Effects of Prostaglandin Cyclic Endoperoxides on the Lung Circulation of Unanesthetized Sheep

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ABSTRACT Although prostaglandins E₂ and F₂₀ have been suggested as mediators of the pulmonary hypertension seen after endotoxin infusion or during alveolar hypoxia, their precursors, the endoperoxides (prostaglandins G₂ and H₂) are much more potent vasoconstrictors in vitro. In this study we compared the effects of prostanadolin (PG)H₂, a stable 9-methylene ether analogue of PGH₂ (PGH₂-A), PGE₂, and PGF₂₀ on pulmonary hemodynamics in awake sheep. The animals were prepared to allow for measurement of (a) lung lymph flow; (b) plasma and lymph protein concentration; (c) systemic and pulmonary vascular pressures; and (d) cardiac output. We also determined the effect of prolonged PGH₂-A infusions on lung fluid balance and vascular permeability by indicator dilution methods, and by assessing the response of lung lymph. Both PGH₂ and PGH₂-A caused a dose-related increase in pulmonary artery pressure: 0.25 μg/kg × min tripled pulmonary vascular resistance without substantially affecting systemic pressures. Both were 100 times more potent than PGE₂ or PGF₂₀ in this preparation. PGH₂-A, as our analysis of lung lymph and indicator dilution measurements show, does not increase the permeability of exchanging vessels in the lung to fluid and protein. It does, however, augment lung fluid transport by increasing hydrostatic pressure in the pulmonary circulation. We conclude: (a) that PGH₂ is likely to be an important mediator of pulmonary vasoconstriction; (b) its effects are probably not a result of its metabolites PGE₂ or PGF₂₀.

This work was done while Dr. Bowers was supported by a National Research Service Award in interdisciplinary lung research from the National Heart and Lung Institute (HL 07123). This work was done during Dr. Brigham’s tenure as an Established Investigator of the American Heart Association. Dr. Oates is the Joe and Morris Werthan Professor of Investigative Medicine.

Received for publication 20 February 1978 and in revised form 18 September 1978.

INTRODUCTION

The agents mediating the pulmonary hypertension seen with alveolar hypoxia and gram-negative endotoxin infusion have not been identified. Because prostaglandins (PG)₁ E₂ and F₂₀ are released from the lungs during these reactions, they have been implicated as the mediators, but neither is an impressive vasoconstrictor in vitro (1, 2). In contrast, their precursors, the endoperoxides PG₁G₂ and PG₁H₂, are powerful vasoconstrictors, ≈100 times more potent in constricting isolated smooth muscle (3).

Because the endoperoxides are unstable and difficult to synthesize in the large amounts needed for in vivo studies, we first used a stable 9-methylene ether analogue of PGH₂ (PGH₂-A; [15S] hydroxy-11α, 9α-[epoxymethano] prosta-5Z, 13E-dienoic acid, [4]) to assess the effects of endoperoxides on pulmonary vascular pressures, permeability of the lung microcirculation, and lung fluid balance in awake sheep. We then prepared PGH₂ itself, in amounts large enough for brief steady-state infusions, and compared its effects to those of the analogue, PGE₂ and PGF₂₀.

PGH₂ and PGH₂-A were potent vasoconstricators, 100 times more potent than PGE₂ and PGF₂₀. PGH₂-A, as our studies of lung lymph and indicator dilution measurements showed, did not increase the permeability of exchanging vessels in the lung to fluid and protein, although it did augment fluid transport by increasing hydrostatic pressure in these vessels.

METHODS

Materials. We prepared PGH₂ by incubating arachidonic acid with sheep seminal vesicle microsomes. After isolating PGH₂ by silicic acid chromatography, we confirmed the structure by mass spectrometry (5, 6). We stored PGH₂ in an

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1 Abbreviations used in this paper: PG, prostaglandin; PGH₂-A, stable 9-methylene ether analogue of PGH₂.
acetone solution at −60°C and infused it with normal saline so that the amount of acetone delivered was <0.1 ml over 15 min. This amount of acetone infused alone had no effect on vascular pressures or lymph flow.

PGH₂ analogue, which was supplied by Upjohn Co., Kalamazoo, Mich. was synthesized as described by Bundy (4). We stored PGH₂-A in absolute ethanol solutions at 4°C, then diluted it with normal saline shortly before an experiment.

PGE₃ and PGF₆₉ were also supplied by Upjohn Co. We dissolved them in normal saline and adjusted pH to between 6 and 7 with bicarbonate buffer before infusion.

**Experimental preparation.** We prepared sheep by a series of thoracotomies as described (7–9). Through a left thoracotomy, we put catheters in the pulmonary artery and left atrium and a Doppler ultrasonic flow cuff (Park Electronics Laboratory, Beaverton, Oreg.) around the main pulmonary artery. In some sheep, we put a Foley balloon catheter in the left atrium. Several days later, through a right thoracotomy, we cannulated the efferent lymph vessel emerging from the caudal mediastinal lymph node, resected the tail of the node, and passed catheters into the thoracic aorta and vena cava through neck vessels. Because lymph flow from sheep prepared this way responds to changes in pulmonary venous pressure, but not to changes in systemic venous pressure, it comes primarily from the lungs (7).

After the last operation, we waited until the lung lymph flow, vascular pressures, and cardiac output were stable and the lymph was free of blood before doing experiments. In several sheep, lymph flow stopped spontaneously. We used these animals in experiments measuring only vascular pressures and cardiac output or for indicator dilution studies.

**Protein analysis.** We measured total protein concentration in lymph and blood plasma with an automated system (Auto-Analyzer, Technicon Instruments, Corp., Tarrytown, N. Y.) using a modified biuret method (10); duplicate samples differed <5%.

**Assessment of vascular permeability.** We used total protein concentrations to calculate protein osmotic pressure (Π) from the regression equation of Landis and Pappenheimer (11). Then we calculated the difference between plasma and lymph protein osmotic pressure (ΔΠ): ΔΠ = Π plasma − Π lymph. After normalizing lymph flow and ΔΠ to base line to compensate for variations among sheep, we compared graphically the relationship between ΔΠ and lymph flow for these experiments to two relationships established by previous studies: (a) increased pulmonary venous pressure and (b) histamine infusion (3). The first relationship is an example of increased lymph flow caused by high pressure in pulmonary exchanging vessels of normal permeability, whereas the second is an example of high lung lymph flow due to high vascular permeability.

**Indicator dilution studies.** To obtain in vivo measurements of extravascular lung water, cardiac output, and pulmonary capillary permeability, we injected a bolus of ⁴¹Cr-tagged erythrocytes, ¹³¹I-labeled albumin, and [¹⁴C]urea and [¹⁴C]water into the right atrium and sampled blood from the aorta as discussed in several earlier publications (12–16).

First we ran curves under base-line conditions, then infused PGH₂-A at 0.01, 0.10, or 0.25 μg/kg × min into the superior vena cava and repeated curves during the steady-state response period. Later, we counted samples of blood for gamma and beta activity, plotted normalized time-concentration curves, calculated flow as the inverse of the area under the intravascular tracer curves, and calculated extravascular water volume accumulation using a Krogh-cylindrical capillary model, the details of which have been published (16).

**Experimental protocols**

During all experiments the sheep were awake and standing in a cage. In each experiment we measured vascular pressures using calibrated miniature strain gauges (Micron Instruments, Inc., Los Angeles, Calif.) positioned at the level of the left atrium. With the pulmonary artery diameter (measured when we installed the flow cuff), and a signal proportional to the blood velocity from a Doppler flow meter (Parks Electronics model 902), we calibrated an electronic recorder (Hewlett-Packard 770 series Hewlett-Packard Co., Palo Alto, Calif.) and directly recorded blood flow in the pulmonary artery (17).

We also recorded pulmonary and systemic vascular pressures continuously during each experiment. We measured lymph flow at 15-min intervals by recording the volume drained into graduated tubes, and we measured total protein concentration in plasma from blood drawn each hour and lymph pooled at 30-min intervals.

**Increased pressure studies**

Once in each of nine sheep we measured responses to increases in left atrial pressure. After at least 1 h of base-line observation we inflated the left atrial balloon enough to increase left atrial pressure by 15–20 cm H₂O and kept pressure stable for 4 h. A steady-state lymph flow rate was reached ≈2 h after the balloon was inflated (18).

**Prostaglandin studies**

**Effects on pulmonary hemodynamics.** (a) PGH₂-A: We infused PGH₂-A at 0.01 μg/kg × min (10 experiments in 8 sheep), 0.1 μg/kg × min (13 experiments in 8 sheep), or 0.25 μg/kg × min (14 experiments in 10 sheep) through the superior vena cava catheter. We measured base-line and steady-state cardiac output and vascular pressures. (b) PGH₂: Three times in three sheep we infused PGH₂ at 0.1 or 0.25 μg/kg × min into the superior vena cava catheter and measured base-line and steady-state cardiac output and vascular pressures. In one sheep we infused 0.1 μg/kg × min into the left atrium. (c) Three times in three sheep we infused PGE₃ and PGF₆₉ at rates from 0.1 to 30 μg/kg × min and measured steady-state base line and experimental cardiac output and vascular pressure.

**Effects on lung lymph flow and protein concentration.** (a) We infused PGH₂-A at either 0.01 μg/kg × min (4 times in 4 sheep), 0.10 μg/kg × min (8 times in 8 sheep), or 0.25 μg/kg × min (10 times in 10 sheep) while measuring lung lymph flow, vascular pressures, and blood and lymph protein concentrations.

**Indicator dilution studies.** Nine times in seven sheep we infused 0.01, 0.10, and 0.25 μg/kg × min of PGH₂-A into the superior vena cava, measuring steady-state base line and experimental cardiac output, extravascular lung water volume and [¹⁴C]urea permeability surface area product by quadruple indicator dilution methods before injection of PGH₂-A and during the plateau of the pulmonary artery pressure response.

**PGH₂-A, Indomethacin Studies**

Twice in two sheep we infused PGH₂-A at 0.1 and 0.25 μg/kg × min, while giving 5 mg/kg × h of indomethacin intravenously beginning 1 h before PGH₂-A infusion.

**Statistics**

Where the summary data are given, we show the average ±SE of measurement. We compared the significance of data
by the Wilcoxon rank sum test or Student's t test, accepting
P < 0.05 as significant. Where appropriate, we tested data for
normal distribution using the Kolmogorov-Smirnov test at
80% confidence level (19).

RESULTS

Increased left atrial pressure. We evaluated the ef-
facts of elevated pulmonary venous pressure once in
each of nine sheep. Lymph flow and lymph to plasma
protein concentration ratios were like the results re-
ported (18, 6, 7): for an average increase in left atrial
pressure of 14 cm H2O, lymph flow doubled, and lymph
protein concentration always fell absolutely and rela-
tive to plasma.

Infusion of PGH2 and its analogue: hemodynamics.
PGH2 and its analogue PGH2-A had identical hemo-
dynamic effects. The data are summarized in Tables I
and II and illustrated in Fig. 1. Both substances caused
a dose-related increase in pulmonary vascular resist-
ance leading to a threefold increase in pulmonary artery
pressure at the 0.25 μg/kg × min dose. There was a
small, dose-related drop in cardiac output. Infusion of
PGH2 into the left atrium caused no change in pulmo-
nary or systemic pressures or cardiac output, but left
atrial PGH2-A infusions caused pulmonary hemo-
dynamic changes similar to intravenous infusion of the
same substance.

PGE2 and PGF2α caused little change in pulmonary
vascular resistance until the dose reached 10 μg/kg
× min, almost 100 times the effective PGH2 dose (Fig.
2). At higher doses, pulmonary arterial and left atrial
pressure rose as cardiac output fell. At the higher doses
the animals developed respiratory distress and often
collapsed.

TABLE I

<table>
<thead>
<tr>
<th>Infusion rate</th>
<th>Pulmonary artery</th>
<th>Left atrium</th>
<th>Cardiac output</th>
<th>Pulmonary vascular resistance</th>
<th>Pulmonary vascular resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cm H2O</td>
<td>mls</td>
<td>(cm H2O·s)/ml</td>
<td>experimental/base line</td>
<td></td>
</tr>
<tr>
<td>Base line (n = 3)</td>
<td>21±4*</td>
<td>1±3</td>
<td>88±8</td>
<td>0.25±0.07</td>
<td>1.00</td>
</tr>
<tr>
<td>0.10 μg/kg × min (n = 3)</td>
<td>42±6</td>
<td>5±1</td>
<td>96±9</td>
<td>0.50±0.10</td>
<td>2.00±1</td>
</tr>
<tr>
<td>0.25 μg/kg × min (n = 1)</td>
<td>53</td>
<td>5</td>
<td>80</td>
<td>0.73</td>
<td>2.90</td>
</tr>
</tbody>
</table>

* Mean±SEM.

TABLE II

<table>
<thead>
<tr>
<th>Infusion rate</th>
<th>Pulmonary artery</th>
<th>Mean pressure</th>
<th>Systolic diastolic pressure aorta</th>
<th>Cardiac output</th>
<th>Pulmonary vascular resistance</th>
<th>Pulmonary vascular resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cm H2O</td>
<td>Torr</td>
<td>mls</td>
<td>(cm H2O·s)/ml</td>
<td>experimental/base line</td>
<td></td>
</tr>
<tr>
<td>Base line (n = 17)</td>
<td>21±1</td>
<td>1±1</td>
<td>107±2</td>
<td>99±5</td>
<td>0.22±0.02</td>
<td>1.0</td>
</tr>
<tr>
<td>0.01 μg/kg × min (n = 10)</td>
<td>25±1*</td>
<td>2±1</td>
<td>109±3</td>
<td>96±7*</td>
<td>0.28±0.02*</td>
<td>1.2±105*</td>
</tr>
<tr>
<td>0.1 μg/kg × min (n = 13)</td>
<td>37±4*</td>
<td>2±1</td>
<td>108±2</td>
<td>90±6*</td>
<td>0.42±0.04*</td>
<td>2.0±0.20*</td>
</tr>
<tr>
<td>0.25 μg/kg × min (n = 14)</td>
<td>52±2*</td>
<td>1±1</td>
<td>112±2</td>
<td>86±5*</td>
<td>0.62±0.05*</td>
<td>2.9±0.14*</td>
</tr>
</tbody>
</table>

Average weight of the sheep, 41.5 kg (mean±SEM).
* Significantly different from base line (P < 0.05).
**PGH₂-A: effects on lung lymph flow and protein concentrations.** As shown in Fig. 3, infusion of PGH₂-A caused a dose-related increase in lung lymph flow, corresponding to increases in pulmonary artery pressure. Although the lymph flow increased substantially at higher doses, the lymph protein concentration fell. These data are summarized in Table III. The fall in lymph protein concentration as lymph flow increases is a characteristic effect of high pressure (8). In fact, the effect of PGH₂-A and high left atrial pressure on ΔP are indistinguishable (Fig. 4). The ΔP increases linearly with lymph flow after both interventions as a result of the fall in lymph protein concentration relative to plasma protein concentration (Table III). The two regression lines (of ΔP vs. lymph flow) in Fig. 4, one derived from high left atrial pressure experiments, the other from endoperoxide studies, are not significantly different (P > 0.3), and are in clear contrast to the line derived from histamine studies where permeability was increased.

**PGH₂-A infusions after treatment with indomethacin.** Pretreatment with 5 mg/kg × h of indomethacin had no effect on the response of pulmonary pressures or lymph flow rate to PGH₂-A infusion.

**Indicator dilution studies.** There was no significant change from base line in the steady-state extravascular lung water or [¹⁴C]urea permeability surface area product during PGH₂-A infusions. The data are summarized in Table IV.

**DISCUSSION**

This study shows that PGH₂ and a 9-methylene cyclic ether analogue are potent and specific pulmonary vasoconstrictors in doses which have little effect on the systemic circulation. A 0.25-µg/kg × min i.v. dose tripled pulmonary vascular resistance, whereas as little as 0.01 µg/kg × min had an effect. Although studies in vitro (3, 20) suggest this potency of the endoperoxide, its specificity for the pulmonary circulation in vivo is unexpected. Few, if any, known endogenous sub-

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**FIGURE 1** Hemodynamic effects of PGH₂-A and PGH₂ in the pulmonary circulation. Ppa, mean pulmonary artery pressure; Pla, mean left atrial pressure; PAo, systolic pressure in the aorta; R pulm, pulmonary vascular resistance.

**FIGURE 2** Comparison of the effects of PGH₂, PGH₂-A, PGE₃, and PGF₂α on pulmonary vascular resistance normalized to base line.

**FIGURE 3** Typical response of pulmonary vascular pressures, lymph flow and lymph:plasma protein concentration ratio to increasing intravenous infusion rates of PGH₂-A. Data are averaged over 15-min intervals.
Permeability
acteristic
failure
The
null
population
lymph)
study
shows
we
could
an
endothelium
induced
pulmonary
hypertension?
In
calfs,
Anderson
et
al. (21)
blocked
this
effect
with
indomethacin
and
implicated
prostaglandins
as mediators.
Anderson
thought
PGF_{20}
was
probably
the
agent,
because
the
concentration
of
this
prostaglan
din
rose
in
pulmonary
venous
blood
after
endothelin
infusion.
Our
study
shows
that
the
precursor
endo
teroxide
PGH_{2}
is
a
100
times
more
potent
pulmonary
vasoconstrictor
than
PGF_{20}.
Since
Anderson
et
al.
(21)
found
that
the
lung
releases
considerable
amounts
of
PGF_{20}
in
response
to
endothelin
infusion,
PGH_{2}
(an
obligatory
intermediate)
must
have
been
formed
in
sub
tantial
amounts
too.
If
so,
PGH_{2}
is
more
likely
to
have
caused
pulmonary
hypertension
than
PGF_{20}.

Do
PGH_{2}
and
PGH_{2}-A
act
by
aggregating
platelets?
Both
will
aggregate
platelets
in
vitro
(3, 5),
but
their
effects
on
pulmonary
vascular
resistance
probably
are
not
a
result
of
intravascular
platelet
aggregation
because:
(a)
the
high
pulmonary
artery
pressure
produced
by
infusion
of
PGH_{2}
and
PGH_{2}-A
returned
to
normal
within
5
min
after
the
infusion
was
stopped;
and
(b)
infusion
of
PGH_{2}
into
the
left
atrium
had
no
apparent
physiological
effects.
If
platelet
aggregation
and
vascu
lar
plugging
were
involved
the
effect
should
persist
for
longer
than
5
min.

From
our
data,
we
cannot
determine
whether
the
effects
of
PGH_{2}
are
a
direct
result
of
its
action
on
the
smooth
muscle
of
the
resistance
vessels
of
the
lung,
or
whether
conversion
to
its
metabolite
thromboxane
A_{2}
is
necessary
first.
Thromboxane
A_{2}
is
more
potent
than
PGH_{2}
in
contracting
large
arterial
smooth
muscle
and
in
inducing
aggregation
of
platelets
in
vitro
(22, 23).
Because
it
is
formed
from
PGH_{2}
in
the
lung
(24),
it
is
pos
sible
that
the
hemodynamic
effects
of
PGH_{2}
are
mediated
through
this
more
active
metabolite.
Our
finding
that
PGH_{2}-A,
the
anologue
(which
is
not
metabolized
to
thromboxane
A_{2}),
had
effects
similar
to
those
of
biosynthesized
PGH_{2}
suggests
that
PGH_{2}
itself
may
cause
vasoconstriction.
However,
if
the
anologue
mimics
thromboxane
A_{2}
physiologically,
our
conclusion
that
the
identical
vasoconstriction
PGH_{2}
and
PGH_{2}-A
cause
is
an
innate
effect
of
both
may
be
wrong.
Instead,
PGH_{4}'s
conversion
to,
and
PGH_{2}-A's
imitation
of,
thromboxane
A_{2}
could
explain
their
com
mon
effect.

The
response
to
infusion
of
exogenous
PGH_{2}
into
the
pulmonary
circulation
does
not
prove
that
PGH_{2},
when
synthesized
in
the
lung,
had
an
identical
effect.
This
could
occur
if
PGH_{2}
is
synthesized
in
amounts
comparable
to
those
infused
and
if
PGH_{2}
has
access
to
the
smooth
muscle
of
the
resistance
vessels.
The
exquisite
sensitivity
of
the
pulmonary
circulation
to
PGH_{2}
sug
gests
that
amounts
synthesized
in
the
lung
could
be
physiologically
significant.
Lung
vessels
would
also

![Figure 4](image-url)

**Figure 4**
Normalized
net
osmotic
pressure
difference
(ΔΠ
= Π
II
at
plasma-II
lymph)
as
a
function
of
normalized
lymph
flow.
The
null
hypothesis
that
lines
(1)
and
(2)
are
derived
from
the
same
population
cannot
be
rejected
(Ρ
> 0.30).
Line
(3)
derived
from
studies
of
histamine
infusion
shows
the
characteristic
failure
of
ΔΠ
to
increase
with
lymph
flow
when
vascular
permeability
is
high.

**Table III**
Effects
of
the
Endoperoxide
Analogue
on
Steady-State
Lung
Lymph
Flow
and
Protein
Concentration

<table>
<thead>
<tr>
<th>Infusion rate</th>
<th>Lymph flow</th>
<th>Plasma</th>
<th>Lymph</th>
<th>Protein concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>experimental/base line</td>
<td>g/dl</td>
<td></td>
<td>lymph/plasma</td>
</tr>
<tr>
<td>Base line (n = 10)</td>
<td>1.00</td>
<td>6.4±0.2</td>
<td>4.3±0.2</td>
<td>0.67±0.01</td>
</tr>
<tr>
<td>0.01 μg/kg × min (n = 4)</td>
<td>1.13±0.1*†</td>
<td>6.4±0.5</td>
<td>4.1±5*</td>
<td>0.64±0.03</td>
</tr>
<tr>
<td>0.10 μg/kg × min (n = 8)</td>
<td>1.65±0.1*</td>
<td>6.7±0.3</td>
<td>4.0±0.2*</td>
<td>0.59±0.02*</td>
</tr>
<tr>
<td>0.25 μg/kg × min (n = 10)</td>
<td>2.50±0.3*</td>
<td>6.8±0.2</td>
<td>3.4±0.2*</td>
<td>0.51±0.03*</td>
</tr>
</tbody>
</table>

* Significantly
different
from
base
line
(Ρ < 0.05).
† Mean±SEM.
constrict in response to PGH₂ released into venous blood by another organ. This effect might be particularly important if the ability of the lung to metabolize PGH₂ were impaired by disease.

The results of this study agree with those of Kadowitz et al. (25) who found PGH₂-A to be a potent pulmonary vasoconstrictor in dogs. But, our findings on the effects of PGH₂ itself differ from those of Kadowitz et al. He found PGH₂ to be weaker than PGH₂-A, while we find it to be equivalent in strength. This difference may have occurred because we gave PGH₂ by continuous infusion and Kadowitz et al. used a 2-μg bolus. It is interesting that Kadowitz et al. found that PGH₂ contracted isolated pulmonary veins more powerfully than PGH₂-A.

Vascular permeability. The equivalent effects of high pulmonary venous pressures and PGH₂-A infusion on lung lymph protein concentration and osmotic pressures (Fig. 4) indicate that PGH₂-A causes pulmonary hypertension without increasing vascular permeability. Others have found that prostaglandins alter permeability in some vascular beds (26, 27) but we found no evidence that lung vessel integrity changed. This effect is like that of serotonin but unlike the response to histamine in this preparation: histamine causes increased flow of lymph with a relatively high protein concentration (8), whereas serotonin causes an increased flow of lymph of low protein content (9). With histamine, the osmotic pressure difference at high lymph flow falls, but with serotonin, mechanically increased pulmonary venous pressure, and, as this study shows, PGH₂-A infusion, the oncotic pressure difference between lymph and plasma increases as lymph flow increases (Fig. 4). Thus, the increase in transvascular fluid filtration caused by the prostaglandins is apparently due solely to their effects on pressure in exchanging vessels.

Inactivation of PGH₂ in vivo. PGH₂ was apparently rapidly inactivated in the sheep circulation because injections into the left atrium did not change systemic or pulmonary pressures. This indicates that PGH₂ was inactivated during one passage from the left atrium to the pulmonary circulation.

Site of action of PGH₂-A. Although we cannot state with certainty the site of action of PGH₂-A, at least some of the vasoconstriction must have been downstream from exchanging vessels. If the vasoconstriction had all been upstream to the exchanging site, lymph flow should not have increased. The latter phenomenon, pulmonary hypertension without increased lymph flow, is characteristic of the response of alveolar hypoxia in this preparation, as Bland et al. (28) showed. This difference between the effects of PGH₂-A infusions and alveolar hypoxia suggests that prostaglandin endoperoxides do not mediate hypoxic pulmonary vasoconstriction.

CONCLUSIONS

(a) PGH₂ and PGH₂-A are potent vasoconstrictors in the pulmonary circulation in doses that have little effect on the systemic circulation. (b) PGH₂-A does not increase lung microvascular permeability, but increases filtration from lung exchanging vessels by increasing vascular pressures. (c) Because it is much more potent, PGH₂ (or an active metabolite) is more likely to be an important mediator of pulmonary vasoconstriction than either PGE₂ or PGF₂α. (d) PGH₂ is rapidly inactivated in the sheep circulation. (e) PGH₂-A causes some vasoconstriction downstream to exchanging vessels in the lung.

ACKNOWLEDGMENTS

We acknowledge the valuable technical assistance of Patty J. Owen, Lou H. Scott, and Ann Payne in these studies, and thank Dewain Patterson for typing the manuscript.

This work was supported by grants HL 19153 (Specialized Center of Research in Pulmonary Vascular Diseases) and GM 15431.
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