Nonadrenergic Effects of Isoproterenol in Dogs with Hypoxic Pulmonary Vasoconstriction

POSSIBLE ROLE OF PROSTAGLANDINS

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ABSTRACT To determine whether the pulmonary vasodilation produced by isoproterenol is mediated solely by its beta adrenergic effects, we studied the hemodynamic responses to isoproterenol in three groups of dogs with pulmonary vasoconstriction produced by continuous ventilation with 10% oxygen: (a) hypoxia alone, (b) hypoxia and propranolol 0.3 mg/kg i.v. bolus followed by an infusion of 5 μg/kg per min, and (c) hypoxia after pretreatment with an inhibitor of cyclooxygenase, either indomethacin or meclofenamate 5 mg/kg s.c. twice daily for 2 d prior to study. All groups had similar values for mean pulmonary artery pressure (PAPm) and pulmonary vascular resistance (PVR) during room air and hypoxic ventilation. Isoproterenol in doses of 0.0025, 0.005, and 0.05 μg/kg per min produced a dose-related decline in PAPm and PVR during hypoxia in group 1. Despite β-blockade with propranolol (group 2), isoproterenol at all three doses significantly reduced PAPm and PVR. The responses to isoproterenol were comparable in the presence or absence of propranolol; at 0.05 μg/kg per min the effects of isoproterenol were blunted, but not abolished, by propranolol. Similar results were observed even when five times the dose of propranolol was given. Isoproterenol at all three doses had no effect, however, on PAPm and PVR in the cyclooxy-

genase inhibitor-pretreated group. These data suggest that the pulmonary vasodilator effects of isoproterenol are not mediated solely by pulmonary vascular beta adrenergic receptors, and that vasodilator prostaglandins may play a role in the responses to this drug.

INTRODUCTION

Ventilation with hypoxic gas mixtures causes an increase in pulmonary arterial pressure in most animal species (1). The mechanisms responsible for hypoxic pulmonary vasoconstriction remain unclear, but the autonomic nervous system does not appear to play a major role since the hypoxic pressor response can be elicited in the isolated lung (2, 3), in sympathectomized animals (4), and in animals whose tissue catecholamine stores have been depleted with reserpine (5). Both alpha (constrictor) and beta (dilator) adrenergic receptors exist in the pulmonary circulation (6, 7) but α-adrenergic blockade does not abolish the hypoxic pressor response (5, 8) and β-adrenergic blockade potentiates it only slightly (7–9), if at all (3). The seemingly minor role of the β-adrenergic receptor in the physiologic modulation of pulmonary vasomotor tone contrasts sharply with the effects of isoproterenol, a β-adrenergic agonist, on pulmonary vascular tone: Isoproterenol lowers both pulmonary arterial pressure and resistance to near-normal levels when administered to animals with acute hypoxic pulmonary vasoconstriction (5, 10).

Recent studies have linked prostaglandins with the vascular responses to adrenergic stimuli (11–13). The cutaneous vasodilation produced by sympathetic nerve stimulation is unaffected by antiadrenergic agents or β-adrenergic blockade, but is partially antagonized by

inhibitors of prostaglandin synthesis (14). Campbell et al. (15) demonstrated that cyclooxygenase inhibition with either indomethacin or meclofenamate inhibited sympathetically mediated renin release and Malik (16) has shown that indomethacin inhibited the norepinephrine-induced efflux of prostaglandin E (PGE)[1]-like material from the isolated rat spleen and potentiated the vasoconstrictor response to norepinephrine. Similarly, Wennmalm and Brundin (17) have shown that β-adrenergic blockade did not significantly alter the release of PGE from the isolated rabbit heart exposed to epinephrine. Since endogenous prostaglandins such as PGI_2 (18–20) and PGE_1 (21) exert potent pulmonary vasodilator effects when they are administered to animals during hypoxic ventilation, we wondered whether the profound vasodilator effects of isoproterenol in this setting could be mediated by vasodilator prostaglandins. Accordingly, we studied the pulmonary vascular effects of isoproterenol in intact dogs during hypoxic ventilation in three experimental settings: (a) isoproterenol alone, (b) after β-adrenergic blockade, and (c) after pretreatment with inhibitors of prostaglandin synthesis.

METHODS

Mongrel dogs of either sex, weighing between 16 and 20 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, MA) to regulate the minute ventilation so that the arterial pH and P_{CO_2} were maintained within the normal range. A polyethylene catheter was inserted into a femoral artery and catheters were inserted into two peripheral limb veins for the administration of drugs, or vehicle in the control experiments. A Swan-Ganz balloon-tipped flotation catheter was inserted into a femoral vein and advanced to a lower lobe branch of either main pulmonary artery. Pulmonary artery, pulmonary artery wedge, and femoral artery pressures were measured using Statham PR23ID and PR23AC pressure transducers (Statham Instruments, Inc., Oxnard, CA), respectively, and the pressure tracings were continuously displayed on a physiologic recorder (Electronics for Medicine, Inc., Pleasantville, NY). Heart rate was measured from a lead II electrocardiogram. Airway pressure was monitored using a manometer attached to the endotracheal tube. Timed collections of minute ventilation were measured in a Tissot gasometer and their oxygen content was determined using a paramagnetic oxygen analyzer (Beckman Instruments, Inc., Fullerton, CA). From this data, total body oxygen consumption was determined, corrected to standard temperature and pressure, dry. Arterial and mixed venous blood samples were collected anaerobically in heparinized syringes and total hemoglobin and oxyhemoglobin contents and arterial blood gases were measured using an IL 282 Co-oximeter and IL 813 blood gas analyzer (Instrument Laboratory, Inc., Lexington, MA), respectively. Cardiac output was then calcu-

lated from this data using the Fick equation. Pulmonary vascular resistance, defined as the mean pulmonary artery pressure minus the mean pulmonary artery wedge pressure (millimeters Hg) divided by the cardiac output (liters/minute), is reported in units.

After 30 min of room air ventilation, hemodynamic parameters were measured and continuous ventilation with a gas mixture consisting of 10% oxygen and 90% nitrogen was begun. Previous experience in our laboratory (22) has demonstrated that this procedure produces a doubling of pulmonary vascular resistance, and that the degree of vasoconstriction is stable for 3 h of continuous hypoxic ventilation. Pentobarbital sodium (3–5 mg/kg i.v.) was given periodically as needed to maintain the level of anesthesia. This agent was used because several studies have demonstrated that pentobarbital, even in massive doses, does not depress the hypoxic pressor response in animals (23–25). A control group of seven dogs were maintained on continuous hypoxic ventilation for 3 h to verify the stability of the hypoxic pressor response. In the six animals receiving isoproterenol we repeated the hemodynamic studies after 1 h of continuous hypoxic ventilation (hypoxia) and then infused isoproterenol in doses of 0.0025, 0.005, or 0.05 μg/kg per min for 30 min in random order through a peripheral venous line, using a peristaltic pump (Sage Instruments, Cambridge, MA) to maintain a constant infusion rate. We monitored continuously the systemic and pulmonary arterial pressures and repeated the hemodynamic measurements 30 min after the infusion of each dose was begun (hypoxia + isoproterenol).

A group of six animals were given propranolol 0.3 mg/kg i.v. bolus followed by a continuous infusion of 5 μg/kg per min (P_1) and a separate group of seven animals were given propranolol 1.5 mg/kg i.v. bolus followed by a continuous infusion of 25 μg/kg per min (P_5), using a pressure pump (Harvard Apparatus Co.) to maintain constant flow. 30 min after the propranolol infusion was begun room air measurements were made and hypoxic ventilation was instituted. 1 h later we repeated the hemodynamic measurements (hypoxia + propranolol), and started an isoproterenol infusion, 0.0025, 0.005, or 0.05 μg/kg per min into a peripheral limb vein for 30 min. Repeat hemodynamic measurements were made 30 min after beginning each dose of isoproterenol (hypoxia + propranolol + isoproterenol).

A separate group of six dogs received subcutaneous injections of either indomethacin (3) or meclofenamate (3), 5 mg/kg twice daily for 2 d. The final dose of either cyclooxygenase 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 inhibited by this dosage in several species (27–29). The pretreated animals underwent similar study, receiving the same doses of isoproterenol for 30 min each after 1 h of continuous hypoxic ventilation.

To evaluate the hemodynamic effects of isoproterenol in animals with normal pulmonary vascular tone, we administered isoproterenol in doses of 0.0025, 0.005, and 0.05 μg/kg per min for 30 min, in random order, to six dogs ventilated with room air. Hemodynamic measurements were made 30 min after each infusion was begun. Another group of six animals were treated with propranolol (P_1), hemodynamic measurements were made after 30 min, and they then received infusions of the same doses of isoproterenol. Repeat measurements were made 30 min after each dose.

To determine whether cyclooxygenase inhibitors exerted a nonspecific inhibitory effect on drug-induced pulmonary

vasodilation, we studied the responses to sodium nitroprusside during hypoxic ventilation in a group of five control dogs and a group of five dogs pretreated with indomethacin. After base-line room air and hypoxia measurements were made, these animals received an infusion of sodium nitroprusside, 0.5, 1.5, and 3.0 μg/kg per min for 30 min at each dose, and hemodynamic measurements were made at the end of each dose segment.

To determine the influence of propranolol on the effects of a known vasodilator, prostaglandin, two dogs were treated with propranolol 1.5 mg/kg i.v. bolus followed by 25 μg/kg per min infusion (P_5) during hypoxic ventilation. After 1 h of hypoxia they received an infusion of prostacyclin (PGI_2) 5 μg/kg per min into a peripheral limb vein for 2 min. Prostacyclin was stored in absolute ethanol at $-70°C$. 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, 5, 10, 15, and 20 min. Similarly, the effects of sodium nitroprusside were evaluated in a separate group of four dogs treated with propranolol (P_1).

Plasma levels of propranolol were measured using techniques previously described (30). Blood samples were drawn for propranolol levels at times coinciding with hemodynamic measurements in six dogs in the P_1 group and in all seven dogs in the P_5 group.

The data are presented as the mean±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 unpaired data to compare the data from the P_1 and P_5 groups (31).

RESULTS

The hemodynamic effects of incremental doses of isoproterenol during room air ventilation in the absence and in the presence of propranolol are shown in Fig. 1. In the dogs receiving isoproterenol only, isoproterenol produced significant increases in heart rate in a dose-related manner. Similarly, cardiac output increased significantly at the highest dose compared to control. Mean arterial pressure decreased significantly only at the highest dose, and pulmonary arterial pressure increased at the two highest doses, while pulmonary vascular resistance was unchanged. Compared to the control data from the isoproterenol alone group, propranolol had no effect on normoxic pulmonary vascular tone, but heart rate and cardiac output were slightly lower and mean aortic pressure was slightly higher in the group receiving propranolol. Isoproterenol produced no hemodynamic changes in the propranolol-treated group. At the two highest doses of isoproterenol there were significant differences between the two groups in cardiac output, heart rate, and mean pulmonary artery pressure ($P < 0.05$). Neither isoproterenol nor propranolol affected mean pulmonary artery wedge pressure.

The effects of continuous ventilation with 10% O_2 for 3 h in a group of control dogs is shown in Table I. Hypoxia produced significant and stable elevations
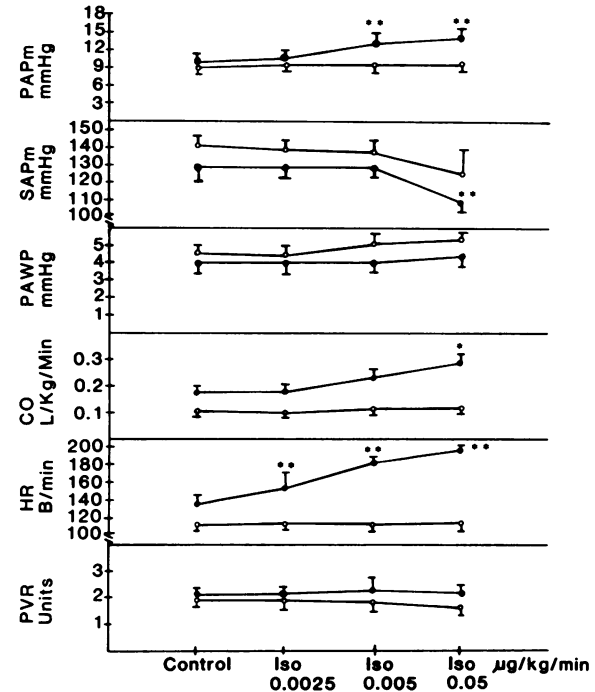

FIGURE 1 The effects of isoproterenol infusion during room air ventilation in six dogs receiving isoproterenol only (●) and in six dogs receiving isoproterenol and propranolol 0.3 mg/kg i.v. bolus followed by a continuous infusion of 5 μg/kg per min (P_1, O); PAPm denotes mean pulmonary arterial pressure; SAPm mean systemic arterial pressure; PAWP pulmonary artery wedge pressure; CO, cardiac output, HR, heart rate, PVR, pulmonary vascular resistance. $^*P < 0.05$, $^{**}P < 0.01$ compared with control.

in mean pulmonary arterial pressure and pulmonary vascular resistance during a 3-h period. Mean aortic blood pressure, heart rate, and cardiac output were unaffected by hypoxia at the intervals when measurements were performed.

The hemodynamic effects of isoproterenol alone and in the presence of propranolol or cyclooxygenase inhibitors during hypoxic ventilation are shown in Fig. 2 and Table II. Hypoxia produced significant and comparable elevations in all three groups in mean pulmonary artery pressure and pulmonary vascular resistance. The heart rate was 20% lower in the propranolol group, but there were no other hemodynamic effects of propranolol during hypoxia.

Isoproterenol reduced mean pulmonary arterial pressure and pulmonary vascular resistance and increased cardiac output in a dose-related manner in the group receiving isoproterenol only. Isoproterenol at all three doses comparably reduced mean pulmonary artery pressure and pulmonary vascular resistance in the propranolol group compared with the group receiving isoproterenol alone, although propranolol blunted the

TABLE I
Hemodynamic and Blood Gas Data in the Prolonged Hypoxia Group

	Control	Hypoxia (1 h)	Hypoxia (2 h)	Hypoxia (3 h)
PAPm, mmHg	11.0±1.21	19.3±2.97*	20.1±2.91*	19.7±3.23*
SAPm, mmHg	141.7±5.36	127.6±4.91	137.0±6.24	136.7±6.07
CO, liter/kg/min	0.14±0.017	0.16±0.012	0.15±0.015	0.14±0.014
HR, B/min	164±4.0	162±2.6	168±7.6	167±8.0
PVR, U	1.9±0.37	4.4±0.54‡	5.1±0.66‡	5.2±0.68‡
pHa, U	7.41±0.016	7.38±0.026	7.35±0.034	7.37±0.034
paCO$_2$, mmHg	33±1.0	34±1.6	36±3.0	35±2.2
paO$_2$, mmHg	78.9±2.00	30.9±2.15‡	30.1±2.45‡	34.3±2.98‡

Values are mean±SEM, n = 7; PAPm, mean pulmonary artery pressure; SAPm, mean systemic artery pressure; CO, cardiac output; HR, heart rate; PVR, pulmonary vascular resistance; pHa, arterial blood pH; paCO$_2$, arterial partial pressure of CO$_2$; paO$_2$, arterial partial pressure O$_2$.
* $P < 0.01$.
‡ $P < 0.001$.
P values are with reference to room air measurements. Values during hypoxia were not different at 1, 2, or 3 h ($P > 0.05$).

effects of isoproterenol at a dose of 0.05 μg/kg per min. Both the cardiac output and heart rate at the highest dose of isoproterenol were significantly different between the group pretreated with propranolol and the group receiving isoproterenol only ($P < 0.05$ and $P < 0.01$, respectively). There were no significant differences in the pulmonary vascular responses to hypoxia or isoproterenol between the P$_1$ and P$_5$ groups (Fig. 3). Plasma propranolol concentrations were 180±18 (range 114–263) ng/ml in the P$_1$ group and 591±58 (range 383–831) in the P$_5$ group.

The control values in the cyclooxygenase inhibitor pretreated group reflect normal room air hemodynamics. Hypoxic ventilation produced elevations in mean pulmonary artery pressure and pulmonary vascular resistance without affecting systemic arterial pressure or heart rate. In contrast to the effects of isoproterenol during hypoxia alone or during hypoxia and propranolol, isoproterenol had no effect on pulmonary vascular tone in the cyclooxygenase inhibitor pretreated group at any of the doses given. Isoproterenol produced a slight increase in heart rate at the highest doses in this group, although neither the cardiac output nor the heart rate were significantly changed. The results ob-
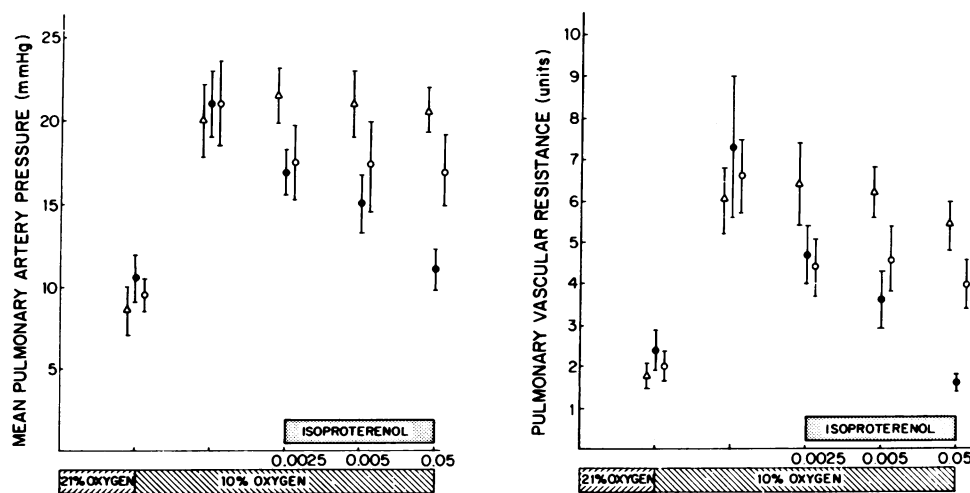

FIGURE 2 The effects of isoproterenol infusion in doses of 0.0025, 0.005, and 0.05 μg/kg per min during hypoxia on mean pulmonary artery pressure and pulmonary vascular resistance in six dogs receiving isoproterenol only (●), in six dogs receiving isoproterenol and propranolol (P$_1$, ○), and in six dogs receiving isoproterenol after pretreatment with a cyclooxygenase inhibitor (Δ).

TABLE II
Hemodynamic Effects of Isoproterenol during Hypoxic Ventilation

| | Group I (n = 6) | | | | | Group II (n = 6) | | | | | Group III (n = 6) | | | | |
| | | | I | | | | | I | | | | | I | | |
	RA	H	0.0025	0.005	0.05	RA	H	0.0025	0.005	0.05	RA	H	0.0025	0.005	0.05
PAPm, mmHg	10.7 ±1.20	20.8 ±2.26	16.8* ±1.40	14.7* ±1.76	10.7* ±1.33	9.5 ±0.96	21.0 ±2.74	17.7* ±2.11	17.7* ±2.57	17.0* ±2.35	8.5 ±1.57	19.8 ±2.33	21.5 ±1.73	21.1 ±1.78	20.3 ±1.31
PAWP, mmHg	4.3 ±0.92	4.0 ±0.68	4.5 ±0.88	4.0 ±0.68	4.0 ±1.21	4.5 ±0.50	4.7 ±0.82	5.5 ±0.99	5.2 ±0.87	5.2 ±0.87	2.8 ±0.48	2.7 ±0.56	2.8 ±0.48	3.0 ±0.58	2.3 ±0.56
SAPm, mmHg	128.7 ±13.04	117.5 ±10.95	106.3 ±8.37	113.8 ±9.13	120.7 ±11.34	142.2 ±5.51	131.0 ±8.63	111.3 ±13.45	114.3 ±16.33	123.0 ±9.95	136.5 ±4.67	124.3 ±5.81	122.8 ±6.78	125.3 ±7.23	120.2 ±5.05
HR, B/min	149 ±15.4	158 ±15.5	146 ±14.9	151 ±13.5	163 ±9.6	113 ±6.1	122 ±7.9	118 ±7.5	117 ±8.0	118 ±8.3	175 ±6.2	160 ±8.2	163 ±6.7	167 ±6.7	176 ±6.1
CO, liter/kg/min	0.16 ±0.023	0.15 ±0.031	0.14 ±0.025	0.16 ±0.032	0.22‡ ±0.024	0.11 ±0.012	0.13 ±0.019	0.13 ±0.015	0.13 ±0.014	0.14 ±0.024	0.13 ±0.010	0.12 ±0.12	0.12 ±0.012	0.12 ±0.007	0.14 ±0.008
TSR, U	44.8 ±4.59	48.5 ±7.43	42.9 ±6.42	40.1 ±6.07	30.3 ±4.26	60.6 ±8.32	54.2 ±8.81	41.7* ±7.70	43.2‡ ±7.95	45.2 ±7.38	43.2 ±3.61	42.4 ±2.51	41.5 ±4.11	42.2 ±4.06	35.4 ±2.47
PVR, U	2.4 ±0.49	7.3 ±1.69	4.7* ±0.74	3.6* ±0.71	1.6* ±0.21	2.0 ±0.36	6.6 ±0.94	4.4* ±0.69	4.6* ±0.78	4.1* ±0.69	1.7 ±0.30	6.0 ±0.81	6.4 ±0.98	6.2 ±0.67	5.4 ±0.58

Group I: No pretreatment.
Group II: Pretreatment with propranolol 0.3 mg/kg i.v. bolus followed by a continuous infusion of 5 μg/kg per min.
Group III: Pretreatment with indomethacin or meclofenamate 5 mg/kg s.c. twice daily for 2 d.
RA denotes room air ventilation; H hypoxic ventilation; I isoproterenol infusion during hypoxic ventilation in doses of 0.0025, 0.005, and 0.05 μg/kg per min.
Values are mean±SEM.
* $P < 0.01$.
‡ $P < 0.05$.
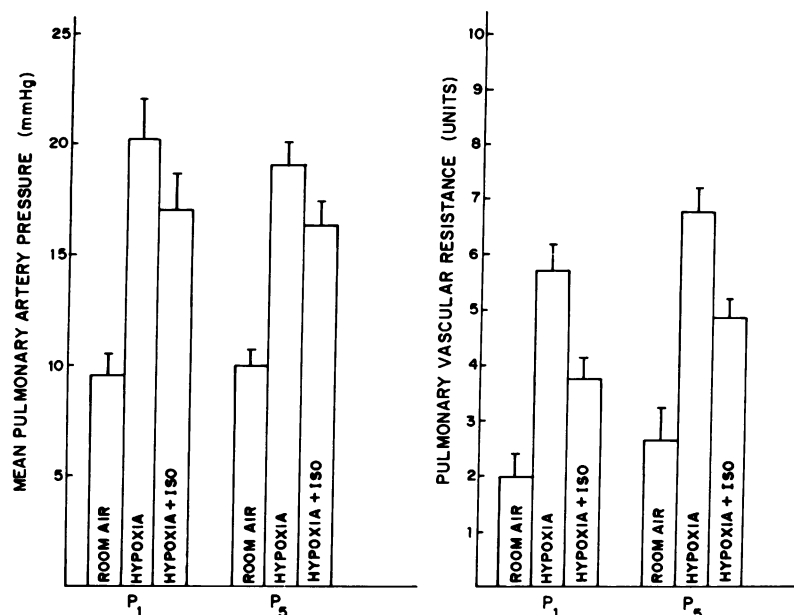P values are with reference to hypoxia measurements.

FIGURE 3 Comparison of mean pulmonary artery pressure and pulmonary vascular resistance at three stages of study: room air ventilation, hypoxic ventilation, and hypoxic ventilation + isoproterenol 0.05 μg/kg per min. The P_1 group ($n = 6$) received propranolol 0.3 mg/kg i.v. bolus followed by a continuous infusion of 5 μg/kg per min; the P_5 group ($n = 7$) received propranolol 1.5 mg/kg i.v. bolus followed by an infusion of 25 μg/kg per min. There were no statistical differences between the groups.

tained with indomethacin and meclofenamate were the same.

Isoproterenol had no effect on systemic arterial pressure during hypoxia in any of the three groups. Total systemic resistance at the highest dose was lower in the isoproterenol alone group compared to the group receiving cyclooxygenase inhibitors ($P < 0.05$).

The effects of sodium nitroprusside during hypoxia in five control dogs, in five dogs pretreated with indomethacin, and in four dogs receiving an infusion of propranolol (P_1) are shown in Fig. 4. Nitroprusside comparably reduced mean pulmonary artery pressure and pulmonary vascular resistance in a dose-related manner in all three groups.

The effects of an infusion of prostacyclin (PGI$_2$) 5 μg/kg per min for 2 min during hypoxia in two control dogs and in two dogs receiving propranolol (P_5) are shown in Fig. 5. Prostacyclin reduced mean pulmonary artery pressure to near-control levels. Within 30 min of discontinuation of the prostacyclin infusion pulmonary arterial pressure returned to base-line hypoxia levels in both groups.

DISCUSSION

Previous studies have reported that the hypoxic pressor response is either potentiated by or decays during pro-

longed or intermittent hypoxic ventilation (32, 33), rendering the interpretation of pharmacologic interventions during hypoxia quite difficult. We have previously demonstrated, however, that the continuous ventilation of dogs with 10% oxygen results in a twofold increase in pulmonary arterial pressure that remains stable for at least 3 h (22), and current studies support this observation. Since the onset of action of the three vasodilators used (isoproterenol, nitroprusside, and prostacyclin) is rapid and the duration of effect is brief once the infusion is discontinued, we were able to study the dose-response effects of these agents during a hemodynamically stable period of hypoxic ventilation.

The observations that alpha or beta blockade (8, 9), surgical or pharmacological vagotomy (7, 33), sympathectomy (5, 34), and inhibition of prostaglandin synthesis (22) fail to substantially alter resting pulmonary tone suggest that the normal pulmonary circulation is in a near maximally dilated state and that this low resistance is not maintained by an active process. Thus, during normoxic ventilation, the administration of isoproterenol resulted in an increase in pulmonary arterial pressure concomitant with the increase in cardiac output, indicating an absence of further vasodilation.
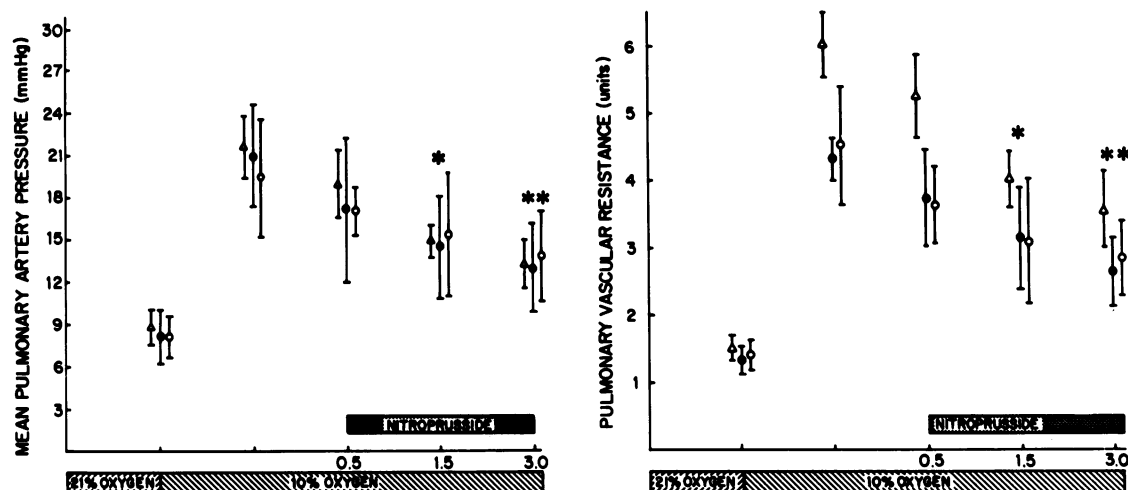
FIGURE 4 The effects on mean pulmonary artery pressure and pulmonary vascular resistance on the infusion of incremental doses of sodium nitroprusside during hypoxic ventilation in five control dogs, (●), five dogs pretreated with indomethacin (△), and four dogs receiving a continuous infusion of propranolol (P_1) (O). There were no statistical differences between the groups. ●●$P < 0.01$ compared to hypoxia.

During hypoxic ventilation, pulmonary arterial pressure increases as a result of constriction of the pulmonary vasculature. In this setting, isoproterenol decreased both the mean pulmonary artery pressure and the pulmonary vascular resistance. This pulmonary vasodilatation was blunted, but not abolished, by β-adrenergic blockade with propranolol. It was, however, totally prevented by inhibitors of prostaglandin synthesis.
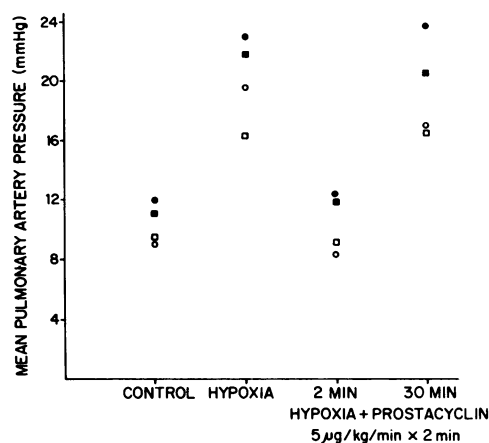

FIGURE 5 Prostacyclin infusion during continuous hypoxic ventilation in two control dogs (■, ●) and two dogs receiving propranolol 1.5 mg/kg i.v. bolus followed by a continuous infusion of 25 µg/kg per min (P_5) (□, O). Control, room air ventilation; hypoxia, 10% oxygen continuous ventilation; hypoxia + prostacyclin, infusion of prostacyclin during continuous hypoxic ventilation. Symbols represent individual animals studied.

It is likely that the dose of propranolol that we used resulted in an effective β-adrenergic blockade, since the heart rates after propranolol were 15–20% lower than the pre-drug levels in the treated group and the levels in the group not receiving propranolol. Furthermore, the plasma propranolol concentrations are comparable to the levels that have been demonstrated to produce significant β-blockade (35, 36). Finally, propranolol blocked the isoproterenol-induced tachycardia (dose ratio > 60, unpublished observations), an accepted indicator of β-blockade (37). To further assure the adequacy of β-blockade, we treated a group of animals with five times the conventional dose of propranolol, and we still found a pulmonary vascular response to isoproterenol.

Barer and McCurrie (7) studied the effects of β-agonists and antagonists alone and in concert in open chested cats under conditions of controlled lobar flow. In contrast to our observations, they noted that propranolol raised pulmonary vascular resistance both during room air and hypoxic ventilation, and that left ventricular failure often resulted from the infusion of propranolol. In agreement with our studies, Barer and McCurrie found that, despite massive doses of propranolol, isoproterenol still elicited a reduction in mean pulmonary artery pressure in hypoxic cats. The discrepancies between these studies may be the result of species variation of pulmonary vascular β-receptor activity, or differences in the methods of study (lobar infusion of propranolol in open chested animals with controlled flow vs. systemic infusion in intact animals).

It is unlikely that inhibition of prostaglandin syn-

thesis exerts a nonspecific effect on the ability of the pulmonary vasculature to dilate, since nitroprusside exerted a pulmonary vasodilator effect in dogs pretreated with indomethacin. Similarly, the pulmonary vasodilator action of prostacyclin in dogs with hypoxic pulmonary vasoconstriction is not affected by indomethacin (22). In addition, the present study demonstrates that propranolol does not reduce the pulmonary vasodilator effects of nitroprusside or prostacyclin, implying that the pharmacologic blockade by propranolol is specific.

Campbell et al. (15) suggested that prostaglandins may be involved in adrenergic-mediated renin release at a point distal to the β-receptor. Zwillich et al. (38) have demonstrated that the isoproterenol-induced increases in ventilation and metabolic rate were not blocked by propranolol in doses sufficient to produce cardiovascular beta blockade. They suggested that, either there are differences between the effectiveness of propranolol blockade of the cardiovascular and respiratory systems, or the isoproterenol effect that they observed may be independent of the β-adrenergic system. Our demonstration that the pulmonary vasodilator effect of isoproterenol was not completely blocked by massive doses of propranolol but was blocked by cyclooxygenase inhibitors supports the concept of a prostaglandin mediated effect of isoproterenol, particularly at low doses. The blunting of the isoproterenol effect at the high doses by propranolol suggests that a mixed beta and arachidonic acid metabolite effect may be present. The demonstration that propranolol does not reduce the pulmonary vascular effects of prostacyclin further suggest that the activity of prostaglandins synthesized and/or released subsequent to drug administration are independent of pulmonary β-adrenoreceptors.

ACKNOWLEDGMENTS

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