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Influence of Prostaglandins E_1 and $F_{2\alpha}$ on Pulmonary Vascular Resistance in the Sheep[1] (37992)

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The effects of the prostaglandins on the cardiovascular system in man and experimental animals have been studied extensively in recent years (1, 2). These substances have been shown to produce marked effects upon the circulation although dose and species variation have been observed (1–3). It has been reported recently that the sheep is insensitive to prostaglandins in that doses that produce striking effects in other animal species did not alter systemic arterial blood pressure or heart rate (4). Although the prostaglandins have little or no effect on the systemic circulation in the sheep, to our knowledge nothing is known about their effects on the pulmonary circulation in this species. Since prostaglandins are present in the normal sheep lung and the lung serves as a major organ for inactivation of these lipids (5–7), a study was undertaken to determine the effects of PGE_1 and $PGF_{2\alpha}$ on pulmonary vascular resistance in the intact sheep using a new right heart catheterization procedure.

Methods. Six sheep weighing from 26 to 41 kg were anesthetized with pentobarbital sodium 30–45 mg/kg iv and were strapped to a fluoroscopic table. A specially designed 20F balloon catheter was introduced from the 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 pressure in the perfused lobar artery. Catheters with side holes were passed into the main pulmonary artery and femoral artery and into a small lobar vein and the left atrium transseptally. All pressures were measured with Statham P23D transducers and recorded an oscilloscopic recorder model DR-8 (Electronics for Medicine, Inc., White Plains, N. Y.). 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 sheep breathed room air enriched with oxygen spontaneously. The methods used in these experiments were similar to those employed in the dog and have been described in detail previously (8).

After all catheters were positioned and the animals heparinized (1000 units/kg), the balloon on the perfusion catheter was distended with 2–4 ml Hypaque until pressure in the lobar artery decreased to near left atrial pressure. The left lower lung lobe was then perfused at controlled blood flow with a Sarns roller pump (model 3500) with blood withdrawn from the right atrium. The pumping rate averaged 200 ml/min and was not changed during the experiment. A standard lead II electrocardiogram was recorded on the oscilloscopic recorder.

Prostaglandins E_1 and $F_{2\alpha}$, supplied by the Upjohn Company, Kalamazoo, Michigan, were dissolved in 100% ethyl alcohol, 5 mg/ml, and stored in a freezer. Immediately before use an aliquot of the stock

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solution was diluted to a concentration of 200 μg/ml with saline and infused into the lobar artery at 0.1 ml/min (20 μg/min) with a Harvard infusion pump. After a 20 min equilibration period all 6 animals received an infusion of PGE_1 whereas 5 of the 6 received $PGF_{2\alpha}$. The order of infusion of the prostaglandin was randomized and all vascular parameters had returned to control value before a second prostaglandin was given. Pulmonary vascular responses to the prostaglandins were consistent in each animal so that interaction between prostaglandins was minimal. The period between prostaglandin infusions was at least 60 min in each animal. The hemodynamic data were evaluated using methods described by Snedecor for paired and group comparisons (9).

Results. The effects of $PGF_{2\alpha}$ on vascular pressures in the intact spontaneously breathing sheep are summarized in Fig. 1. Infusion of $PGF_{2\alpha}$, 20 μg/min, directly in the lobar artery increased lobar arterial perfusion pressure. The onset of this pressor effect was rapid and pressure was increased significantly 60 sec after the onset of the infusion. Pressure rose progressively during the first 7 min of the infusion period at which time a peak was reached and pressure was maintained during the final 3 min of the infusion. No significant change in pressure occurred in the small lobar vein, the left atrium, the main pulmonary artery or the aorta during the $PGF_{2\alpha}$ infusion. Pressure in the lobar artery decreased toward control value when the prostaglandin infusion was terminated; however, lobar arterial pressure was significantly greater than control 20 min after the termination of the infusion.

The effects of PGE_1 on the pulmonary circulation in the intact sheep are shown in Fig. 2. Infusion of PGE_1, 20 μg/min directly into the lobar artery decreased lobar arterial perfusion pressure. The onset of the depressor response was rapid and lobar arterial pressure decreased from a control value of 23 ± 2 mm Hg to 16 ± 2 mm Hg, in 4 min and pressure was maintained at this level for the remainder of the infusion. Pressure in the lobar artery returned toward control value after the termination of the prostaglandin infusion and was not significantly different from control 20 min later. During the PGE_1 infusion no significant

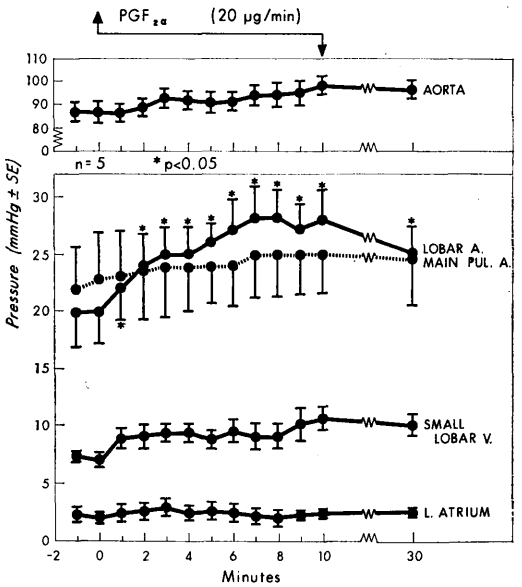

FIG. 1. Effect of $PGF_{2\alpha}$ on vascular pressures in the aorta, main pulmonary artery, perfused lobar artery, small lobar vein and the left atrium in 5 sheep. $PGF_{2\alpha}$ was infused directly into the lobar artery at 20 μg/min for a period of 10 min.

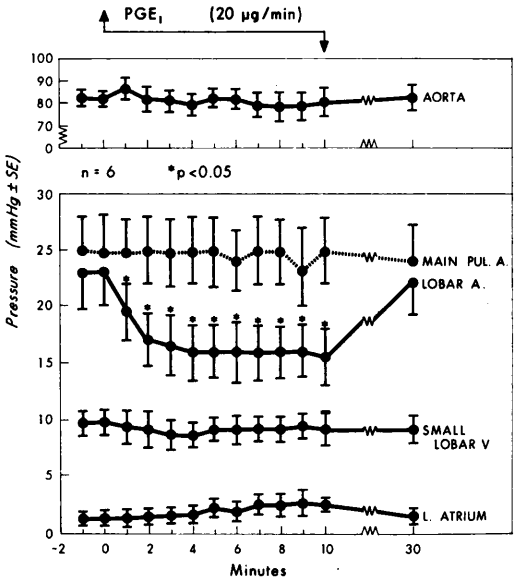

FIG. 2. Effect of PGE_1 on vascular pressures in the aorta, main pulmonary artery, perfused lobar artery, small lobar vein, and the left atrium in 6 sheep. The prostaglandin was infused directly into the lobar artery at 20 µg/min for a period of 10 min.

change in pressure in the main pulmonary artery, small lobar vein, left atrium or the aorta was observed. There was no consistent change in respiratory rate during infusion of either prostaglandin.

Discussion. Results of the present study show that $PGF_{2\alpha}$ increases lobar arterial pressure in the sheep. Since lobar blood flow was maintained constant with a pump and left atrial pressure did not change, the increase in lobar arterial pressure reflects an increase in vascular resistance across the left lower lung lobe. These results are in agreement with other published studies in which $PGF_{2\alpha}$ increased calculated pulmonary vascular resistance in several other animal species (10–13). The present results are consistent with studies in which the effects of $PGF_{2\alpha}$ were investigated in the dog and swine using similar right heart and transseptal catheterization techniques (14, 15). However, the site of vasoconstriction in the lung appears to be different in sheep and dog. In sheep the rise in lobar arterial pressure occurred in the absence of a consistent change in the pressure gradient between the small lobar vein and the left atrium; therefore, vasoconstriction occurred primarily in vessels upstream from the small lobar veins. In canine lungs $PGF_{2\alpha}$ actively constricted lobar veins. The sheep and swine are similar in that in both species $PGF_{2\alpha}$ was without effect on lobar veins, but different in that the effect of this prostaglandin was much greater in swine (15).

The progressive decrease in lobar arterial perfusion pressure in the absence of a change in left atrial pressure indicates that under conditions of controlled blood flow PGE_1 actively dilates the sheep pulmonary vascular bed. Since the decrease in lobar arterial pressure was not accompanied by a change in the pressure gradient from the small lobar vein to the left atrium, the decrease in pulmonary vascular resistance was probably the result of vasodilatation of vessels upstream from small veins. These results are in agreement with studies in the isolated rabbit lung and the intact dog and swine (14–16). Although PGE_1 decreased pulmonary vascular resistance in the dog, swine and sheep, the effects of this lipid on the lobar veins are different in the dog where PGE_1 caused venodilatation but only dilated upstream vessels in the sheep and swine (14, 15).

Since prostaglandins may affect bronchial smooth muscle it is possible that changes in bronchomotor tone may influence the response of the pulmonary vascular bed to these substances. However, the effect of changes in bronchomotor tone are small when compared to the effects of the prostaglandins on pulmonary vascular resistance (17). In addition, studies in the dog indicate that the effects of $PGF_{2\alpha}$ on pulmonary vascular resistance may be independent of changes in airway resistance (18).

Present results which show that the prostaglandins did not alter systemic arterial pressure are consistent with the results of a previous study in which these agents had little effect on blood pressure and heart rate in this species (4). Therefore, it appears that there is a marked difference in the response of the systemic and pulmonary circulations to prostaglandins in the sheep.

Summary. The effects of $PGF_{2\alpha}$ and PGE_1 on pulmonary vascular resistance in the intact sheep were investigated using a new right heart catheterization technique. $PGF_{2\alpha}$ increased lobar arterial pressure but did not change pressures in the small lobar vein or left atrium. PGE_1 decreased lobar arterial pressure but did not alter pressure in the small lobar vein or the left atrium. These results indicate under conditions of controlled blood flow $PGF_{2\alpha}$ increases pulmonary vascular resistance by constricting vessels upstream from the small lobar veins whereas PGE_1 decreases pulmonary vascular resistance by dilating upstream vessels, presumably the lobar arteries. Neither prostaglandin altered systemic arterial pressure. It is concluded that in the sheep lung the precapillary vessels are responsive to prostaglandins E_1 and $F_{2\alpha}$.

1. Bergstrom, S., Carlson, L. A., and Weeks, J. R., Pharmacol. Rev. **20**, 1 (1968).

2. Nakano, J., *in* "The Prostaglandins" (R. W. Ramwell, ed.), Vol. 1, p. 239. Plenum, New York (1973).

3. Weeks, J. R., Annual Rev. Pharmacol. **12**, 317 (1972).

4. Oakes, G., Mofid, M., Brinkman, C. R., and Assali, N. S., Proc. Soc. Exp. Biol. Med. **142**, 194 (1973).

5. Anggard, E., and Bergstrom, S., Acta Physiol. Scand. **58**, 1 (1963).

6. Ferreira, S. H., and Vane, J. R., Nature (London) **216**, 868 (1967).

7. McGiff, J. C., Terragno, N. A., Strand, J. C., Lee, J. B., Lonigro, A. J., and Ng, K. K. F., Nature (London) **223**, 742 (1969).

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

9. Snedecor, G. E., "Statistical Methods," 5th ed. Iowa College Press, Ames, Iowa (1956).

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

11. Nakano, J., and Cole, B., Am. J. Physiol. **217**, 222 (1969).

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

13. Said, S. I., *in* "Prostaglandins Symposium of the Worcester Foundation for Experimental Biology" (R. W. Ramwell and J. E. Shaw, eds.), p. 267, Interscience Publisher, New York (1968).

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

15. Kadowitz, P. J., Joiner, P. D., and Hyman, A. L., Proc. Soc. Exp. Biol. Med. **145**, 53 (1974).

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

17. Daly, I. deB., and Hebb, C., Pulmonary and Bronchial Vascular Systems, p. 158, Edward Arnold Ltd., London (1966).

18. Hyman, A. L., Joiner, P. D., and Kadowitz, P. J., Fed. Proc. Fed. Amer. Soc. Exp. Biol. **32**, 787 (1973).

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