

# Influence of Prostaglandin Synthesis Inhibitors on Pulmonary Vasodilatory Effects of Hydralazine in Dogs with Hypoxic Pulmonary Vasoconstriction

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**ABSTRACT** To determine whether hydralazine, a systemic vasodilator, exerted a similar effect on the pulmonary circulation, we studied the circulatory changes in dogs during three interventions: (a) the control state during room air ventilation; (b) during continuous hypoxic ventilation with 10% oxygen, and maintaining continuous hypoxic ventilation; and (c) after 1 mg/kg hydralazine intravenously.

Ventilation with 10% oxygen caused the mean pulmonary artery pressure to increase from  $10 \pm 1.2$  to  $23 \pm 2.4$  mm Hg ( $P < 0.01$ ) and the pulmonary arteriolar resistance to increase from  $1.51 \pm 0.19$  to  $5.87 \pm 1.10$  U ( $P < 0.01$ ). Hydralazine significantly lowered the pulmonary artery pressure ( $23.0 \pm 2.4$  to  $14.3 \pm 1.5$  mm Hg,  $P < 0.01$ ) and the pulmonary arteriolar resistance ( $5.87 \pm 1.10$  to  $2.87 \pm 0.52$  U,  $P < 0.01$ ). Femoral artery pressure, pulmonary artery wedge pressure, heart rate, and cardiac output remained unchanged throughout.

To ascertain the contribution of the prostaglandin system to the pulmonary vasodilator effects of hydralazine, we pretreated a group of dogs with the prostaglandin synthetase inhibitor, indomethacin, 5 mg/kg s.c., twice daily for 2 d. These animals then underwent identical studies.

The pretreated dogs had comparable base-line and hypoxia hemodynamic data. However, hydralazine had no effect on pulmonary artery pressure ( $23.3 \pm 1.6$  vs.  $21.7 \pm 2.3$  mm Hg, NS) or pulmonary arteriolar resistance ( $8.03 \pm 1.09$  vs.  $7.14 \pm 1.42$ , NS) during continuous hypoxic ventilation in the indomethacin-pretreated group. Pretreatment with indomethacin did not, however, block the pulmonary vasodilator effects of intra-

venous prostacyclin ( $\text{PGI}_2$ ). Pretreatment with meclofenamate, a cyclo-oxygenase inhibitor structurally unrelated to indomethacin, also blocked the effects of hydralazine during hypoxic ventilation. These data suggest that hydralazine exerts a pulmonary vasodilatory effect during hypoxia-induced pulmonary vasoconstriction, and that this vasodilator effect may be mediated by prostaglandins.

## INTRODUCTION

Prostaglandins are metabolites of arachidonic acid which exert a variety of effects on platelet function and vascular smooth muscle in various animal species (1). In the lung, prostaglandins  $\text{F}_{2\alpha}$  (2, 3) and  $\text{E}_2$  (4) have been demonstrated to cause vasoconstriction, but prostaglandins  $\text{E}_1$  (5, 6) and  $\text{I}_2$  (prostacyclin) (7–9) promote vasodilatation. However, the contribution of these prostaglandins to the modulation of the pulmonary circulation in normal and disease states has not been clearly defined (10–17).

The prostaglandin system has also been linked to the pharmacologic actions of several drugs that have effects on the cardiovascular system, including nitroglycerin (18), propranolol (19), and furosemide (20). Hydralazine is a vasodilator whose antihypertensive effect may also be mediated by prostaglandins (21–23). In addition to its systemic effects, hydralazine has recently been demonstrated to lower pulmonary arteriolar resistance in patients with pulmonary hypertension secondary to hypoxic lung disease (24), and in patients with idiopathic pulmonary hypertension (25). If hydralazine has a pulmonary vasodilatory effect, it is possible that this effect is mediated by prostaglandins. This study evaluates the hemodynamic effects of hydralazine in the setting of acute, hypoxic pulmonary hypertension and examines the influence of the administration of inhibitors of prostaglandin synthesis on the hemodynamic effects of hydralazine.

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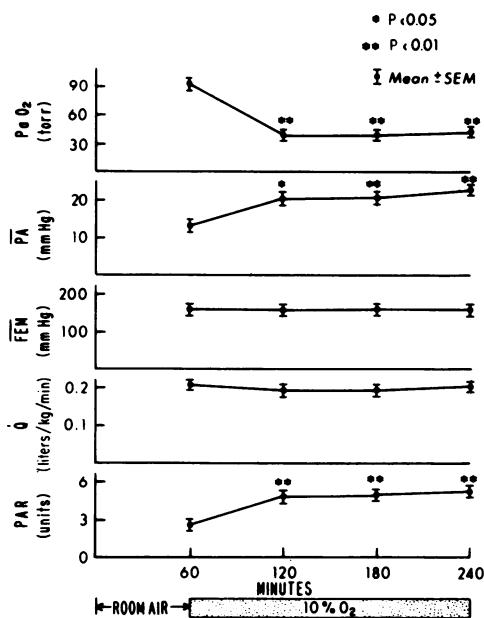


FIGURE 1 The effects of continuous hypoxic ventilation on the hemodynamics of five untreated intact dogs;  $P_{aO_2}$ , arterial partial pressure of oxygen; PA, mean pulmonary artery pressure; FEM, mean femoral artery pressure; Q, cardiac output; PAR, pulmonary arteriolar resistance.  $P$  values are with reference to control measurements. Values during hypoxia were not different at 120, 180, and 240 min. ( $P > 0.05$ ).

## METHODS

Mongrel dogs of either sex, weighing between 12 and 18 kg, were anesthetized with pentobarbital sodium (30 mg/kg i.v.) and intubated with a cuffed endotracheal tube. The animals were ventilated with room air, using an animal respirator (Harvard Apparatus Co., S. Natick, Mass.) to regulate the minute ventilation so that the arterial  $PCO_2$  and pH were maintained within the normal range. A polyethylene catheter was inserted into a femoral artery, and a second catheter was inserted into a peripheral limb vein for the administration of drugs. A balloon-tipped flotation catheter was inserted into a femoral vein and advanced under fluoroscopic guidance to a branch of either main pulmonary artery. Pulmonary artery, pulmonary artery wedge, and femoral artery pressures were measured using Statham PR231D and PR23AC pressure transducers (Statham Instruments, Inc., Oxnard, Calif.), respectively, and the pressure tracings were continuously displayed on a physiologic recorder (Electronics for Medicine, Inc., Pleasantville, N. Y.). Heart rate was measured from a lead II electrocardiogram. Airway pressure was monitored by a manometer connected to the endotracheal tube. Timed collections of minute ventilation were measured in a Tissot gasometer and their oxygen content was analyzed using a Beckman gas analyzer (Beckman Instruments, Inc., Fullerton, Calif.). From this data, total body oxygen consumption was determined, corrected to STPD. Arterial and mixed venous blood samples were collected anaerobically in heparinized syringes, and  $PO_2$ ,  $PCO_2$ , pH, total hemoglobin, and oxyhemoglobin contents were measured using an IL 213 blood gas analyzer and IL 182 Co-oximeter (Instrumentation Laboratory, Inc., Lexington, Mass.). Cardiac output was then calculated from this data using the Fick equation. Pulmonary arteriolar resistance, defined as

the mean pulmonary artery pressure minus the pulmonary artery wedge pressure (millimeters Hg) divided by the cardiac output (liters per minute), is reported in units.

After 30 min of room air ventilation, hemodynamic parameters were measured (control group), and continuous ventilation with a gas mixture consisting of 10% oxygen and 90% nitrogen was begun. Pentobarbital sodium (3–5 mg/kg i.v.) was given periodically as needed to maintain the level of anesthesia. After 1 h of continuous hypoxic ventilation, we repeated the hemodynamic studies (hypoxia group), and then injected hydralazine 0.5, 1.0, or 1.5 mg/kg through the peripheral venous line. We monitored continuously the systemic and pulmonary arterial pressures and repeated the measurements 60 min after the injection of hydralazine (hypoxia plus hydralazine group).

A separate group of dogs received subcutaneous injections of either indomethacin or meclofenamate, 5 mg/kg, twice daily for 2 d. The final dose of either cyclo-oxygenase inhibitor was given 2 h before study. Indomethacin and meclofenamate were dissolved in a 2 M excess of sodium carbonate, and neutral phosphate buffer was added to bring each dose to a total volume of 1 ml. Previous experience has documented that prostaglandin synthesis is effectively inhibited by this dosage in several species (18, 26–30). The pretreated animals underwent identical study, receiving hydralazine 1 mg/kg i.v. after 1 h of continuous hypoxic ventilation.

To determine the influence of indomethacin on the effects of a known vasodilator, three dogs were pretreated with indomethacin 5 mg/kg s.c. twice daily for 2 d, and after 1 h of continuous hypoxic ventilation, received an infusion of prostacyclin 5  $\mu$ g/kg per min into a peripheral limb vein for 2 min. Prostacyclin was stored in absolute ethanol at  $-70^\circ\text{C}$ . Immediately before use, the ethanol was evaporated under a stream of nitrogen, and prostacyclin was dissolved in sterile physiologic saline. Pulmonary and systemic arterial pressures were recorded at 2, 7, 10, 15, and 20 min.

The data are presented as the mean  $\pm$  SEM. Statistical analysis was performed by one-way analysis of variance followed by a multiple range test when the  $F$  value indicated significant differences among group means, and by the  $t$  test for paired data to compare the data from the two groups (31).

## RESULTS

Fig. 1 shows the effects of continuous hypoxic ventilation on the hemodynamics of a group of five untreated dogs. The increases in mean pulmonary arterial pressure and pulmonary arteriolar resistance during continuous hypoxic ventilation remained stable for a 3-h period. Mean aortic pressure, cardiac output, and pulmonary artery wedge pressure were unchanged compared with base-line room air levels.

The data during room air ventilation reflect normal base-line hemodynamics in the group receiving no pretreatment and the group pretreated with indomethacin (Tables I and II). The pulmonary artery pressures were identical ( $10.0 \pm 1.2$  vs.  $10.6 \pm 1.2$  mm Hg, NS), as were the pulmonary artery wedge pressures and the mean heart rate. The pulmonary arteriolar resistance was slightly higher in the indomethacin-pretreated group ( $1.51 \pm 0.19$  vs.  $2.50 \pm 0.48$  U), and the mean femoral artery pressure was higher in the indomethacin-pretreated group ( $145.7 \pm 6.5$  vs.  $153.0 \pm 9.7$  mm Hg), but these differences were not statistically significant.

TABLE I  
*Hemodynamic Data in the Hydralazine-treated Group*

	Control (C)	Hypoxia (H)	Hypoxia plus hydralazine (H + h)	Statistical comparisons
$\overline{\text{FEM}}$ , mm Hg	145.7±6.5	158.9±5.8	135.4±12.1	C—H C—H + h H—H + h
Ppa, mm Hg	10.0±1.2	23.0±2.4	14.3±1.5	C—H* C—H + h H—H + h*
Ppw, mm Hg	4.9±0.8	5.3±0.8	5.1±0.7	C—H C—H + h H—H + h
$\dot{Q}$ , liters/kg/min	0.211±0.022	0.197±0.016	0.200±0.013	C—H C—H + h H—H + h
AVO <sub>2</sub> , vol %	3.239±0.360	3.453±0.309	3.163±0.363	C—H C—H + h H—H + h
HR, beats/min	140.0±7.6	158.6±5.9	151.4±7.4	C—H C—H + h H—H + h
TSR, Units	43.7±3.2	50.6±2.4	41.9±3.7	C—H C—H + h H—H + h
PAR, Units	1.51±0.19	5.87±1.10	2.87±0.52	C—H* C—H + h† H—H + h*

Values are mean±SEM. *n* = 7.  $\overline{\text{FEM}}$ , mean femoral artery pressure; Ppa, mean pulmonary artery pressure; Ppw, pulmonary arterial wedge pressure;  $\dot{Q}$ , cardiac output; AVO<sub>2</sub>, arteriovenous oxygen difference; HR, heart rate; TSR, total systemic vascular resistance; PAR, pulmonary arteriolar resistance.

\* *P* < 0.01.

† *P* < 0.05.

The total systemic resistance was significantly higher in the indomethacin-pretreated group (43.7±3.2 vs. 58.6±6.9 U, *P* < 0.05).

Ventilation with 10% oxygen induced significant and equivalent elevations of pulmonary arterial pressure in both groups (Table III). Systemic arterial pressure, pulmonary arterial wedge pressure, and heart rate were not changed. Cardiac output decreased slightly in both groups. The levels of pulmonary artery pressure remained stable during the period of hypoxic ventilation, and the arterial pH and PCO<sub>2</sub> were equivalent in both groups. The arterial PO<sub>2</sub> ranged between 35 and 45 torr in all the animals during this phase of the study.

The intravenous injection of hydralazine 1 mg/kg resulted in a significant fall in the pulmonary artery pressure in the nonpretreated group. This response was apparent within 20 min after the injection, and persisted

for 1.5–2 h. The pulmonary arteriolar resistance was lowered as well, but it remained slightly higher than the control value. Cardiac output, pulmonary artery wedge pressure, heart rate, and arteriovenous oxygen difference were not affected by hydralazine. Mean systemic pressure was lowered by hydralazine, but this was not statistically significant.

The dose-response relationships with hydralazine are shown in Fig. 2. The dogs receiving hydralazine 0.5 mg/kg evinced minimal pulmonary or systemic vasodilatation. At doses of 1.0 and 1.5 mg/kg more pronounced pulmonary vasodilatation was seen, accompanied by modest decreases in systemic arterial pressure.

In contrast to the responses observed in the animals receiving no pretreatment, the dogs that had been pretreated with indomethacin evinced no change in either pulmonary artery pressure or pulmonary arteriolar re-

TABLE II  
*Hemodynamic Data in the Indomethacin Plus Hydralazine Group*

	Control (C)	Hypoxia (H)	Hypoxia plus hydralazine (H + h)	Statistical comparisons
$\overline{\text{FEM}}$ , mm Hg	153.0±9.7	156.3±9.2	138.9±11.9	C—H C—H + h H—H + h
Ppa, mm Hg	10.6±1.2	23.3±1.6	21.7±2.3	C—H* C—H + h* H—H + h
Ppw, mm Hg	4.6±0.7	5.0±0.4	5.3±0.7	C—H C—H + h H—H + h
$\dot{Q}$ , liters/kg/min	0.227±0.032	0.199±0.024	0.204±0.024	C—H C—H + h H—H + h
AVO <sub>2</sub> , vol %	3.107±0.239	3.433±0.291	3.123±0.170	C—H C—H + h H—H + h
HR, beats/min	140.0±7.6	162.9±8.1	151.4±5.9	C—H C—H + h H—H + h
TSR, Units	58.6±6.9	68.0±7.0	59.6±8.4	C—H C—H + h H—H + h
PAR, Units	2.50±0.48	8.03±1.09	7.14±1.42	C—H* C—H + h† H—H + h

Values are mean±SEM.  $n = 7$ .  $\overline{\text{FEM}}$ , mean femoral artery pressure; Ppa, mean pulmonary artery pressure; Ppw, pulmonary arterial wedge pressure;  $\dot{Q}$ , cardiac output; AVO<sub>2</sub>, arteriovenous oxygen difference; HR, heart rate; TSR, total systemic vascular resistance; PAR, pulmonary arteriolar resistance.

\*  $P < 0.01$ .

†  $P < 0.05$ .

sistance after hydralazine (Fig. 3). Systemic arterial pressure fell slightly in this group, but there were no significant changes in any of the hemodynamic variables after hydralazine in this group when compared with hypoxia alone.

To exclude the possibility that the blockade of the pulmonary effects of hydralazine may be due to an action of indomethacin which is unrelated to the inhibition of prostaglandin synthesis, meclofenamate, an inhibitor of cyclo-oxygenase which is structurally unre-

TABLE III  
*Blood Gas Data*

	Control		Hypoxia		Hypoxia + hydralazine	
	(-) Indo	(+) Indo	(-) Indo	(+) Indo	(-) Indo	(+) Indo
PO <sub>2</sub> , torr	95±1.9	94±4.9	39±1.5	35±1.9	39±1.5	37±2.6
PCO <sub>2</sub> , torr	33±1.1	32±2.3	30±0.8	30±1.5	30±0.8	28±2.3
pH	7.43±0.015	7.44±0.011	7.44±0.008	7.44±0.011	7.43±0.011	7.44±0.015
Hemoglobin, g/100 ml	13.5±0.34	13.7±0.64	14.9±0.30	13.8±0.94	14.9±0.42	14.4±0.76

Values are mean±SEM. The differences between the (-) Indo (no indomethacin) group and the (+) Indo (indomethacin) group at each intervention were not significant.

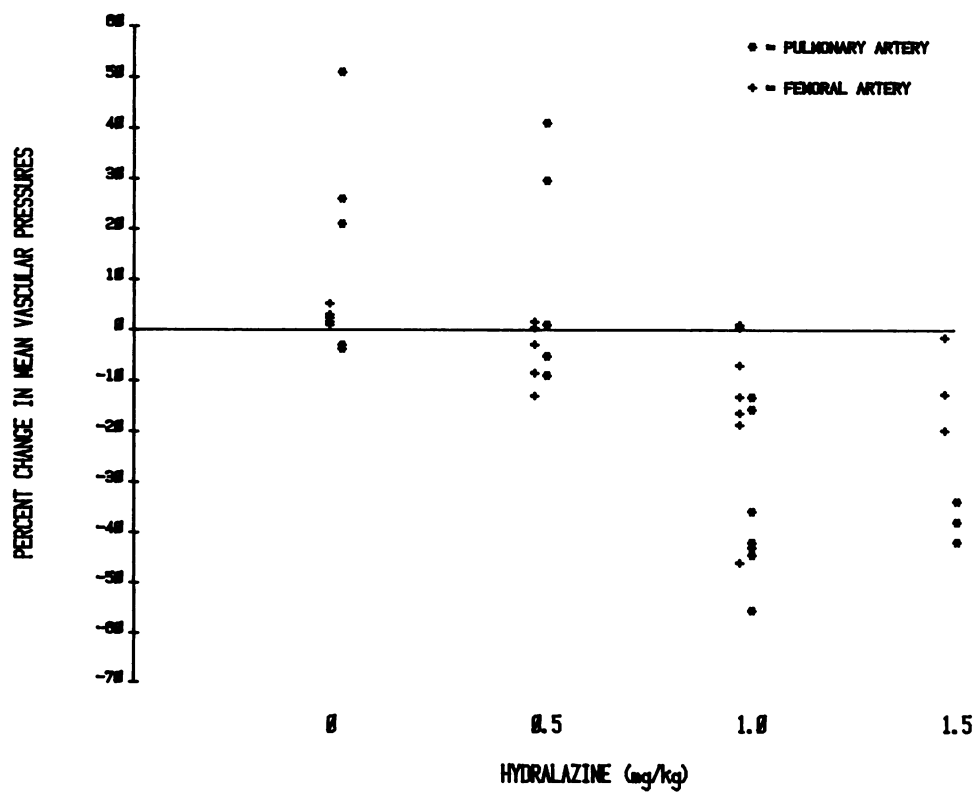
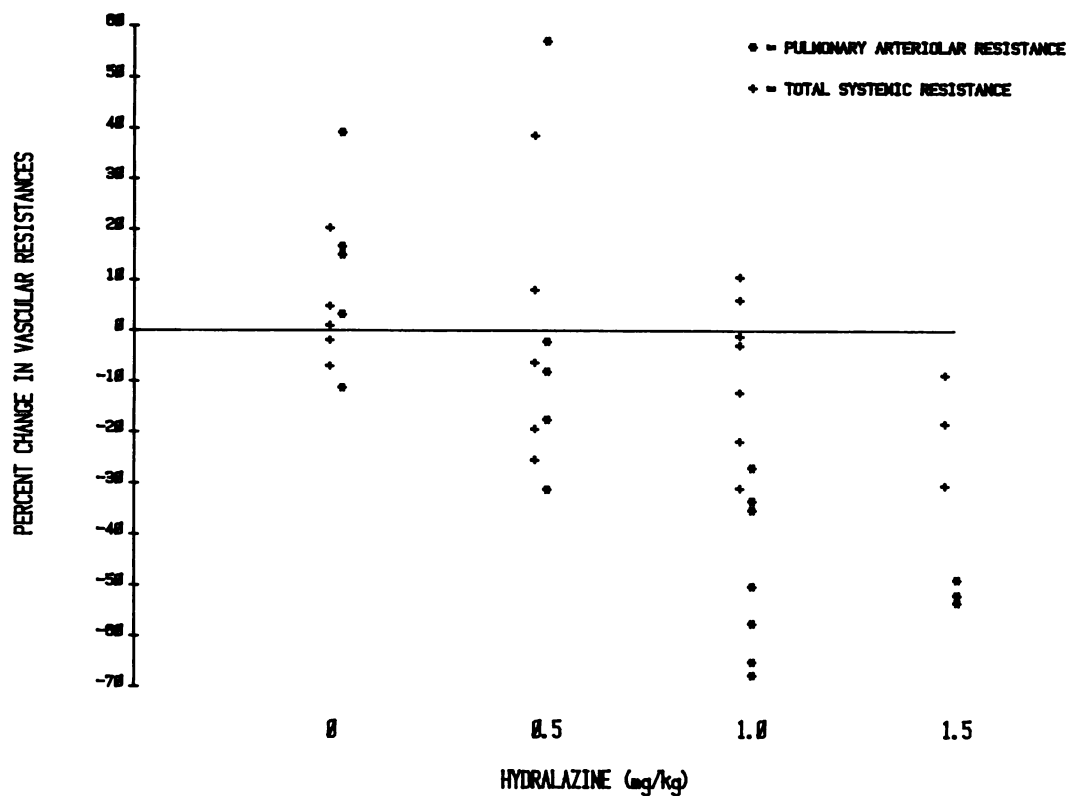


FIGURE 2 Dose-response relationships to the intravenous administration of hydralazine during continuous hypoxic ventilation.

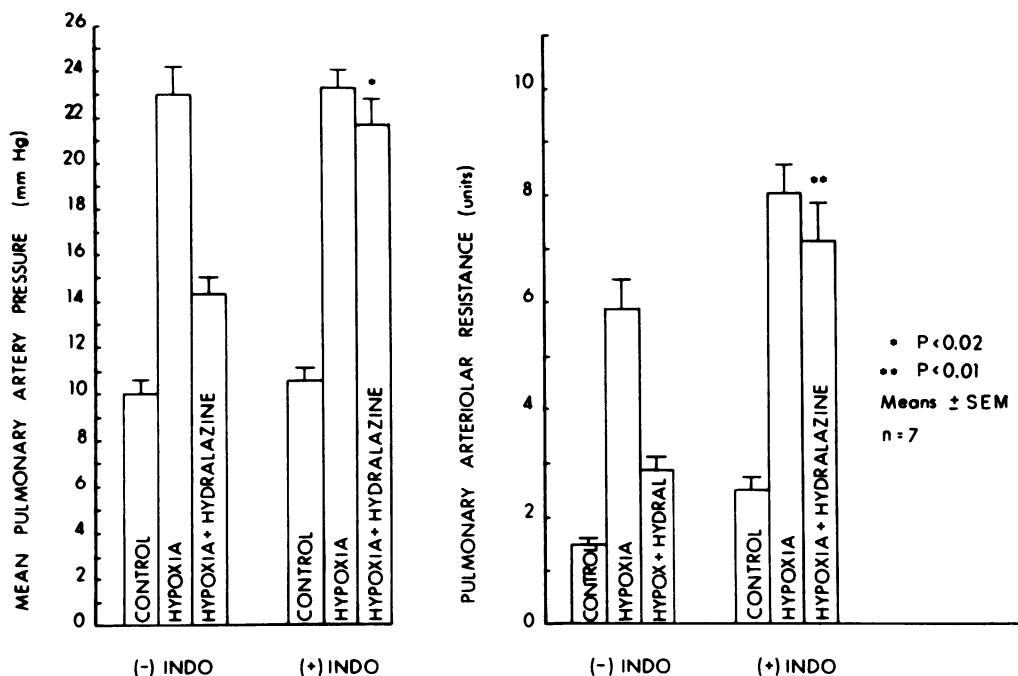


FIGURE 3 Comparison of mean pulmonary artery pressure and pulmonary arteriolar resistance at three stages of study: (a) control, room air ventilation; (b) hypoxia, 10% oxygen ventilation; (c) hypoxia plus hydralazine, 10% oxygen ventilation plus hydralazine 1 mg/kg i.v. (-) Indo group received no pretreatment; (+) indo group received indomethacin, 5 mg/kg s.c. twice daily for 2 d. *P* values refer to comparisons of (-) indo and (+) indo groups.

lated to indomethacin, was given to a group of dogs ( $n = 3$ ), and the identical protocol for the indomethacin experiment was followed. Control pulmonary artery pressure in this group was  $6.0 \pm 3.4$  mm Hg, and control pulmonary arteriolar resistance was  $1.3 \pm 0.7$  U. 1 h after

1 mg/kg of hydralazine had been given to this group, mean pulmonary artery pressure was unchanged compared with hypoxia alone ( $15.3 \pm 2.7$  vs.  $16.7 \pm 2.3$  mm Hg). Similarly, pulmonary arteriolar resistance was not affected by hydralazine in the dogs receiving meclofenamate pretreatment ( $5.2 \pm 0.9$  vs.  $4.9 \pm 0.9$  U).

To determine whether the pulmonary vasculature of dogs pretreated with cyclo-oxygenase inhibitors still maintained the ability to dilate upon exposure to a drug which was not dependent on prostaglandin synthesis for its effect, we studied the effects of the intravenous infusion of prostacyclin ( $\text{PGI}_2$ ),  $5 \mu\text{g/kg}$  per min for 2 min, on the hemodynamics of three dogs pretreated with indomethacin (Fig. 4). Hypoxic ventilation raised mean pulmonary arterial pressure to comparable levels, but prostacyclin caused a prompt reduction in mean pulmonary arterial pressure, and this effect persisted for <20 min after the infusion was discontinued.

## DISCUSSION

There has recently been a rekindled interest in the clinical usefulness of vasodilators to treat patients with pulmonary hypertension. In addition to hydralazine, pharmacologic agents of diverse chemical structure including tolazoline (32), isoproterenol (33), diazoxide (34), and phentolamine (35) have been reported to be

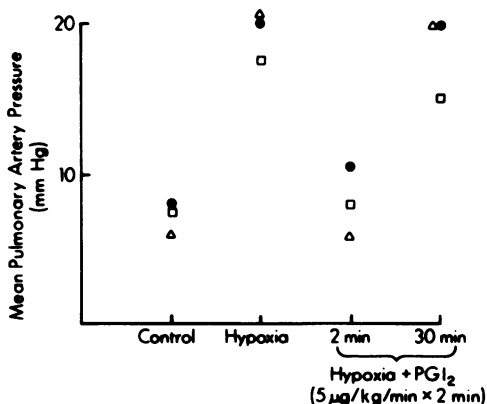


FIGURE 4 Prostacyclin infusion during continuous hypoxic ventilation in three dogs pretreated with indomethacin 5 mg/kg s.c. twice daily for 2 d. Control, base-line room air ventilation; hypoxia, continuous ventilation with 10% oxygen; hypoxia plus prostacyclin, infusion of prostacyclin ( $\text{PGI}_2$ ), during continuous hypoxic ventilation. Symbols represent individual animals studied.

useful pulmonary vasodilators. Although it is unlikely that all these drugs exert their effects on the pulmonary vasculature through a common mechanism, these observations have given investigators the opportunity to evaluate the effects of these drugs in experimental pulmonary hypertension. This knowledge could lead to our increased understanding of the mechanisms of pulmonary vascular reactivity. This study demonstrates that hydralazine causes pulmonary vasodilatation in the setting of acute hypoxic vasoconstriction, and suggests that this effect may be mediated by prostaglandins.

During continuous hypoxic ventilation, the administration of hydralazine resulted in a reduction of pulmonary arterial pressure in anesthetized animals. Because cardiac output and pulmonary arterial wedge pressure were not altered, the decline in pulmonary artery pressure reflects a change in pulmonary vascular tone. A decrease in pulmonary blood volume could account for the observed pressure changes, but it is unlikely that hydralazine, an arteriolar dilator (36), would have an effect on venous capacitance. Furthermore, the volumes of blood removed for analysis and the amount of fluid infused to maintain catheter patency were always kept below 40 ml, respectively, for each study. It is also not likely that the fall in pulmonary artery pressure demonstrated resulted from the decay of the hypoxic pressor response, since this and other studies have demonstrated that continuous hypoxic ventilation in dogs produces a stable degree of pulmonary hypertension for at least 3 h (37).

The hemodynamics during ventilation both with room air and 10% oxygen were comparable in both groups. However, hydralazine had no effect on either pulmonary artery pressure or pulmonary arteriolar resistance in the dogs that were pretreated with either indomethacin or meclofenamate. In addition to its inhibition of prostaglandin synthetase, indomethacin has several other pharmacologic actions, but these are generally seen at doses much higher than those given in this study (26). The observation that prostacyclin lowered pulmonary arterial pressure in the presence of indomethacin makes it unlikely that indomethacin exerts a nonspecific effect on the ability of the pulmonary vasculature to respond to vasodilators.

The precise role of prostaglandins in the regulation of the pulmonary circulation remains unclear. Bergofsky (41) has suggested that other vasoactive compounds, such as histamine, may be mediators of hypoxic pulmonary vasoconstriction. Other investigators have suggested that vasoconstrictor prostaglandins released as a result of the hypoxic stimulus lead to pulmonary hypertension. Kadowitz and others (8, 11, 14–16) have postulated that vasodilator prostaglandins may contribute to the maintenance of the normal condition of a low pressure state in the pulmonary arterial tree. They further suggest that vasoconstriction during hypoxia may

be the result of the inhibition of synthesis of these prostaglandin compounds.

Of the vasoactive prostaglandins, prostacyclin is the most potent pulmonary vasodilator (7–9). Prostacyclin is produced in the lung (38–40) and in other organs.

It seems possible, therefore, that hydralazine lowers pulmonary artery pressure by stimulating the production of a vasodilator prostaglandin, possibly prostacyclin, either in the lung or at a distal site. Although measurements of prostaglandin metabolites in experimental preparations similar to ours are needed to confirm this hypothesis, the inhibition of the pulmonary vasodilator effects of hydralazine by indomethacin suggests that a vasodilator prostaglandin plays a crucial role in the hemodynamic responses observed with hydralazine administration.

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