PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 149, 356–361 (1975)

Comparison of the Effects of Prostaglandins $F_{1\alpha}$, $F_{2\alpha}$, $F_{1\beta}$, and $F_{2\beta}$ on the Canine Pulmonary Vascular Bed[1] (38807)

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The prostaglandins are a group of closely related naturally occurring acidic lipids which possess diverse biological activity (1–3). The effects of the prostaglandins on the peripheral circulation have been studied extensively and in most peripheral vascular beds E series prostaglandins are potent vasodilators whereas F type prostaglandins are weak vasoconstrictor agents (3–8). In the canine pulmonary vascular bed PGE_1 is a moderately active vasodilator whereas PGE_2 is a weak vasoconstrictor agent (9–11). In contrast $PGF_{2\alpha}$ is one of the most potent pressor substances known in the canine pulmonary vascular bed, and infusion rates which establish concentrations of less than 9 ng/ml in lobar arterial blood increase pulmonary vascular resistance by more than 100% (9, 10). Although the effects of $PGF_{2\alpha}$ on the pulmonary vascular bed have been documented, nothing is known about the direct effects of $PGF_{1\alpha}$, $PGF_{1\beta}$, and $PGF_{2\beta}$ on the pulmonary circulation. The purpose of the present investigation was to compare the effects of $PGF_{1\alpha}$, $PGF_{1\beta}$, $PGF_{2\alpha}$, and $PGF_{2\beta}$ on the canine pulmonary vascular bed under conditions of controlled blood flow in the intact spontaneously breathing dog.

Methods. Thirty-five mongrel dogs (16–25 kg) were anesthetized with pentobarbital sodium (30 mg/kg iv) and were strapped in the supine position to a Philips fluoroscopic table. The trachea was intubated with a cuffed endotracheal tube and the animals spontaneously breathed room air. A specially designed 20F double-lumen balloon catheter was positioned in the artery of the left lower lung lobe from the external jugular vein under fluoroscopic guidance (Philips 6-in. intensifier). A Teflon catheter with its tip positioned 2 cm distal to the balloon catheter was used to measure perfusion pressure in the lobar artery. Catheters with side holes near the tip were passed into the main pulmonary artery and the aorta and into a small pulmonary lobar vein and the left atrium transseptally. Precautions were taken to ensure that pressure measurements were made in lobar veins 2–3 mm in diameter without wedging. Briefly, a 0.9-mm-diameter Teflon catheter was passed through a 3-mm catheter that had been previously wedged in a small intrapulmonary vein. The 0.9-mm catheter was then withdrawn 1–3 cm from the wedge position until pressure dropped abruptly. The 0.9-mm catheter was then fixed in position with a Cope adaptor after the larger catheter had been withdrawn to the left atrium. After injection of 1–2 ml Hypaque (sodium diatrizoate, 50% Winthrop Labs) into the 0.9-mm catheter, the contrast media passed upstream initially and then passed rapidly to the left atrium. In addition, after injection into the lobar artery, no delay was seen in passage of the contrast media downstream in the area of the vein in which the 0.9-mm catheter was positioned. The catheter positions and methods have been described in detail (12).

All vascular pressures were measured with Statham P23D transducers, and mean pressures were recorded on an oscilloscopic recorder model DR-8 or DR-12 (Electronics for Medicine, Inc., White Plains, NY). 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) the balloon on the perfusion catheter

[1] Supported by U.S. Public Health Service Grants HL 15580 and HL 11802 and a grant from the American Heart Association.

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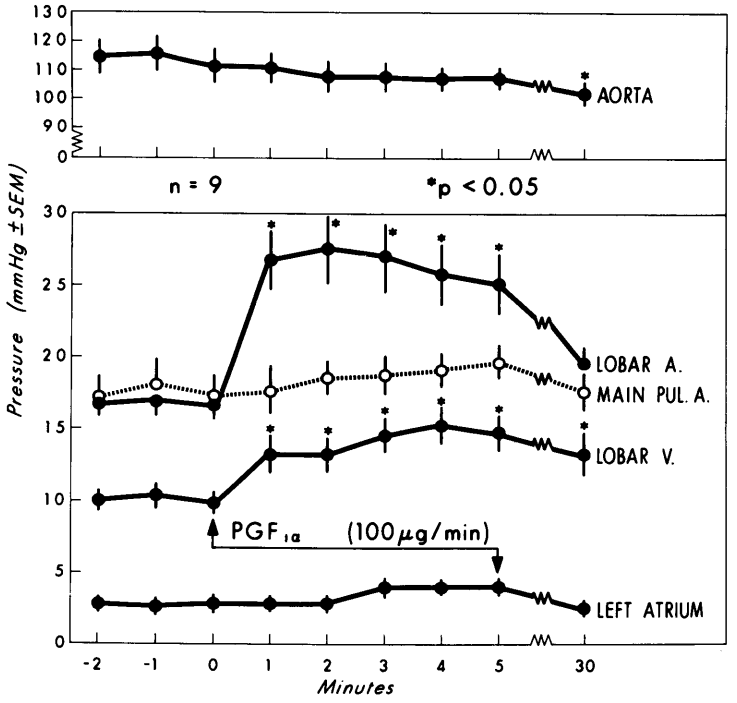

FIG. 1. Effect of infusion of $PGF_{1\alpha}$, 100 μg/min, into the lobar artery on mean vascular pressures in the lobar artery, the small intrapulmonary lobar vein, the left atrium, the main pulmonary artery, and the aorta. The prostaglandin was infused for a period of 5 min. n indicates number of dogs studied.

was distended with 2–4 ml Hypaque until pressure in the lobar artery and small vein decreased to near left atrial pressure. The vascularly isolated 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 pressure approximated pressure in the main pulmonary artery and was not thereafter changed. The pumping rate averaged 350 ml/min in these experiments. A standard lead II electrocardiogram was monitored on the oscilloscopic recorder. Prostaglandins $F_{1\alpha}$, $F_{2\alpha}$, $F_{1\beta}$, and $F_{2\beta}$ were dissolved in 100% ethanol 5 mg/ml and stored in a freezer. On the day of use, an aliquot of the stock solution was diluted to a concentration of 0.5 mg/ml with saline and infused into the lobar artery at 0.2 ml/min (100 μg/min) with a Harvard infusion pump. All data are presented as mean ± SE and were evaluated using methods described by Snedecor and Cochran (13) for group and paired comparison. A P value of less than 0.05 was considered significant.

Results. The effects of infusion of equivalent concentrations of four prostaglandins of the F series were compared in four groups of intact spontaneously breathing dogs. Infusion of $PGF_{1\alpha}$, 100 μg/min, into the lobar artery resulted in a significant increase in lobar arterial pressure (Fig. 1). The rise in pressure was maximal within 1 min. This pressor effect began to decrease past the second minute of infusion and showed a significant decrease by the fifth minute. The rise in lobar arterial pressure was accompanied by a significant rise in pressure in the small intrapulmonary lobar vein but no change in pressure in the left atrium. During infusion of $PGF_{1\alpha}$ there was no significant change in pressure in the aorta or the main pulmonary artery or in the respiratory rate. Pressure in the lobar artery returned to 50% of control value within 5 min whereas pressure in the small vein was still significantly greater than control

25 min after infusion. The effects of $PGF_{1\alpha}$ on mean pressure gradients in the lung are summarized in Table I. During infusion of $PGF_{1\alpha}$ there was a significant increase in the pressure gradient from the lobar artery to the lobar small vein and fro them small vein to the left atrium.

TABLE I. EFFECT OF $PGF_{1\alpha}$ AND $PGF_{2\alpha}$ ON MEAN PRESSURE GRADIENTS IN THE CANINE PULMONARY VASCULAR BED.

	Lobar artery to left atrium	Lobar artery to lobar vein	Lobar vein to left atrium
		mm Hg ± SEM	
Control	13.9±1.3	6.9±0.8	7.0±0.7
$PGF_{1\alpha}$ $n = 9$	24.8±2.6*	14.3±2.4*	10.4±1.0*
Control	16.3±1.9	8.8±1.9	7.5±0.4
$PGF_{2\alpha}$ $n = 6$	33.2±3.5*	14.5±2.6*	18.7±1.9*

* Significantly different from corresponding ontrol ($P < 0.05$, paired comparison).

In a second group of dogs infusion of $PGF_{2\alpha}$, 100 μg/min, into the lobar artery resulted in a marked rise in lobar arterial pressure (Fig. 2). The onset was rapid and pressure rose sharply during the first minute of the infusion period after which a steady state was reached and maintained during the 5-min infusion period. The rise in lobar arterial pressure was accompanied by a significant rise in lobar venous pressure but no change in left atrial pressure. During the infusion of $PGF_{2\alpha}$ there was a significant increase in mean gradient between the lobar artery and the small vein and between the small vein and the left atrium (Table I). During the $PGF_{2\alpha}$ infusion there was no significant change in pressure in the aorta and the main pulmonary artery or in the respiratory rate. After the infusion pressures

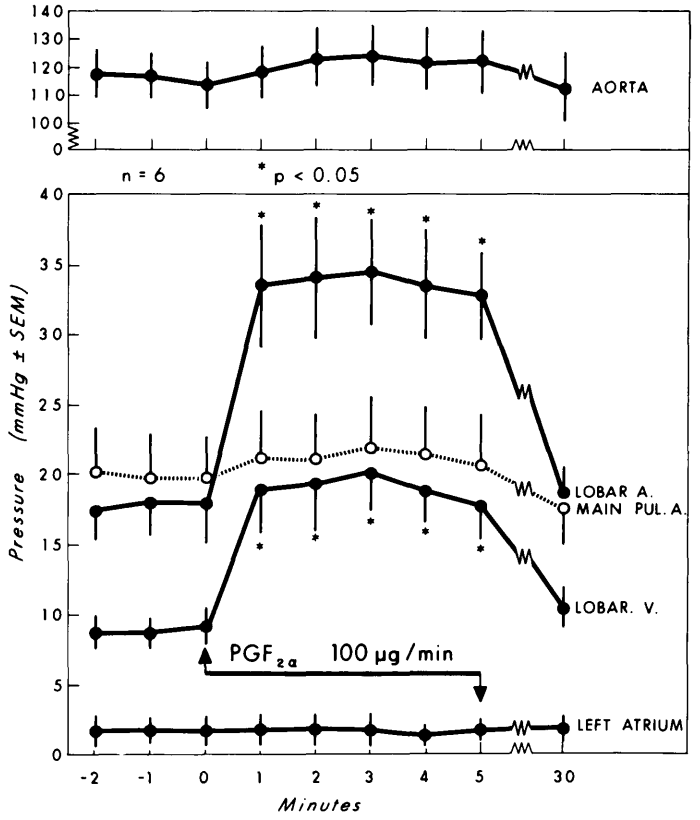

FIG. 2. Effect of infusion of $PGF_{2\alpha}$, 100 μg/min, into the lobar artery on mean vascular pressures in the dog. The prostaglandin was infused for a period of 5 min. n indicates number of dogs studied.

in the lobar artery and vein returned to 50% of control value within 8 min and were not significantly different from control 25 min after the infusion.

The effects of $PGF_{1\beta}$ and $PGF_{2\beta}$ were studied in two other groups of dogs. Infusion of $PGF_{1\beta}$, 100 μg/min, into the lobar artery, caused a very small but significant increase in lobar arterial pressure but was without significant effect on pressure in the lobar vein, the left atrium, the main pulmonary artery, or the aorta (Fig. 3). $PGF_{2\beta}$, 100 μg/min, into the lobar artery was without significant effect on pressure in the lobar artery and vein, the left atrium, or the main pulmonary artery (Fig. 3). During infusion of $PGF_{2\beta}$ there was a significant decrease in pressure in the aorta (Fig. 3). In three other dogs, infusion of 10% ethanol, 0.2 ml/min, the vehicle for the prostaglandins, into the lobar artery was without significant effect on pressure in the lobar artery and vein, the aorta, the main pulmonary artery, and the left atrium.

Discussion. In previous studies from this laboratory $PGF_{2\alpha}$ was found to increase pulmonary vascular resistance in the intact dog, swine, and lamb (9, 10, 14, 15). In the present investigation the effects of equivalent doses of four prostaglandins of the F series, were compared in the canine pulmonary vascular bed under conditions of controlled pulmonary blood flow. Results of the present study show that $PGF_{1\alpha}$ and $PGF_{2\alpha}$ increase lobar arterial pressure whereas $PGF_{1\beta}$ and $PGF_{2\beta}$ possessed little if any effect when infused into the lobar artery. Since blood flow to the lung was held constant and left atrial pressure did not change, the increase in lobar pressure in response to $PGF_{1\alpha}$ and $PGF_{2\alpha}$ reflects an increase in pulmonary vascular resistance. These data indicate that in the pulmonary vascular bed the configuration of the hydroxyl group at carbon 9 is an important determinant of pressor activity whereas a change in number of side-chain double bonds only modifies the activity slightly. Although $PGF_{2\alpha}$ and $PGF_{1\alpha}$ are only weak pressor substances in the peripheral vascular bed, activity here also appears to be dependent on the configuration of the 9 hydroxyl group since $PGF_{1\beta}$ was without significant pressor activity (3, 4).

The increase in lobar arterial pressure with $PGF_{1\alpha}$ and $PGF_{2\alpha}$ was accompanied by a rise in pressure in the small intrapulmonary lobar vein. Analysis of mean pressure gradients across the lung show that both agents increase the gradient from lobar artery to small vein and from the small vein to the left atrium. The peak increase in total gradient (lobar artery to left atrium) occurred 2–3 min after onset of infusion and reflected an increase in pulmonary vascular resistance of 78% and 104%, respectively. In response to $PGF_{1\alpha}$ the upstream gradient was more than doubled whereas resistance in the venous segments increased by 49%. These data suggest that $PGF_{1\alpha}$ increases pulmonary vascular resistance in the dog by constricting lobar veins and vessels upstream to the small veins but that the predominant effect was on the upstream vessels, presumed to be small arteries. In contrast, $PGF_{2\alpha}$ increased the upstream gradient by 65% whereas resistance to flow in the venous segments was more than doubled. These results indicate that $PGF_{2\alpha}$ increases pulmonary vascular resistance by constricting lobar veins and upstream vessels but the predominant effect was on the venous segments.

In addition to constricting the canine pulmonary vascular bed, $PGF_{2\alpha}$ is a bronchoconstrictor agent in this species (10). However, the effects of this substance on the vascular bed appear to be independent of its action on the airways since the pressor response was similar in normal and nonrespiring lung lobes (10).

The role of the prostaglandins in the regulation of the pulmonary vascular bed is uncertain although the capacity of the organ to synthesize these lipids is equal to the renal medulla and surpassed only by the seminal vesicle (16–19). In addition, it has been reported that PGE_2 and $PGF_{2\alpha}$ are released from the lung by a variety of physiologic and pathophysiologic stimuli including distention, hyperinflation, anaphylaxis, pulmonary embolization, and alveolar hypoxia (20–24). In addition to synthesis and release, the lung is an important

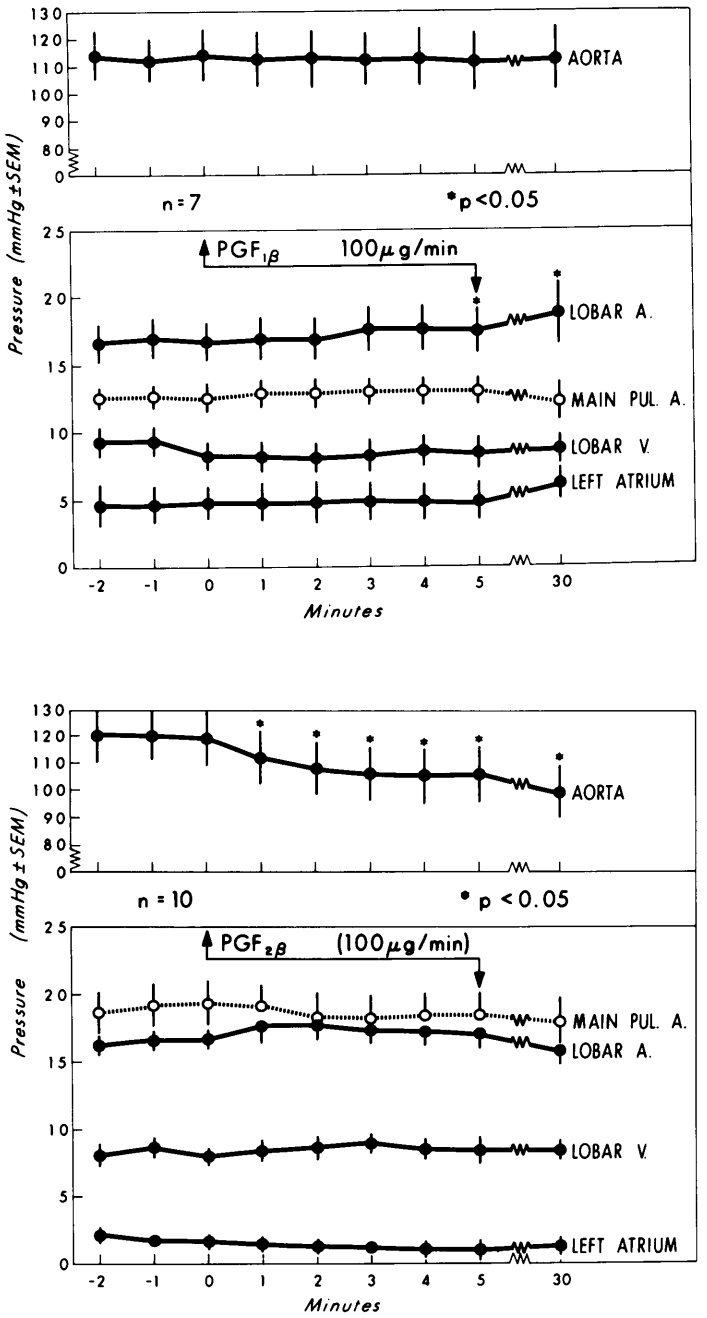

FIG. 3. Influence of infusion of $PGF_{1\beta}$, top and $PGF_{2\beta}$ bottom panel, 100 μg/min, on mean vascular pressures in the lobar artery, the small intrapulmonary lobar vein, the left atrium, the main pulmonary artery, and the aorta. The prostaglandin was infused for a period of 5 min. n indicates number of dogs studied in each series.

organ for metabolism of these substances and E and F series prostaglandins are rapidly inactivated in the lung (25–27). Although the role of the prostaglandins remains speculative, their synthesis and release along with their marked activity may suggest an important role in the regulation of the pulmonary circulation. Pre-

liminary studies in this laboratory with inhibitors of prostaglandin synthesis suggest that the intrapulmonary generation of prostaglandins may serve to maintain the pulmonary vascular bed in a dilated state under resting conditions.

In summary, the effects of four F series prostaglandins on the pulmonary vascular bed were compared under conditions of controlled pulmonary blood flow in the intact spontaneously breathing dog. $PGF_{1\alpha}$ and $PGF_{2\alpha}$ increased lobar arterial pressure whereas $PGF_{1\beta}$ and $PGF_{2\beta}$ had little if any effect when infused into the lobar artery. The increase in lobar arterial pressure in response to $PGF_{1\alpha}$ and $PGF_{2\alpha}$ was associated with a significant increase in lobar venous pressure but no change in left atrial pressure. These data indicate that $PGF_{1\alpha}$ and $PGF_{2\alpha}$ increase pulmonary vascular resistance by constricting lobar veins and vessels upstream to small veins, presumed to be small arteries. It is concluded that in the pulmonary vascular bed the configuration of the hydroxyl group at carbon 9 is an important determinant of pressor activity.

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Received: Oct. 21, 1974. P.S.E.B.M., 1975, Vol. 149.