Influence of a Prostaglandin Endoperoxide Analogue on the Canine Pulmonary Vascular Bed

PHILIP J. KADOWITZ AND ALBERT L. HYMAN

SUMMARY We evaluated the effects of an analogue of the prostaglandin endoperoxide, PGH₂, in the canine pulmonary vascular bed. The analogue increased pulmonary arterial pressure whereas cardiac output and left atrial pressure were unchanged. Although pulmonary vascular resistance was increased markedly, only small increases in systemic vascular resistance were observed. In experiments in which blood flow to a lobe was maintained constant, the analogue produced dose-related increases in lobar arterial and small vein pressure but little change in left atrial pressure. These data suggest that the analogue increased resistance to flow by constricting intrapulmonary veins and upstream vessels presumed to be small arteries. The increase in resistance was similar when the lung was perfused with dextran or with blood. In addition, the analogue increased inflation pressure; however, similar increments in vascular resistance were obtained in ventilated and nonventilated lung lobes. Indomethacin, in doses which abolished responses to arachidonic acid, did not attenuate the response to the analogue. These results suggest that interaction with formed elements, increases in airway tone, or stimulation of prostaglandin synthesis contribute little if anything to the pressor response to the analogue. These data show that the analogue is far more potent than the biseenoic prostaglandins in the pulmonary vascular bed and suggest that endoperoxides may represent an active form of the prostaglandins in the lung.

PROSTAGLANDINS E₂ and F₃₀ (PGE₂ and PGF₃₀) are formed in the lung from the precursor, arachidonic acid, and their effects on the pulmonary vascular bed have been investigated in a variety of species. In dog, cat, sheep, swine, and calf PGF₃₀ was found to be a potent pulmonary presor substance, whereas in dog, swine, and lamb, PGE₂ elicited small increases in pulmonary vascular resistance. The prostaglandin precursor, arachidonic acid, has been reported to have pressor activity in the canine pulmonary vascular bed and its effects are blocked by inhibitors of prostaglandin synthesis. Direct evidence for the formation of an endoperoxide intermediate during prostaglandin synthesis has been obtained recently and, in the guinea pig lung, the major products of synthesis are metabolites of intermediates rather than the biseenoic prostaglandins. However, the endoperoxides are highly unstable substances with a half-life of less than 10 seconds in platelet-rich plasma. The instability of the endoperoxides makes it difficult to investigate their biological activity. The synthesis of stable analogues of the endoperoxide permitted the evaluation of the biological activity of these novel intermediates. Stable analogues that are chemically similar to the endoperoxide, PGH₂, have been synthesized. The purpose of the present study was to investigate the effects of 15(S)-hydroxy-11α,9α-(epoxy-methano)prosta-5Z,13E-dienoic acid, a stable PGH₂ analogue, on the canine pulmonary vascular bed. In addition, we evaluated the contribution of changes in broncho-motor tone, interaction with formed elements, and syn-

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Prostonoid Endoperoxide Analogue on the Canine Pulmonary Vascular Bed
thesis of endogenous prostaglandins on the response to
this analogue.

Methods

The cardiopulmonary effects of the analogue were studied
in 70 mongrel dogs of either sex weighing 14–23 kg. Dogs
were anesthetized with pentobarbital sodium (30
mg/kg, iv) and strapped to a Philips heart table in the
supine position. In 23 dogs in which the effects of the
analogue on pulmonary and systemic vascular resistance
were evaluated, a 6F Edslab thermal dilution catheter was
passed into the main pulmonary artery from the external
jugular vein under fluoroscopic guidance (Philips image
intensifier). Pulmonary arterial pressure was measured from
the distal port on the Edslab catheter. A 7F Teflon
catheter was passed into the left atrium transeptally and
large bore catheters were positioned in the aorta from a
femoral artery and in a femoral vein. Cardiac output was
determined with an Edwards thermal dilution computer,
model 9500, after injection of 5 ml of 5% dextrose solu-
tion (cooled to 0°C) into the superior vena cava (proximal
port on the Edslab catheter). Values for cardiac output
averaged 120 ml/kg per min and compared favorably with
cardiac outputs determined by the indicator-dilution tech-
nique in this laboratory. The dogs breathed room air or
room air enriched with O2 spontaneously through a cuffed
endotracheal tube.

In 47 dogs in which constant flow perfusion of the left
lower lobe was employed, a specially designed 20F dou-
ble-lumen balloon catheter was introduced through a jug-
ular vein into the arterial branch of the left lower lung lobe
under fluoroscopic guidance. A 1.5-mm Teflon catheter
with its tip positioned about 2 cm distal to the tip of the
perfusion catheter was used to monitor perfusion pressure
in the lobar artery. Catheters with side holes near the tip
were passed into the main pulmonary artery and femoral
artery and transeptally into a small intrapulmonary vein and
the left atrium. Precautions were taken to ensure that
pressure measurements were made without wedging in
veins 2–3 mm in diameter. Briefly, a 0.9-mm Teflon
catheter with two side holes near the tip was passed through
a 3-mm Teflon catheter that previously had been
wedged in a small intrapulmonary vein. The 0.9-mm cat-
ther was then withdrawn 1–3 cm from the wedge position
until pressure dropped abruptly. The 0.9-mm catheter
was fixed in place with a Cope adaptor after the larger catheter
had been withdrawn to the left atrium. These methods
have been described in detail previously.17,18 All vascular
pressures were measured analogically on pulmonary and systemic vascular resistance.

Pulmonary vascular resistance was calculated by dividing
pulmonary arterial pressure minus left atrial pressure by the cardiac output. Systemic vascular resistance was calculated by dividing
aortic pressure by the cardiac output after having
determined that right atrial pressure was not altered by the
analogue in four experiments. All values were expressed
as mean ± SEM and a P value of less than 0.05 was con-
sidered significant.

Results

CARDIOPULMONARY ACTIONS OF THE ANALOGUE

The cardiopulmonary effects of the PGH2 analogue are
illustrated in Figure 1 and data from 14 experiments are
summarized in Table 1. Injection of the analogue into the
superior vena cava in doses of 1, 3, and 10 μg resulted in a
dose-related increase in pulmonary arterial pressure but

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spontaneously breathing dog. Cardiac output (CO) in liters per minute was determined by the thermal dilution technique.

![Figure 1](image)

**FIGURE 1** Records from an experiment illustrating the effects of injection of 1, 3, and 10 μg of the prostaglandin H2 analogue into the superior vena cava on mean pressure in the aorta (Ao), the main pulmonary artery (PA), and the left atrium (LA) in the intact spontaneously breathing dog. Cardiac output (CO) in liters per minute was determined by the thermal dilution technique.

no change in left atrial pressure or cardiac output. The increase in calculated pulmonary vascular resistance was 34%, 86%, and 158% at 1, 3, and 10μg of the analogue, respectively. Although the analogue elicited large increases in pulmonary arterial pressure, only small increments in aortic pressure were observed (Table 1). The increase in systemic vascular resistance was significant only at the 10-μg dose, at which a 21% rise occurred (Table 1).

To determine whether the analogue was inactivated by the lung, the effects of injection of this substance into the right and left side of the circulation were compared in a second group of dogs. Injection of the analogue, 10 μg, into the left atrium resulted in a significant increase in aortic pressure and, after a delay of approximately 10–18 seconds, an increase in pulmonary arterial pressure (Table 2). Pressure in the left atrium and the cardiac output were unchanged (Table 2). The increase in pulmonary vascular resistance was significantly greater when the analogue was injected into the superior vena cava (150%) than when injected into the left atrium (30%). The increase in systemic vascular resistance was similar when the analogue was injected into the superior vena cava (18%) or the left atrium (21%).

**TABLE 1** Cardiopulmonary Effects of the Endoperoxide Analogue in the Anesthetized Dog

<table>
<thead>
<tr>
<th>Amount injected</th>
<th>Pressure (mm Hg)</th>
<th>Cardiac output (liters/min)</th>
<th>Pulmonary vascular resistance (mm Hg/liter/min)</th>
<th>Systemic vascular resistance (mm Hg/liter/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pulmonary artery</td>
<td>Left atrium</td>
<td>Aorta</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>17.5 ± 1.7</td>
<td>2.4 ± 0.5</td>
<td>108 ± 6.5</td>
<td>2.27 ± 0.21</td>
</tr>
<tr>
<td>1 μg (n = 8)</td>
<td>22.8 ± 2.2*</td>
<td>2.4 ± 0.5</td>
<td>112 ± 6.9*</td>
<td>2.26 ± 0.18</td>
</tr>
<tr>
<td>Control</td>
<td>17.9 ± 1.2</td>
<td>3.0 ± 0.6</td>
<td>111 ± 6.2</td>
<td>1.93 ± 0.17</td>
</tr>
<tr>
<td>3 μg (n = 11)</td>
<td>31.5 ± 2.2*</td>
<td>3.3 ± 0.7</td>
<td>120 ± 6.1*</td>
<td>1.97 ± 0.19</td>
</tr>
<tr>
<td>Control</td>
<td>17.5 ± 1.0</td>
<td>3.8 ± 0.6</td>
<td>121 ± 5.2</td>
<td>1.86 ± 0.14</td>
</tr>
<tr>
<td>10 μg (n = 14)</td>
<td>38.2 ± 2.0*</td>
<td>4.3 ± 0.7</td>
<td>140 ± 5.6*</td>
<td>1.78 ± 0.15</td>
</tr>
</tbody>
</table>

The endoperoxide analogue was injected into the superior vena cava; n = number of dogs.

*P < 0.05 when compared to control, paired comparison.

**PERFUSION EXPERIMENTS**

The above studies establish that the PGH2 analogue increases pulmonary vascular resistance in the dog. To investigate the site of action in the pulmonary vascular bed, experiments were carried out in which blood flow was maintained constant with a pump, and pressures in small (2–3 mm) intrapulmonary veins were measured. In these experiments injection of the analogue as a bolus into the perfused lobar artery in the dose range of 0.03–10 μg resulted in a significant dose-related increase in lobar arterial perfusion pressure (Fig. 2). The increase in lobar arterial pressure was accompanied by a significant dose-related increase in pressure in the small intrapulmonary vein and in pressure gradient from lobar artery to small vein but no significant change in left atrial pressure (Fig. 2).

**EFFECTS IN VENTILATED AND NONVENTILATED LUNGS**

In experiments in which the left lower lobe and the right lungs were ventilated separately using a Carlen’s endobronchial divider and dual-cylinder Harvard respirator, injection of the analogue into the perfused lobar artery elicited a dose-related increase in peak translobar airway pressure (Fig. 3, upper panel). The increase in airway pressure reflects both an increase in airway resistance and a decrease in dynamic compliance. To determine whether the changes in airway and vascular pressure were related, pressor responses were compared in ventilated and nonventilated lung lobes. In these experiments responses were obtained when the left lower lobe was ventilated and when airflow to the lobe was stopped during expiration. The increase in lobar arterial pressure was similar when the lung was ventilated and when ventilation was arrested by occluding the left side of the endobronchial divider (Fig. 3, lower panel).

**INFLUENCE OF DEXTRAN PERFUSION**

To ascertain the contribution of interaction with formed elements, responses to the analogue were compared when the lung was perfused with blood and with a 10% dextran solution. In 10 dogs the increase in lobar arterial perfusion pressure in response to 3 μg of the analogue was 13.8 ± 1.9 mm Hg during lobar perfusion with blood and 12.7 ±
Table 2  Comparison of the Effects of Injection of the Endoperoxide Analogue (10 µg) into the Superior Vena Cava (SVC) and into the Left Atrium (LA)

<table>
<thead>
<tr>
<th>Amount injected</th>
<th>Pressure (mm Hg)</th>
<th>Cardiac output (liters/min)</th>
<th>Pulmonary vascular resistance (mm Hg/liter/min)</th>
<th>Systemic vascular resistance (mm Hg/liter/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pulmonary artery</td>
<td>Left atrium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>17.4 ± 1.6</td>
<td>4.9 ± 0.5</td>
<td>128 ± 9</td>
<td>1.81 ± 0.28</td>
</tr>
<tr>
<td>10 µg, SVC</td>
<td>35.3 ± 2.3*</td>
<td>4.9 ± 0.7</td>
<td>147 ± 8*</td>
<td>1.77 ± 0.33</td>
</tr>
<tr>
<td>Control</td>
<td>18.7 ± 1.7</td>
<td>4.8 ± 0.6</td>
<td>132 ± 9</td>
<td>2.02 ± 0.33</td>
</tr>
<tr>
<td>10 µg, LA</td>
<td>23.7 ± 2.3*</td>
<td>5.4 ± 0.6</td>
<td>160 ± 8*</td>
<td>2.03 ± 0.31</td>
</tr>
</tbody>
</table>

* P < 0.05 when compared to control, paired comparison.

4.0 mm Hg during perfusion with dextran. The increase in lobar pressure was not significantly different when the lung was perfused with blood or with dextran.

INFLUENCE OF INDOMETHACIN

The effects of indomethacin, an inhibitor of prostaglandin synthesis, on the response to the analogue were evaluated in the pulmonary vascular bed. The rise in lobar arterial pressure in response to the analogue was increased significantly after indomethacin, 2.5 mg/kg, iv (Fig. 4, left panel). In five of these nine dogs the effects of indomethacin on responses to arachidonic acid, the precursor for PGE₂ and PGF₂α, were investigated. The increase in lobar arterial pressure and the decrease in aortic pressure in response to injection of 3 mg of arachidonic acid into lobar artery were decreased significantly (Fig. 4, right panel).

RELATIVE POTENCY OF THE ANALOGUE

The structures of arachidonic acid, the fatty acid precursor, the endoperoxide intermediates and analogue, and the bisenoic prostaglandins are shown in Figure 5. The relative potency of the precursor, the endoperoxide analogue, and the bisenoic prostaglandins was compared in the pulmonary vascular bed. The PGH₂ analogue was approximately 10 times more potent than PGF₂α, 300 times more potent than PGE₂, and 3,000 times more potent than arachidonic acid in increasing lobar arterial perfusion pressure in the dog (Fig. 6).

Discussion

Results of the present study show that an analogue of PGH₂ increased pulmonary arterial pressure in the dog. Inasmuch as cardiac output and left atrial pressure were unchanged the increase in pulmonary arterial pressure suggests an increase in pulmonary vascular resistance. The effects of the analogue were dose-related and the substance also increased systemic vascular resistance; however, the effects on the pulmonary circulation were much greater. The effects of the analogue on the systemic vascular bed were similar when this substance was injected into the superior vena cava and the left atrium. These data suggest that the analogue is not inactivated to any great extent.
extent by the canine lung. The site of vasoconstriction was investigated in experiments in which blood flow was controlled and pressure gradients across the left lower lobe were measured. Results of these experiments show that the analogue increased lobar arterial perfusion pressure in a dose-related manner over an extremely wide range of dose. Moreover, doses which establish concentrations of less than 2 ng/ml in lobar arterial blood increased lobar vascular resistance by more than 50%. The increase in lobar arterial pressure was associated with a dose-related increase in pressure in small intrapulmonary veins and an increase in the gradient of pressure from lobar artery to small vein but with little change in left atrial pressure. These data suggest that the increase in vascular resistance in the lobe is the result of vasoconstriction in intrapulmonary veins and upstream vessels presumed to be small arteries. The relative contribution of various segments of upstream vessels to the pressor response is unknown;

![Figure 4](image)

**FIGURE 4** Left panel: influence of indomethacin (2.5 mg/kg, iv) on the increase in lobar arterial pressure in response to injection of 0.3 and 1 μg of the endoperoxide analogue into the lobar artery. Right panel: influence of indomethacin (2.5 mg/kg, iv) on the increase in lobar arterial pressure and the decrease in aortic pressure in response to injection of arachidonic acid (3 mg) into the lobar artery.

In addition to increasing vascular resistance in the lung, the PGH₂ analogue increased airway pressure under conditions of positive pressure ventilation. These data are in accord with the studies of Wasserman in which the analogue was shown to increase airway resistance and decrease dynamic compliance in the dog. Although the analogue increased airway pressure, the effects on airway and vascular smooth muscle did not seem to be related, since similar pressor responses were obtained in ventilated and nonventilated lung lobes.

The endoperoxides PGH₂ and PGG₂ and their analogues have been reported to stimulate platelet aggregation. In view of the platelet-aggregating potential of these substances and subsequent release of vasoactive substances, the effects of the analogue were compared in dextran- and blood-perfused lung lobes. Results of these studies show that the analogue elicited similar pressor responses when the lung lobe was perfused with dextran solution or with blood. These data suggest that obstruction of the vascular bed by platelet aggregates or the release of vasoactive substances from elements in blood contribute little if anything to the pressor response, since these elements were not present in the nonsanguineous perfusate. It has been reported that the endoperoxide analogues stimulate synthesis of endogenous PGH₂ and PGG₂ in some tissues. If the response of the pulmonary vascular bed to the analogue were dependent on synthesis of endogenous intermediates, then the response should be attenuated by inhibitors of prostaglandin synthesis. Indomethacin, a synthesis inhibitor in doses reported to decrease the formation of endoperoxides and primary prostaglandins, did not attenuate the pressor response to the analogue in the lobe. These data indicate that synthesis of endogenous endoperoxides or prostaglandins contributes little if anything to the pressor response. The extent of inhibition of synthesis in these experiments was assessed by comparing responses to arachidonic acid, the precursor of the bisenoic prostaglandins, before and after indomethacin. The increase in lobar arterial pressure and the decrease

![Figure 5](image)

**FIGURE 5** Structures for arachidonic acid, the precursor for the bisenoic prostaglandins, the endoperoxides (PGH₂ and PGG₂), the endoperoxide analogue, and the bisenoic prostaglandins (PGE₂ and PGF₃α).
in aortic pressure in response to arachidonic acid were decreased by more than 95%. These data suggest that synthesis was decreased markedly in the lung by indomethacin. The explanation for the enhanced pressor response to the analogue after indomethacin is uncertain. Previous studies have shown, however, that the effects of \( \text{PGF}_2 \) and \( \text{PGE}_2 \) on the pulmonary vascular bed were enhanced by this synthesis inhibitor.24

Results of the present studies show that the endoperoxide analogue increased resistance to flow by constricting intrapulmonary veins and upstream vessels and, in terms of relative potency, was approximately 10 times more potent than \( \text{PGF}_2 \), 300 times more potent than \( \text{PGE}_2 \), and 3,000 times more potent than arachidonic acid. Studies with platelets and isolated smooth muscle indicate that the potencies of the \( \text{PGH}_2 \) analogue and \( \text{PGH}_2 \) are similar, whereas both substances are far more active than the bisenoic prostaglandins.14, 15, 21, 25 The present studies show that the endoperoxide analogue is a potent pressor substance in the canine pulmonary vascular bed. This observation, along with the finding that the major products of prostaglandin synthesis in the lung are metabolites of intermediates,2 suggests that endoperoxides may represent an active form of the prostaglandins in the lung. It is possible therefore that pathophysiological stimuli that release prostaglandins may release even larger quantities of these active intermediates which could have pronounced effects on the pulmonary vascular bed and airways.

References

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