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Differential Effects of Prostaglandins A_1 and A_2 on Pulmonary Vascular Resistance in the Dog[1] (38789)

PHILIP J. KADOWITZ[2] AND ALBERT L. HYMAN

Cardiopulmonary Laboratory, Departments of Pharmacology and Surgery, Tulane University School of Medicine, New Orleans, Louisiana 70112

The prostaglandins are a group of naturally occurring acidic lipids which possess diverse biological activity (1–3). The cardiovascular actions of these compounds have been extensively investigated and in most peripheral vascular beds E and A type prostaglandins are potent vasodilators whereas $PGF_{2\alpha}$ is a weak vasoconstrictor agent (3–8). The effects of PGE_1 and $PGF_{2\alpha}$ on the pulmonary vascular bed have been studied in the swine, lamb and dog and in all three species $PGF_{2\alpha}$ is a potent vasoconstrictor agent whereas PGE_1 is a moderately active vasodilator (9–12). Although the effects of PGA_1 and PGA_2 on the hindlimb, cutaneous, renal, mesenteric and coronary vascular beds have been documented, little is known about the direct effects of these substances on the pulmonary circulation (3–7, 13). The purpose of the present investigation was to study the effects of PGA_1 and PGA_2 on the pulmonary vascular bed under conditions of controlled pulmonary blood flow in the intact dog.

Methods. Seventeen mongrel dogs unselected as to sex weighing 16–23 kg were anesthetized with urethane 1.0 g/kg iv and were strapped in the supine position to a Philip's fluoroscopic table. The trachea was intubated with a cuffed endotracheal tube and the animals spontaneously breathed room air enriched with oxygen. A 20 F double lumen balloon catheter was introduced from the left external jugular vein and positioned in the artery of the left lower lung lobe under fluoroscopic guidance. A 2.0 mm catheter with its tip positioned about 2 cm from the tip of the balloon catheter was used to measure pressure in the lobar artery. Catheters with side holes were passed into the main pulmonary artery and the aorta and into a small intrapulmonary lobar vein and the left atrium transseptally. Precautions were taken to ensure that pressure measurements were made in intrapulmonary veins 2–3 mm in diameter without wedging. These methods have been described in detail previously (14). All vascular pressures were measured with Statham P23D transducers and mean pressures recorded on an oscilloscopic recorder, model DR-8 (Electronics for Medicine, Inc., White Plains, N.Y.). The middle of the right atrium was used as the zero pressure reference for all transducers. After all catheters were positioned and the animals heparinized (500 units/kg iv) the balloon on the perfusion catheter was distended with 2–4 ml Hypaque (sodium diatrizoate, 50% Winthrop Labs) until pressure in the lobar artery and small vein decreased to near left atrial pressure. The left lower lobe was then perfused with a Sarns roller pump (model 3500) with blood withdrawn from the right atrium. The pumping rate was adjusted so that lobar arterial perfusion pressure approximated pressure in the main pulmonary artery and was not changed during the experiment. The pumping rate averaged 345 ml/min in these experiments. A standard lead II electrocardiogram was monitored on the oscilloscopic recorder.

Prostaglandins A_1 and A_2, supplied by the Upjohn Company, Kalamazoo, MI, were dissolved in 100% ethyl alcohol, 5 mg/ml, and stored in a freezer. Immediately before use an aliquot of the stock solution was diluted to a concentration of 1000 μg/ml and infused into the lobar artery at 0.1 ml/min (100 μg/min) with a Harvard infusion pump. The hemodynamic data were evaluated using methods described by Snede-

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[2] Dr. Kadowitz is an established investigator of the American Heart Association.

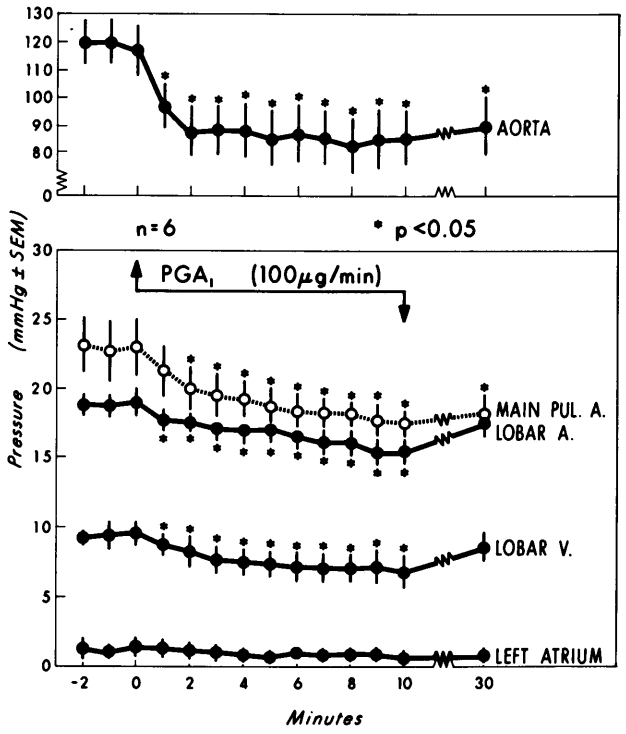

FIG. 1. Effect of PGA_1 on mean vascular pressures in the aorta, the main pulmonary artery, the lobar artery, the lobar vein and the left atrium in the intact spontaneously breathing dog. PGA_1 was infused into the lobar artery at a rate of 100 μg/min for a period of 10 min. n indicates number of dogs studied.

cor and Cochran for paired and group comparisons (15). All values are presented as mean ± SEM and a *P* value of less than 0.05 was considered significant.

Results. The effects of PGA_1 on mean vascular pressures in the intact spontaneously breathing dog are shown in Fig. 1. Infusion of PGA_1, 100 μg/min, into the lobar artery resulted in a significant decrease in lobar arterial pressure. The decrease was rapid in onset and lobar arterial pressure fell gradually during the 10-min infusion period. The fall in pressure in the lobar artery was accompanied by a significant decrease in pressure in the small intrapulmonary lobar vein but no change in pressure in the left atrium. The maximum decrease in pressure in the lobar artery was 3.7 ± 0.3 mmHg whereas the maximum fall in venous pressure was 3.1 ± 0.2 mmHg. During infusion of PGA_1 there was a significant reduction in pressure in the aorta and in the main pulmonary artery. However, there was no significant change in the respiratory rate. Pressures in the lobar artery and vein returned toward control value after the prostaglandin infusion and were not significantly different from control 20 min after infusion. Pressures in the aorta and the main pulmonary artery were significantly lower than control 20 minutes after the infusion.

The effects of PGA_2 on mean vascular pressures were studied in a second group of intact spontaneously breathing dogs and the results of these experiments are summarized in Fig. 2. Infusion of PGA_2, 100 μg/min into the lobar artery resulted in a significant increase in lobar arterial pressure. The onset of this effect was rapid and pressure rose sharply for the first 3 min after which a steady state was reached and pressure was well maintained during the rest of the 10-min infusion period. The rise in lobar arterial pressure was associated with a significant increase in lobar venous pressure. The maximum increase in arterial

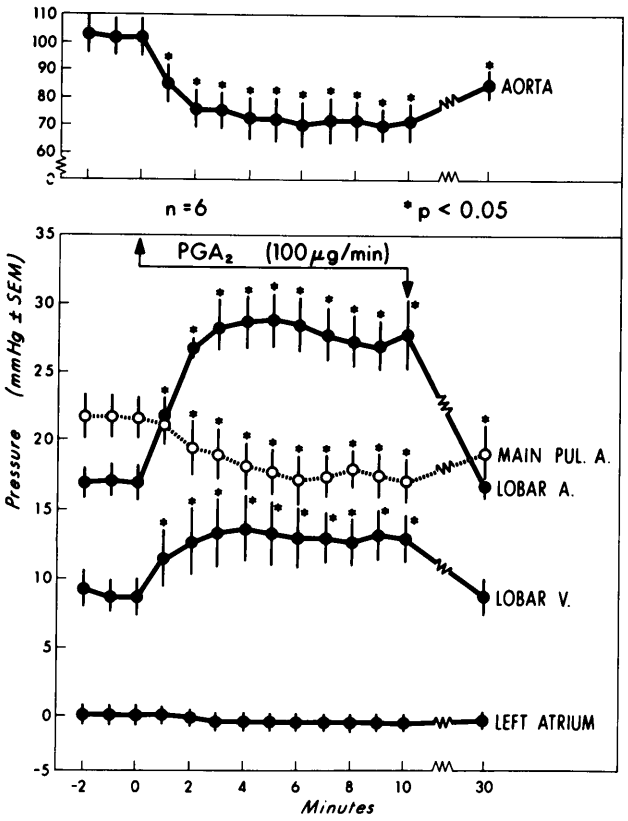

FIG. 2. Effect of PGA_2 on mean vascular pressures in the aorta, the main pulmonary artery, the lobar artery, the lobar vein, and the left atrium in the intact spontaneously breathing dog. PGA_2 was infused into the lobar artery at a rate of 100 μg/min for a period of 10 min. n indicates number of animals studied.

pressure was 10.8 ± 1.3 mmHg whereas the peak increase in venous pressure was 4.3 ± 0.5 mmHg. The maximum rise in lobar arterial pressure was significantly greater than the maximum increase in venous pressure. During infusion of PGA_2 there was a significant decrease in pressure in the aorta and the main pulmonary artery but no change in pressure in the left atrium or in the respiratory rate. All vascular pressures returned toward control value after the infusion and pressure in the lobar artery and vein were not significantly different from control 20 min later. Pressure in the aorta and the pulmonary artery were still significantly lower than control 20 min after infusion. In two other dogs infusion of 20% ethyl alcohol in saline, 0.1 ml/min, into the lobar artery was without effect on vascular pressures in the dog.

In three other animals the effects of PGA_2 were evaluated in experiments in which the left lower lobe was perfused with dextran instead of blood. In these experiments the lung was perfused with low molecular weight dextran warmed to 37° and buffered to pH 7.4 and the perfused dextran was removed from the vein draining the lobe with a transseptally placed 18F withdrawal catheter. During dextran perfusion, infusion of PGA_2, 100 μg/min into the lobar artery produced a significant increase in lobar arterial pressure (Fig. 3). The increase in lobar arterial pressure was not significantly different in experiments in which the lung was perfused with dextran or with blood (Figs. 2 and 3).

Discussion. Results of the present study show that in the intact spontaneously breathing dog PGA_1 decreases lobar arterial pressure when infused into the lobar artery. Since blood flow to the lung was held con-

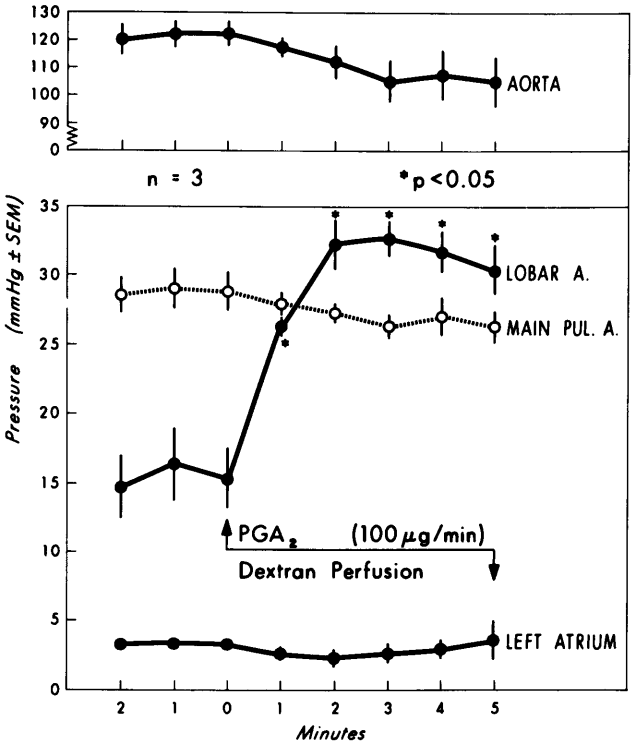

FIG. 3. Effect of PGA_2 on mean vascular pressures in the aorta, the main pulmonary artery, the lobar artery and the left atrium in the dextran perfused lung lobe. The dextran was perfused at a rate of 250 ml/min and removed by way of a transseptally placed withdrawal catheter in the lobar vein. PGA_2 was infused into the lobar artery at a rate of 100 μg/min for 5 min. n indicates number of dogs tested.

stant by a pump and left atrial pressure did not change, the decrease in pressure reflects a decrease in resistance to flow in the lung. The fall in lobar arterial pressure was associated with a slightly smaller decrease in pressure in the small intrapulmonary lobar vein. These data suggest that the decrease in resistance was the result of vasodilatation in the intrapulmonary veins and to a lesser extent in vessels upstream to small veins, presumably small arteries. In contrast, PGA_2, which differs only in a side chain double bond, increased lobar arterial pressure when infused into the lobar artery. The rise in lobar arterial pressure was associated with a smaller rise in venous pressure but no change in left atrial pressure. These data suggest that in the intact dog PGA_2 increases pulmonary vascular resistance by constricting intrapulmonary lobar veins and vessels upstream to small veins presumably small arteries. However, the predominant effect appeared to be on upstream vessels since the increase in gradient from lobar artery to small vein was much greater than the increase in gradient from small vein to left atrium. PGA_1 and PGA_2 are not rapidly inactivated in the lung and infusion of these substances into the lobar artery resulted in a significant decrease in pressure in the aorta and the main pulmonary artery. Although the effects of PGA_2 on pressure in the perfused lobar artery and main pulmonary artery are different, the effects of this substance in the normally perfused lung lobes are uncertain since blood flow to these lobes was not measured in these experiments.

The effects of PGA_2 were similar in experiments in which the lung was perfused with dextran or with blood so that the pressor response was not the result of platelet aggregation or release of vasoactive substances from elements in blood.

Results of the present study in the pulmonary vascular bed are in agreement with most studies in the peripheral vascular bed in which PGA_1 was found to be a vasodilator agent (3, 4, 6, 13). However, the effects of PGA_2 on the pulmonary and peripheral vascular beds are different. Although PGA_2 is a potent peripheral dilator (3, 5), in the pulmonary vascular bed it is a pressor substance. The reason for the apparent difference in the peripheral and pulmonary circulation is unknown. However, several other endogenous substances, such as bradykinin, histamine and acetylcholine, are similar to PGA_2 in that they are pulmonary vasoconstrictors and peripheral vasodilators (16–18). The effects of A type prostaglandins are of interest since these substances are more resistant to pulmonary inactivation than E and F type prostaglandins and may serve as circulating hormones (19–21). In addition, these agents are relatively free of stimulatory activity on nonvascular smooth muscle and have been used with some success in the treatment of essential hypertension (22).

Summary. The effects of PGA_1 and PGA_2 were studied in the canine pulmonary vascular bed. Infusion of PGA_1 into the lobar artery decreased lobar arterial and venous pressure but did not change left atrial pressure. In contrast, PGA_2 infusion increased lobar arterial and venous pressure and the effects of this substance were similar in experiments in which the lung was perfused with dextran or with blood. These data indicate that under conditions of controlled blood flow PGA_1 decreases pulmonary vascular resistance by dilating intrapulmonary veins and to a lesser extent vessels upstream to the small veins, presumably small arteries. The present data show that PGA_2 increases pulmonary vascular resistance by constricting intrapulmonary veins and upstream vessels. The predominant effect of PGA_2 was on upstream vessels and the pressor effect was not due to interaction with formed elements in blood or platelet aggregation.

1. Bergstrom, S., Carlson, L. A., and Weeks, J. R., Pharmacol. Rev. **20**, 1 (1968).
2. Weeks, J. R., Ann. Rev. Pharmacol. **12**, 317 (1972).
3. Nakano, J., in "The Prostaglandins", p. 23, J. B. Lippincott Co., Philadelphia (1972).
4. Higgins, C. B., Vatner, S. F., and Braunwald, E., Amer. Heart J. **85**, 349 (1973).
5. Kadowitz, P. J., Brit. J. Pharmacol. **46**, 395 (1972).
6. Kadowitz, P. J., Sweet, C. S., and Brody, M. J., J. Pharmacol. Exp. Ther. **179**, 563 (1971).
7. Kadowitz, P. J., Sweet, C. S., and Brody, M. J., J. Pharmacol. Exp. Ther. **176**, 167 (1971).
8. Greenberg, R. A, and Sparks, H. V., Amer. J. Physiol. **216**, 567 (1969).
9. Hyman, A. L., J. Pharmacol. Exp. Ther. **165**, 267 (1969).
10. Kadowitz, P. J., Joiner, P. D., and Hyman, A. L., Proc. Soc. Exp. Biol. Med. **145**, 1258 (1974).
11. Kadowitz, P. J., Joiner, P. D., and Human, A. L., Proc. Soc. Exp. Biol. Med. **145**, 53 (1974).
12. Kadowitz, P. J., Joiner, P. D., Hyman, A. L., and George, W. J., J. Pharmacol. Exp. Ther. **192**, 677 (1975).
13. Nakano, J., Proc. Soc. Exp. Biol. Med. **127**, 1160 (1968).
14. Hyman, A. L., J. Appl. Physiol. **27**, 179 (1969).
15. Snedecor, G. W. and Cochran, W. G. "Statistical Methods", 6th edition. The Iowa State University Press, Ames, Iowa, 1967.
16. Hauge, A., Lunde, P. K. M., and Waaler, B. A., Acta Physiol. Scand. **66**, 269 (1966).
17. Hyman, A. L., J. Pharmacol. Exp. Ther. **161**, 78 (1968).
18. Hyman, A. L., J. Pharmacol. Exp. Ther. **168**, 96 (1969).
19. 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).
20. Piper, P. J., Vane, J. R., and Wyllie, J. H., Nature (London) **225**, 600 (1970).
21. Ferreira, S. H., and Vane, J. R., Nature (London) **216**, 868 (1967).
22. Westura, E. E., Kannegiesser, H., O'Toole, J. D., and Lee, J. B., Circ. Res. **18**, (Suppl 1) 1, (1970).

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