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Effects of Prostaglandins E_1 and $F_{2\alpha}$ on the Swine Pulmonary Circulation[1] (37746)

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The effects of the prostaglandins on the pulmonary circulation have been investigated in a variety of animal species including dog, cat, rabbit, and calf (1–7). Änggard and Bergström reported that $PGF_{2\alpha}$ increased right ventricular systolic pressure in the anesthetized cat (6). In the dog and calf, $PGF_{2\alpha}$ increased pulmonary arterial pressure, cardiac output and calculated pulmonary vascular resistance (1–3, 7). In the anesthetized dog and perfused rabbit lung, PGE_1 has been shown to decrease pulmonary vascular resistance (2, 4). In a recent study, using a new right heart catheterization technique to perfuse the left lower lobe at constant blood flow, Hyman demonstrated that $PGF_{2\alpha}$ actively constricted both lobar arteries and veins, whereas PGE_1 actively dilated the lobar vessels (5). Although prostaglandins are present in the normal swine lung, and in some respects the circulatory system of the swine is similar to the human circulatory system, very little is known about the effects of these substances on the swine pulmonary circulation (6, 8).

In the present study we investigated the effects of PGE_1 and $PGF_{2\alpha}$ on the intact swine pulmonary circulation using a new right heart catheterization technique to perfuse the left lower lung lobe at controlled blood flow.

Methods. Four adult swine (3 male and 1 female) weighing from 54 to 85 kg were anesthetized with pentobarbital sodium 30–45 mg/kg iv and were strapped to a fluoroscopic table. A specially designed 23F balloon catheter was introduced from the left external jugular vein into the artery of the left lower lung lobe under fluoroscopic guidance. A 0.9 mm Teflon catheter with its tip positioned about 2 cm from the tip of the balloon catheter was used to measure lobar arterial pressure. Catheters with side holes were passed into the main pulmonary artery and femoral artery and into a small lobar vein and the left atrium transeptally. All pressures were measured with Statham P23D transducers and recorded on an oscilloscopic recorder (Electronics for Medicine, Inc., White Plains, NY). Mean pressures were obtained from the pulsatile signal by electrical averaging. Systemic injections were made through a catheter in the femoral vein. The trachea was intubated with a cuffed endotracheal tube and the animals breathed room air enriched with oxygen spontaneously. The techniques used in these experiments were similar to those employed in the dog and have been described in detail previously (9).

After all catheters were positioned and the animals were heparinized (500 units/kg), the balloon on the perfusion catheter was distended with 2 to 4 ml Hypaque until pressure in the perfused lobar artery decreased to near left atrial pressure. The left lower lung lobe was then perfused at controlled flow with a Sarns roller pump (model 3500) with blood withdrawn from the right atrium. The pumping rate averaged 280 ml/min and was not changed during the experiment. A standard lead II electrocardiogram was moni-

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tored on the oscilloscope recorder.

Prostaglandins E_1 and $F_{2\alpha}$, supplied by the Upjohn Co., Kalamazoo, MI, were dissolved in 95% ethyl alcohol (5 mg/ml), and stored in a freezer. An aliquot of the stock solution was withdrawn and diluted to a concentration of 200 μg/ml with physiological saline solution just before being infused into the lobar artery at 0.1 ml/min (20 μg/min) with a Harvard infusion pump. Each animal received a 10 min infusion of both prostaglandins. The order of infusion of the prostaglandin was randomized and all parameters had returned to control value before a second prostaglandin was administered. Responses to PGE_1 and $PGF_{2\alpha}$ were consistent in each animal so that interaction between prostaglandins was not observed. The hemodynamic data were evaluated using methods described by Snedecor (10) for paired and group comparisons. A P value of less than 0.05 was considered significant.

Results. The effects of $PGF_{2\alpha}$ on the pulmonary circulation in the spontaneously breathing swine are summarized in Fig. 1. Direct intralobar artery infusion of $PGF_{2\alpha}$ (20 μg/min) significantly increased lobar arterial perfusion pressure. The onset of the rise was rapid (15–30 sec) and lobar arterial pressure rose rapidly and progressively over the next 5 min. After the peak was reached pressure was well maintained during the rest of the infusion. The maximum increase in lobar pressure averaged 19 ± 5 mm Hg in these experiments. The rise in lobar arterial pressure was accompanied by a significant but smaller rise in pressure in the main pulmonary artery. During the infusion of $PGF_{2\alpha}$ no significant alterations in pressures in the aorta, small lobar vein or left atrium were observed. Pressures in the perfused lobar artery and main pulmonary artery returned toward control value after the prostaglandin infusion was terminated and these pressures were not significantly different from control 20 min after the infusion (Fig. 1).

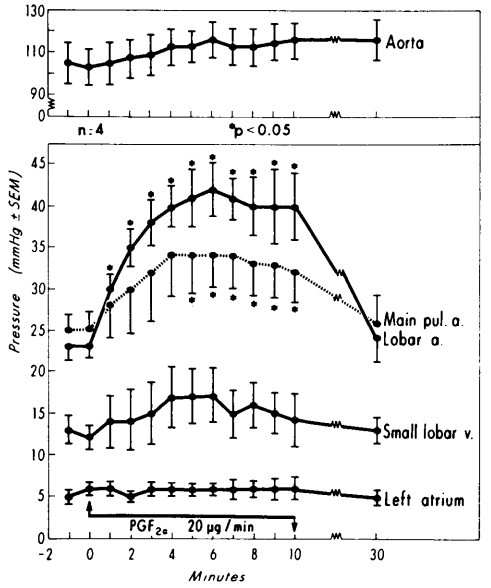

FIG. 1. Effect of $PGF_{2\alpha}$ on vascular pressures in the aorta, main pulmonary artery, perfused lobar artery, small lobar vein and the left atrium in 4 swine. $PGF_{2\alpha}$ was infused directly into the lobar artery at a rate of 20 μg/min for 10 min. Statistical significance was determined by paired comparison.

Infusion of PGE_1 (20 μg/min) directly into the perfused lobar artery caused a significant reduction in lobar arterial perfusion pressure (Fig. 2). The decrease in lobar arterial pressure was gradual and progressive during the 10 min infusion period. The maximum decrease in lobar arterial pressure in these experiments was 6 ± 0.4 mm Hg. During infusion of PGE_1 pressure in the aorta decreased significantly; however, no significant alterations in pressure were observed in the main pulmonary artery, small lobar vein or the left atrium (Fig. 2). Pressures in the perfused lobar artery and aorta returned toward control value after the PGE_1 infusion and these pressures were not significantly different from control 20 min after the termination of the prostaglandin infusion.

Discussion. Results of the present study indicate that $PGF_{2\alpha}$ greatly increases perfusion pressure in the swine left lower lung lobe under conditions of controlled blood flow. Since blood flow was maintained constant by a pump and left atrial pressure did not change, the increase in the lobar arterial pressure reflects an increase in vascular resistance across the perfused lung lobe. The absence of a significant change in the pressure gradient between the small lobar vein and the left atrium suggests that the increase in vascular resistance in response to

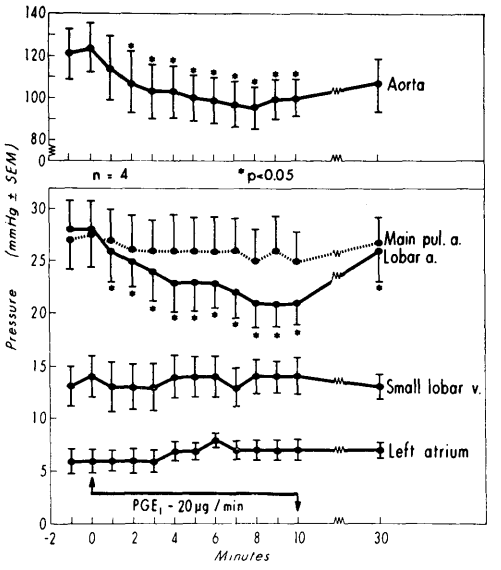

FIG. 2. Effect of PGE_1 on vascular pressures in the aorta, main pulmonary artery, perfused lobar artery, small vein and the left atrium in 4 swine. PGE_1 was infused directly into the lobar artery at a rate of 20 µg/min for 10 min. Statistical significance was determined by paired comparison.

$PGF_{2\alpha}$ was the result of active vasoconstriction in the upstream vessels presumably the lobar arteries. The rise in the main pulmonary arterial pressure during $PGF_{2\alpha}$ infusion might have been the result of vasoconstriction in the naturally perfused lobes, increased blood flow or both.

These data are in accord with other studies in which $PGF_{2\alpha}$ was shown to increase pulmonary vascular resistance in other animal species (1, 2, 7, 11). The present data are in agreement with studies in which the effects of $PGF_{2\alpha}$ were investigated in the dog using a similar right heart catheterization technique (5). However, the dog pulmonary vascular bed was less responsive to $PGF_{2\alpha}$ and in this species the lobar veins were actively constricted by this agent.

The progressive decrease in lobar arterial pressure in the absence of a change in left atrial pressure during PGE_1 infusion indicates that under conditions of controlled blood flow PGE_1 actively dilates the swine pulmonary vascular bed. Since the decrease in lobar arterial pressure was not accompanied by a change in small lobar vein pressure, the decrease in pulmonary vascular resistance was probably due to vasodilation of upstream vessels presumably the lobar arteries. These results are consistent with studies in the isolated rabbit lung and perfused dog lung (4, 5, 12). Although PGE_1 decreased vascular resistance in the swine and canine lung, the effect of this agent on the lobar veins was different (5). In the canine lung PGE_1 dilated both lobar arteries and veins, whereas in the swine this substance dilated only the upstream vessels.

It is possible that changes in the state of lung inflation may influence pulmonary vascular responses to the prostaglandins in the swine since respiration was spontaneous. However this seems unlikely since the prostaglandins caused no consistent change in respiratory rate. Alterations in bronchomotor tone may also influence the response of the lung to these substances; however, studies in the dog indicate that the effects of prostaglandins E_1 and $F_{2\alpha}$ are independent of changes in airway resistance (5). Furthermore, preliminary studies in this laboratory indicate that $PGF_{2\alpha}$ has very little effect on isolated bronchial smooth muscle from the swine.

Summary. The effects of $PGF_{2\alpha}$ and PGE_1 on the swine pulmonary circulation were studied using a new right heart catheterization technique. Infusion of $PGF_{2\alpha}$ into the lobar artery increased lobar arterial pressure but did not change pressures in the small lobar vein or the left atrium. Infusion of PGE_1 into the lobar artery decreased lobar arterial pressure but did not alter pressure in the small lobar vein or the left atrium. These results indicate that under conditions of controlled blood flow in the swine $PGF_{2\alpha}$ increases pulmonary vascular resistance by actively constricting vessels upstream from the small lobar veins. Present results show that PGE_1 decreases pulmonary vascular resistance in this species by actively dilating vessels upstream from small lobar veins, presumably the lobar arteries. It is concluded that in the swine pulmonary circulation the precapillary vessels are very responsive to prostaglandins E_1 and $F_{2\alpha}$.

1. DuCharme, D. W., Weeks, J. R., and Montgomery, R. G., J. Pharmacol. Exp. Ther. **160**, 1 (1968).

2. Nakano, J., and Cole, B., Amer. J. Physiol. **217**, 222 (1969).

3. Giles, T. D., Quiroz, A. C., and Burch, G. E., Experientia **25**, 1056 (1969).

4. Hauge, A., Lunde, P. K. M., and Waaler, B. A., Life Sci. **6**, 673 (1967).

5. Hyman, A. L., J. Pharmacol. Exp. Ther. **165**, 267 (1969).

6. Änggard, E., and Bergström, S., Acta Physiol. Scand. **58**, 1 (1963).

7. Anderson, F. L., Kralios, A. C., Tsagaris, T. J., and Kuida, H., Proc. Soc. Exp. Biol. Med. **140**, 1049 (1972).

8. Douglas, W. R., Space Life Sci. **3**, 226 (1972).

9. Hyman, A. L., Woolverton, W. C., Guth, P. S., and Ichinose, H. J., J. Clin. Invest. **50**, 1028 (1971).

10. Snedecor, G. E., "Statistical Methods," 5th ed. Iowa State Univ. Press, Ames (1956).

11. Said, S. I., Muren, O., and Kirky, B. J., Clin. Res. **16**, 90 (1968).

12. Nakano, J., and Kessinger, J. M., Proc. Soc. Exp. Biol. Med. **133**, 1314 (1970).

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