which PG\textsubscript{I\(_2\)} was a potent inhibitor of platelet aggregation (Bunting et
It has been reported recently that isolated perfused lungs of rats and guinea pigs and the lungs of anesthetized cats spontaneously release a "PGI₂-like" substance (Gryglewski et al., 1976). If the lungs release "PGI₂-like" substances and these factors are formed by endothelial cells in upstream vessels, it is possible that these substances serve to inhibit platelet aggregation and thrombus formation in the lung and to maintain the pulmonary vascular bed in a dilated state. The hypothesis that a dilator substance in the cyclooxygenase pathway may serve to maintain the pulmonary vascular bed in a dilated state is supported by the observation that cyclooxygenase inhibitors, such as indomethacin and meclofenamate, increase pulmonary vascular resistance (Kadowitz et al., 1975). In addition, the pressor response to alveolar hypoxia in the lung appears to be modulated by the formation of a dilator product in the cyclooxygenase pathway (Vaage et al., 1975; Hales et al., 1977). Since PGI₂ is the only known product of arachidonic acid metabolism that has potent vasodilator activity in the lung, it is possible that a "PGI₂-like" substance serves to maintain the pulmonary circulation in a dilated state and to modulate response to vasoconstrictor stimuli, such as alveolar hypoxia.

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