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Pulmonary Vascular Responses of Newborn Goats to Aerosolized Prostaglandin E_1 (39735)[1]

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Prostaglandins of the E series (PGEs) are vasodilators in the perinatal pulmonary circulation (1, 2). They are synthesized and catabolized in the lungs (3). The pulmonary vasodilator effect of PGE_1 results from action on arterial or venous smooth muscle or both. Isolated segments of both pulmonary lobar arteries and veins from dogs relax when treated with PGE_1 (4). Kadowitz *et al.* (5) suggest that in sheep lung PGE_1 dilates predominately vessels upstream from small veins. Slow infusion (2 μg/kg·min) of PGE_1 directly into the left pulmonary artery of newborn goats reduces pulmonary vascular resistance and abolishes the pressor response to hypoxia without affecting systemic arterial pressure (2).

Perfusion–ventilation imbalance with increased pulmonary vascular resistance in the newborn has been reported in cases of severe respiratory distress (6, 7), persistent pulmonary hypertension (8), progressive pulmonary hypertension (9), and persistent fetal circulation (10). PGE_1 may be of value in the treatment of pulmonary hypertension. If PGE_1 delivered as an aerosol also lowers pulmonary vascular resistance without affecting systemic arterial pressure, aerosol administration would eliminate the necessity of delivering prostaglandin into the pulmonary artery.

The following investigation was undertaken to determine effects of inhaled PGE_1 aerosol upon: (i) pulmonary vascular resistance, (ii) pulmonary vascular response to hypoxia, (iii) systemic arterial pressure, and (iv) heart rate of newborn goats. Effects of PGE_1 administered as an aerosol on the pulmonary and systemic circulations are compared to the effects of PGE_1 infused into the left pulmonary artery or into the left ventricle.

Methods. Twenty-six newborn goats (1–7 days of age, 2.2–3.8 kg) were anesthetized with chloralose (50 mg/kg iv, supplemented with 8 mg/kg hourly). Systemic arterial pressure (Statham P23DC transducer), heart rate (Narco Biosystems Biotachometer), and arterial pH, PO_2, and PCO_2 (Radiometer blood gas and pH analyzer) were monitored via a cannula in the descending aorta. A tracheostomy was performed and animals were ventilated mechanically. Thirty-three-percent O_2 in N_2 was delivered to the lungs via trachea at a frequency of 17 breaths/min with equal inspiratory and expiratory times (Bird Mark II ventilator). Inspiratory pressure was kept constant following initial adjustments to establish a $PaCO_2$ of 35 ± 1 mm Hg (mean ± SEM). Left thoracotomy was performed to permit cannulation of the left pulmonary artery. Following the anticoagulant (heparin, 2000 units/kg) the left pulmonary artery was perfused (Cole Parmer Master-flex Model 7016) at a constant flow rate (20 ± 1 ml/kg·min) with blood withdrawn from the inferior vena cava. Left pulmonary arterial perfusion pressure, left atrial pressure, and left pulmonary arterial blood flow (Statham flowmeter with In Vivo Metric electromagnetic flow probe) were monitored continuously. Pulmonary vascular resistance of the left lung was calculated as left pulmonary arterial perfusion pressure minus left atrial pressure divided by the flow per unit weight of animal. Right pulmonary blood flow was left undisturbed. Arterial pH, PO_2, PCO_2, and colonic temperature (T_c) were monitored and maintained (pH, 7.39 ± 0.01; PO_2, 106 ± 9 mm Hg; PCO_2, 35 ± 1 mm Hg; T_c, 39.2 ± 0.2°).

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Indomethacin[4] was administered (3 mg/kg ia) to inhibit synthesis of endogenous prostaglandins (11) and to produce slight pulmonary hypertension (12). Experiments were begun 60 min following indomethacin administration. (Preliminary experiments showed that cardiovascular effects of indomethacin were maximal and stable within 30 min.)

Aerosols were produced by a micronebulizer (Bird Corp.). The micronebulizer is designed to produce a mist of liquid particles 0.5 to 4.0 μm in diameter. The rate at which PGE_1[5] was delivered to the trachea was changed by altering the PGE_1 concentration in 5-ml solutions. PGE_1 was dissolved in ethanol (7.5 mg/ml) and diluted with saline. Five concentrations were used that allowed delivery of PGE_1 to both lungs through the tracheal cannula at 3, 6, 15, 30, and 50 μg of PGE_1/kg·min for 10 min. Control aerosols (ethanol in saline) were applied prior to and following each PGE_1 aerosol treatment. Goats were ventilated with 5% O_2 in N_2 for 45 sec during the 10th minute of each vehicle or PGE_1 aerosolization. This period of breathing 5% O_2 lowered PaO_2 to 23 ± 2 mm Hg.

For comparison, PGE_1 was infused at varied rates into the left pulmonary arterial blood (supplying approximately 35% of total lung mass) or into the left ventricle.

Eleven goats received PGE_1 aerosols, eleven received left pulmonary arterial infusions of PGE_1, and four received left ventricular infusions of PGE_1.

All differences cited are significant at $p < 0.05$ (13). Comparisons of least-square regression slopes with each other and with zero were made (t test). Comparison of the hypoxic pulmonary vasoconstriction during control aerosol with that during PGE_1 aerosol (6 μg/kg·min) was made using a Wilcoxon sign test.

Results. Pulmonary vascular resistance of newborn goats inhaling 6 μg of PGE_1 aerosol/kg·min (10 min) decreased slightly compared to controls. This amount of PGE_1 as an aerosol caused mean left pulmonary vascular resitance to decrease from 0.90 to 0.86 mm Hg·kg·min/ml while control aerosol caused mean left pulmonary vascular resistance to increase from 0.94 to 0.97 mm Hg·kg·min/ml (Fig. 1). The reduction of pulmonary vascular resistance as a result of PGE_1 administered as an aerosol is far less than the reduction caused by PGE_1 infused directly into the left pulmonary arterial blood (Fig. 2).

Hypoxic pulmonary vasoconstriction was reduced 39% during PGE_1 aerosol (6 μg/kg·min) as compared to control. The mean left pulmonary vascular resistance increase resulting from 45-sec hypoxia was 123% during control aerosols and 84% during PGE_1 aerosols (Fig. 1).

PGE_1 aerosols also decreased heart rate and systemic arterial pressure (Fig. 1). The mean heart rate decreased from 214 to 202 beats/min during treatment with 6 μg of PGE_1 aerosol/kg·min but increased from 199 to 209 beats/min during control (ethanol in saline) aerosols. PGE_1 aerosol caused a mean decrease in systolic pressure

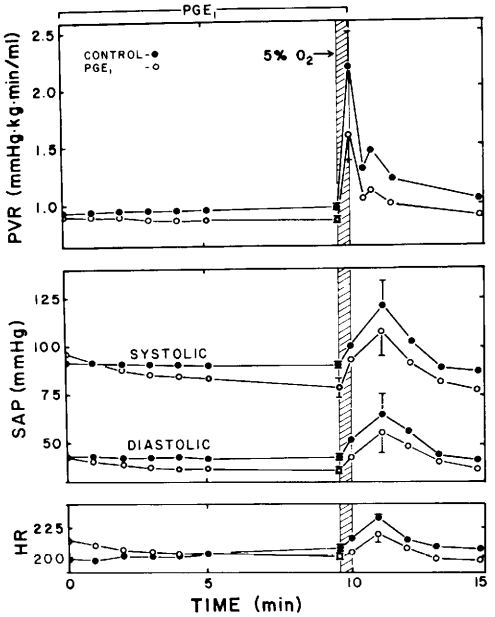

FIG. 1. Effects of PGE_1 administered as an aerosol (6 μg/kg·min for 10 min) on left pulmonary vascular resistance (PVR), systemic arterial pressure (SAP), and heart rate (HR) of seven tracheostomized newborn goats. The animals were ventilated with 5% O_2 during the last 45 sec of aerosol treatment. Open and closed circles are means. Vertical ranges are standard errors of the response.

[4] Kind gift of Dr. C. A. Stone, Merck, Sharp, and Dohme.

[5] Kind gift of Dr. J. E. Pike, Upjohn Co.

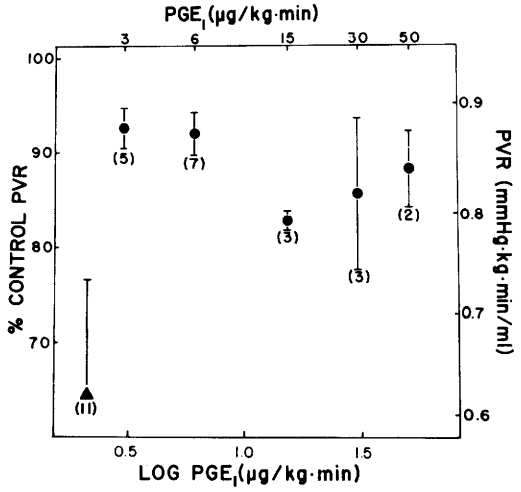

FIG. 2. Effect of PGE_1 aerosol on pulmonary vascular resistance (PVR) of newborn goats. Points are means; vertical ranges are SEM. The effect of pulmonary arterial infusion of PGE_1 (2 μg/kg·min into the left lung) is shown for comparison (▲) (2). Numerals beneath points are sample sizes.

from 98 to 79 mm Hg and a mean decrease in diastolic pressure from 42 to 35 mm Hg. The calculated mean systemic arterial pressure decreased 18% (61 to 50 mm Hg) during the PGE_1 aerosol treatment. As shown in Fig. 3, the decrease in systemic arterial pressure during PGE_1 aerosol treatment is related to the rate of PGE_1 delivery to the trachea.

The hypotensive effects of aerosol administration and left ventricular infusion of PGE_1 on systemic arterial pressure are not different (Fig. 3). However, PGE_1 infused into left pulmonary arterial blood has a less pronounced effect on systemic arterial pressure (Fig. 3). For example, 6 μg of PGE_1 aerosol/kg·min (both lungs) results in a 14% decrease in mean systemic arterial pressure as compared to control. The same amount infused into the left pulmonary arterial blood (supplying 35% of total lung mass) results in a decrease in mean systemic arterial pressure of only 6%.

Discussion. Effects of exogenous E-series prostaglandins upon the pulmonary and systemic circulations depend upon route of administration. PGE_1 infused directly into the pulmonary circulation of newborn goats (2 μg/kg·min into the left pulmonary arterial blood) reduced pulmonary vascular resistance 36% without altering systemic arterial pressure (2). However, 6 μg of PGE_1 aerosol/kg·min reduces pulmonary vascular resistance only slightly (Fig. 2). In addition, this dose of PGE_1 administered as an aerosol or infused into the systemic circulation reduces the systemic arterial pressure (Fig. 3). Therefore, effects of PGE_1 administered as an aerosol on the systemic circulation are similar to the effects of a postpulmonary infusion of PGE_1. The small effect of aerosolized PGE_1 on pulmonary vascular resistance coupled with pronounced systemic effects suggests that aerosolized PGE_1 enters the bloodstream and reaches the systemic circulation without encountering the major pulmonary vascular sites of PGE_1 activity and catabolism.

In newborn goats, PGE_1 administered as an aerosol has minimal effects on the pulmonary circulation and pronounced effects upon the systemic circulation. Therefore, if sites of activity and catabolism of PGE_1 in human and goat lung are the same, aerosol administration of PGE_1 for treatment of pulmonary hypertension would not produce

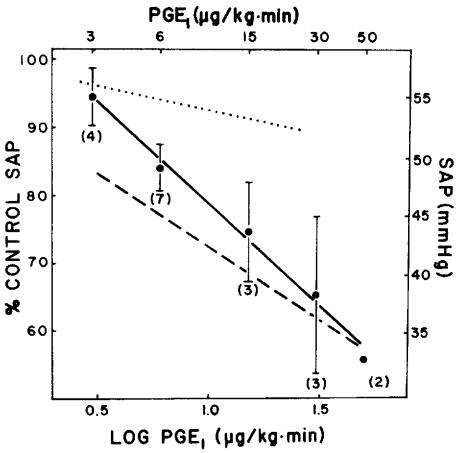

FIG. 3. Effect of PGE_1 delivered as an aerosol on the mean systemic arterial pressure (SAP) of newborn goats. Points are means; vertical ranges are SEM. PGE_1 infused into the left pulmonary artery (....); infused into the left ventricle (----). Numerals beneath points are sample sizes for aerosol PGE_1-treated animals. Solid lines are least-square regressions. Sample size for left ventricular infusion was 16 points at infusion rates between 1.03 and 70 μg of PGE_1/kg·min obtained from four goats. Sample size for left pulmonary arterial infusion was 22 points at infusion rates between 3.2 and 25 μg of PGE_1/kg·min obtained from 11 goats.

the therapeutic effect of decreasing pulmonary vascular resistance without reducing systemic arterial pressure.

Summary. Effects of aerosolized prostaglandin E_1 (PGE_1) on pulmonary vascular resistance, systemic arterial pressure, and heart rate of anesthetized newborn goats were evaluated *in situ* during normoxia and hypoxia by means of an open-chest, pump-perfused lung preparation. Pulmonary vascular resistance, systemic arterial pressure, and heart rate were reduced during 10-min administration of PGE_1 aerosols. PGE_1 aerosols produced small effects on pulmonary vascular resistance and pronounced effects on systemic arterial pressure. The effect of PGE_1 on systemic arterial pressure was not different whether administered as an aerosol or infused directly into the left ventricle. PGE_1 infused into left pulmonary arterial blood has a greater effect on pulmonary vascular resistance and less effect on systemic arterial pressure than PGE_1 administered as an aerosol.

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1. Cassin, S., Tyler, T., and Wallis, R., Proc. Soc. Exp. Biol. Med. **148,** 584 (1975).
2. Tyler, T., Leffler, C., Wallis, R., and Cassin, S., Prostaglandins **10,** 963 (1975).
3. Katz, R. L., and Katz, G. J. Anesthesiology **40,** 471 (1974).
4. Kadowitz, P. J., Joiner, P. D., Hyman, A. L., and George, W. J., J. Pharmacol. Exp. Ther. **192,** 677 (1975).
5. Kadowitz, P. J., Joiner, P. D., and Hyman, A. L., Proc. Soc. Exp. Biol. Med. **145,** 1258 (1974).
6. Chu, J., Clements, J. A., Cotton, E. K., Klaus, M. H., Sweet, A. Y., and Tooley, W. H., Pediatrics **40,** 709 (1967).
7. Moss, A. J., Emmanouilides, G. C., Higashino, S. M., and Adams, F. H., Biol. Neonat. **8,** 177 (1965).
8. Siassi, B., Goldberg, S. J., Emmanouilides, G. C., Higashino, S. M., and Lewis, E., J. Pediat. **78,** 610 (1971).
9. Burnell, R. H., Joseph, M. C., and Lees, M. M., Amer. J. Dis. Child. **123,** 167 (1972).
10. Gersony, W. M., Duc, G. V., and Sinclair, S. C., Circulation **40,** 87 (1969).
11. Flower, R. J., Pharmacol. Rev. **26,** 33 (1974).
12. Tyler, T., Wallis, R., Leffler, C., and Cassin, S., Proc. Soc. Exp. Biol. Med. **150,** 695 (1975).
13. Dixon, W. J., and Massey, F. J., "Introduction to Statistical Analysis." McGraw-Hill, New York (1969).

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