Effects of the 15-methyl analogs of prostaglandins E2 and F2alpha on the pulmonary circulation in the intact dog.

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Research Article

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Effects of the 15-Methyl Analogs of Prostaglandins E_2 and $F_{2\alpha}$ on the Pulmonary Circulation in the Intact Dog

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ABSTRACT The effects of the 15-methyl analogs of prostaglandins E_2 (PGE_2) and $F_{2\alpha}$ ($PGF_{2\alpha}$) on the pulmonary circulation were studied in the intact dog under conditions of controlled blood flow. Infusions of either analog into the lobar artery increased lobar arterial pressure by more than 100%. The rise in lobar arterial pressure was accompanied by a rise in lobar venous pressure and in pressure gradient from lobar artery to small vein but no change in pressure in the left atrium. The methyl analogs were about 10 times more potent than PGE_2 and $PGF_{2\alpha}$ in elevating pulmonary vascular resistance in the dog. The effects of the analogs on the pulmonary vascular bed were similar in experiments in which the lung was perfused with dextran or with blood. Both analogs contracted isolated helical segments of canine intrapulmonary artery and vein in a dose-related manner. In other experiments the effects of passive increases in venous pressure produced by distension of a balloon catheter in the lobar vein were contrasted with the action of the analogs on the pulmonary vascular bed. Balloon distension increased pressure in the lobar artery and small vein but had no effect on pressure in the left atrium. However, in contrast to the increase in gradient with the analogs, balloon distension decreased the pressure gradient from lobar artery to small vein. Results of the present study indicate that the prostaglandin analogs increase pulmonary vascular resistance by actively constricting pulmonary veins and vessels upstream to small veins, presumed to be small arteries. It is concluded that the analogs are potent pressor substances in the pulmonary circulation.

INTRODUCTION

The prostaglandins are a group of naturally occurring lipids which are formed in most organs from essential fatty acid precursors by a microsomal enzyme complex (1–5). Prostaglandins E_2 (PGE_2)[1] and $F_{2\alpha}$ ($PGF_{2\alpha}$) are released from the lung by a variety of physiologic and pathophysiologic stimuli including hypoxia, anaphylaxis, hyperinflation, embolization, and pulmonary edema (6–10). In addition to synthesis and release the lung is a major organ for metabolism, and E and F series prostaglandins are rapidly inactivated in the lung by the enzyme prostaglandin dehydrogenase (11–17). Methylation of PGE_2 and $PGF_{2\alpha}$ has been shown to inhibit their inactivation and increase their antifertility and abortifacient activity 50–100 times (18–22). The 15-methyl analogs are undergoing clinical trials for induction of midtrimester abortion and 15-methyl-$PGF_{2\alpha}$ has been reported to cause shortness of breath and marked increases in pulmonary arterial pressure (23).

The purpose of the present investigation was to study the effects of the 15-methyl analogs of PGE_2 and $PGF_{2\alpha}$ on the pulmonary circulation in the intact spontaneously breathing dog under conditions of controlled blood flow. In addition, the effects of the methyl analogs and the natural prostaglandins were compared on the canine pulmonary vascular bed.

METHODS

61 mongrel dogs of either sex weighing 17–24 kg were anesthetized with pentobarbital sodium (30 mg/kg i.v.) and

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[1] *Abbreviations used in this paper:* PGE_2 prostaglandin E_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$.

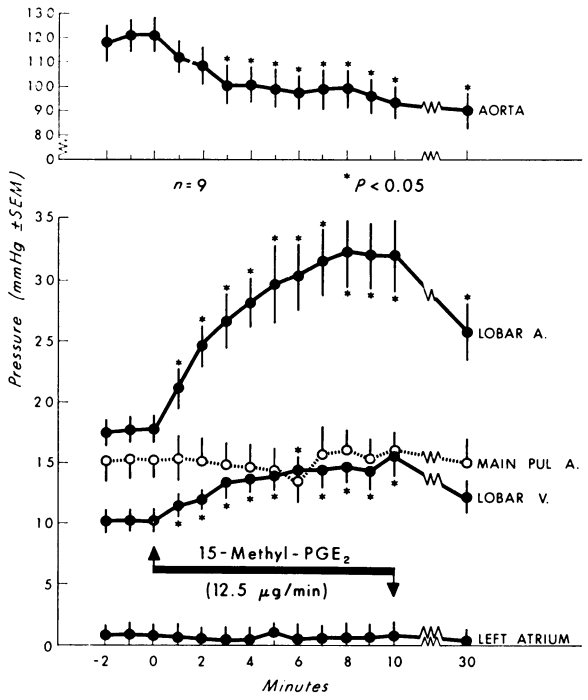

FIGURE 1 Effects of infusion of 15-methyl-PGE_2, 12.5 μg/min, into the lobar artery on mean pressures in the lobar artery, small intrapulmonary vein, left atrium, main pulmonary artery, and the aorta. *n* indicates number of dogs tested.

were strapped to a fluoroscopic table. A specially designed 20F balloon catheter was positioned in the artery of the left lower lobe under fluoroscopic guidance. A Teflon catheter with its tip positioned about 2 cm distal to the balloon was used to measure pressure in the perfused lobar artery. Catheters with side holes near the tip 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 lobar veins 2–3 mm in diameter without wedging. These methods have been described in detail and validated previously (24, 25).

All vascular pressures were measured with Statham P23D transducers (Statham Instruments, Inc., Oxnard, Calif.) zeroed at midchest level and were recorded on an oscilloscopic recorder, model DR-12 (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 a femoral vein. The trachea was intubated with a cuffed endotracheal tube, and the animals spontaneously breathed room air or room air enriched with oxygen.

After all catheters were positioned and the animals heparinized (500 U/kg), the balloon on the perfusion catheter was distended with 2–4 ml Hypaque®, sodium diatrizoate, 50% (Winthrop Laboratories, New York) until pressure in the lobar artery and intrapulmonary lobar vein decreased to near left atrial pressure. The vascularly isolated left lower lung lobe was then autoperfused with a Sarns roller pump (model 3500, Sarns, Inc., Ann Arbor, Mich.) with blood withdrawn from the right atrium. The pumping rate was adjusted so that pressure in the perfused lobar artery approximated pressure in the main pulmonary artery and thereafter was not changed during the course of the experiment. The pumping rate ranged from 190 to 450 ml/min. A standard lead II electrocardiogram was recorded on the Electronics for Medicine recorder.

In experiments in which the effects of passive increases in venous pressure were evaluated, an 8F Dotter-Lukas balloon catheter was passed transseptally into the left atrium from a jugular vein and positioned in the vein draining the left lower lobe. Lobar venous pressure was elevated by slowly distending the balloon with Hypaque®. These experiments permitted us to evaluate the effects of changes in venous pressure on pressure gradients across the left lower lobe under conditions of controlled blood flow in the intact spontaneously breathing dog.

Prostaglandins (15S)-15-methyl-PGE_2 methyl ester, (15S)-15-methyl-$PGF_{2\alpha}$, $PGF_{2\alpha}$, and PGE_2, supplied by The Upjohn Company, Kalamazoo, Mich., were dissolved in 100% ethyl alcohol, 2.5 mg/ml, and stored in the freezer. These solutions were diluted in saline and infused into the lobar artery in volumes of 0.1–0.2 ml/min with a Harvard Infusion Pump (Harvard Apparatus Co., Inc., Millis, Mass.). Infusion of the saline-alcohol vehicle for the prostaglandins into the lobar artery was without effect on pressure in the lobar artery, the small vein, the left atrium, the main pulmonary artery, and the aorta.

For studies in isolated lobar vessels, mongrel dogs weighing 15–25 kg were anesthetized with pentobarbital (30 mg/kg i.v.) and were sacrificed by bleeding. Lung lobes were removed quickly and segments of lobar artery and vein 3–5 mm in diameter were isolated and carefully cleaned of surrounding tissue. The vessels were used immediately or stored overnight at 4°C in physiologic salt solution. Responses to prostaglandins and other standard agonists were similar in fresh and cold stored vessels. The physiologic salt solution contained 125 mM NaCl, 2.7 mM KCl, 1.8 mM $CaCl_2$, and 11 mM glucose. The solution was vigorously bubbled with 100% oxygen and buffered at pH 7.4 with HCl and THAM® (Trizma® base buffer, Sigma Chemical Co., St. Louis, Mo.), 23.8 mM. Helical segments of artery and vein 5–10 mm wide were mounted in 15-ml baths. One end of the segment was fastened to a stainless steel hook and the other to a Grass force-displacement transducer (model FT 03, Grass Instrument Co., Quincy, Mass.). The strips were bathed in physiologic saline solution, bubbled with oxygen, and maintained at 37°C. The stretching force was 4 g for arteries and 3 g for veins. The vessels were allowed to equilibrate for 2 h before exposure to the prostaglandins. Dose-response curves were determined in a cumulative manner. In these experiments the prostaglandin stock solutions were diluted with distilled water. The volume of vehicle added to the bath did not exceed 4% of bath volume and had no effect on resting tension or response to standard agonists.

All data are presented as mean±SE and were calculated by using methods described by Snedecor and Cochran for group and paired comparison (26). The criterion for significance was a P value of less than 0.05.

RESULTS

Effects of the 15-methyl analogs on the pulmonary circulation. The effects of 15-methyl-PGE_2 on the canine pulmonary vascular bed are shown in Fig. 1. Infusion of the analog into the lobar artery at a rate of

TABLE I

Influence of 15-Methyl-PGE$_2$ and 15-Methyl-PGF$_{2\alpha}$ on Pressure Gradients in the Lung

	Gradient			
	Control	15-Methyl-PGE$_2$	Control	15-Methyl-PGF$_{2\alpha}$
		mm Hg±SEM		
Lobar artery-lobar small vein	7±1	17±2*	10±2	21±4*
Lobar small vein-left atrium	9±1	14±2*	8±1	17±1*
Lobar artery-left atrium	17±1	31±3*	18±2	38±4*
Infusion rate, *μg/min*		12.5		12.5
n		9		6

* Significantly different from corresponding control, $P < 0.05$.

12.5 μg/min resulted in a significant rise in lobar arterial pressure. The onset was rapid (15–30 s) and pressure rose in a progressive manner for the first 8 min of the infusion. The rise in pressure in the lobar artery was accompanied by a significant rise in pressure in the small intrapulmonary vein but no change in pressure in the left atrium or the main pulmonary artery. During infusion of the analog there was a decrease in aortic pressure and a marked increase in pressure gradient from the lobar artery to the small vein and from the small vein to the left atrium (Table I). There was little tendency for pressure in the lobar artery and the aorta to return to control values whereas venous pressure was not different from control 20 min after the infusion.

The influence of 15-methyl-PGF$_{2\alpha}$ on the pulmonary vascular bed was examined in a second group of intact spontaneously breathing dogs. Infusion of the analog into the lobar artery at 12.5 μg/min resulted in a marked increase in lobar arterial pressure (Fig. 2). The onset was rapid (10–25 s) and pressure rose in a sharp step-like manner. The peak increase was attained in 2–3 min, after which pressure was well maintained during the rest of the 10-min infusion. The rise in lobar arterial pressure was associated with a marked increase in lobar venous pressure but no change in pressure in the left atrium or the aorta. During infusion of 15-methyl-PGF$_{2\alpha}$ there was a marked increase in pressure in the main pulmonary artery and in gradient from lobar artery to lobar small vein and from small vein to left atrium (Table I). After infusion of the analog, pressure in the main pulmonary artery, the lobar artery, and the lobar vein returned toward preinfusion value and pressure in the vein was not different from control 20 min later.

Comparison of relative potency of the analogs and natural prostaglandins in the pulmonary vascular bed.

The relative potency of the analogs and natural compounds in increasing pulmonary vascular resistance was estimated by comparing dose-response curves for these substances in the intact dog. The dose-response curves for PGF$_{2\alpha}$ and its methyl analog were parallel in the range of concentration evaluated. Pulmonary vascular resistance was increased 50% at an infusion rate of 3 μg/min with the analog whereas 30 μg/min was required for PGF$_{2\alpha}$ (Fig. 3). Therefore, the analog was about 10 times more potent than the natural prostaglandin. Dose-response curves for PGE$_2$ and its analog were not parallel, making comparisons difficult. How-

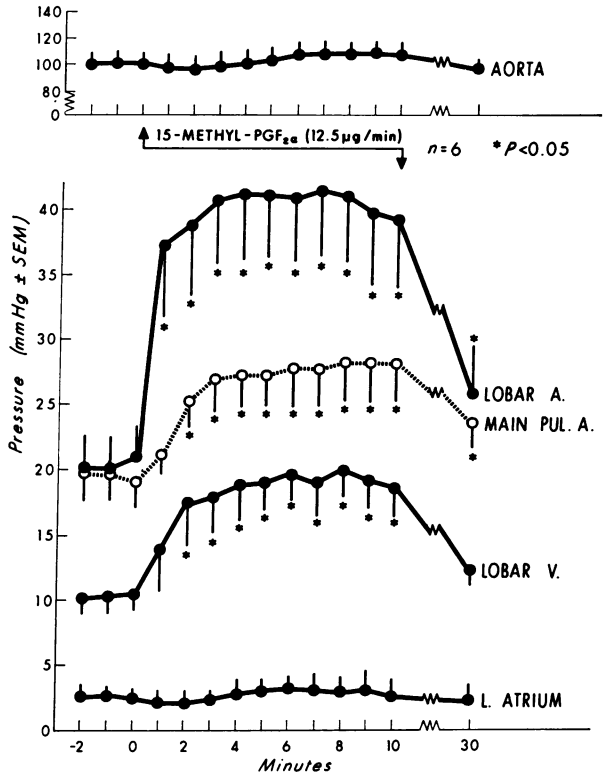

FIGURE 2 Effects of infusion of 15-methyl-PGF$_{2\alpha}$, 12.5 μg/min, into the lobar artery on mean vascular pressures in the lobar artery, small intrapulmonary lobar vein, left atrium, the aorta, and main pulmonary artery. *n* indicates number of dogs studied.

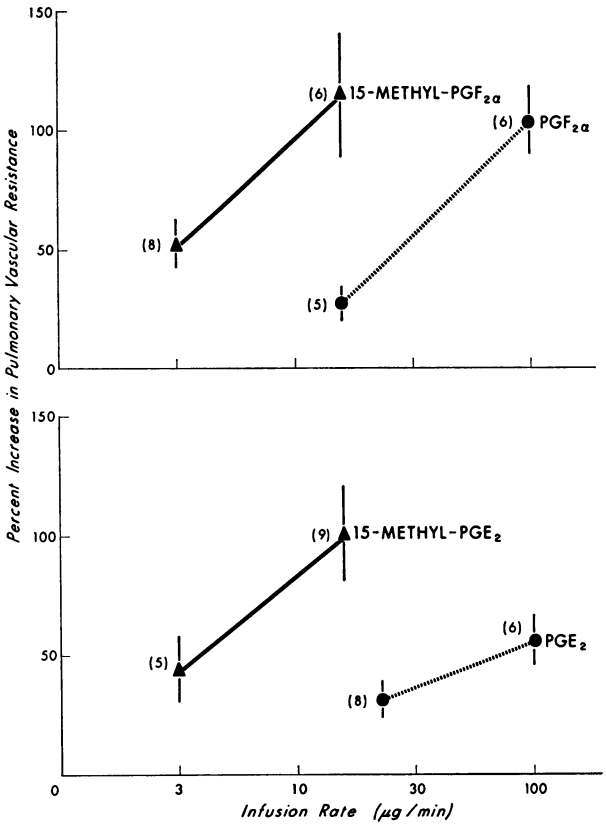

FIGURE 3 Dose-response curves comparing the percent increase in pulmonary vascular resistance in response to $PGF_{2\alpha}$ and PGE_2 and the methyl analogs in the intact dog.

ever, at least 10 times more PGE_2 was required to increase pulmonary vascular resistance 50% (Fig. 3).

Influence of the analogs on vascular resistance in the dextran-perfused lung. The possibility exists that the effects of the analogs on the pulmonary vascular bed may be mediated in part by release of autogenous substances from blood elements or mechanical obstruction of the bed by platelet aggregates. To evaluate the contribution of formed elements, the effects of the analogs were studied in experiments in which the lung was perfused with dextran instead of blood. Low-molecular weight dextran (10% in 5% dextrose or 0.9% saline, buffered to pH 7.4) was warmed to 37°C and perfused at a rate of 300–350 ml/min. The perfused dextran along with small amounts of blood were removed from the veins draining the left lower lobe with a transseptally placed 18F withdrawal catheter. In the intact spontaneously breathing dog, infusion of 15-methyl-PGE_2, 12.5–25 μg/min, or 15-methyl-$PGF_{2\alpha}$, 12.5 μg/min, into the dextran-perfused lung resulted in a significant increase in lobar arterial pressure (Fig. 4). The rate of increase in pressure was more rapid with 15-methyl-$PGF_{2\alpha}$ and with both analogs the maximum rise in pressure was similar in experiments in which the lung was perfused with dextran or with blood (Figs. 1, 2, and 4). During infusion of 15-methyl-PGE_2 there was a significant reduction in aortic pressure but no change in pressure in the main pulmonary artery or the left atrium. 15-Methyl-$PGF_{2\alpha}$ was without effect on pressure in the aorta, the main pulmonary artery or the left atrium.

Effect of passive increase in venous pressure. Experiments were performed to contrast the effects of the prostaglandin analogs and passive changes in venous pressure induced by partially obstructing outflow with a balloon catheter in the lobar vein. The balloon was distended slowly with Hypaque® in 11 instances in five dogs until pressure in the small intrapulmonary vein was elevated to about the same level as observed during infusion of the prostaglandin analogs. Balloon distension produced a significant increase in pressure in the lobar artery and small vein but elicited no change in pressure in the left atrium (Table II). Balloon distension produced a marked increase in pressure gradient from the small vein to left atrium. However, the gradient from lobar artery to small vein was decreased significantly (Table II). During the period of balloon distension there was no change in pressure in the aorta or the pulmonary artery or in heart rate, and pressure in the lobar artery and small vein returned to control value after the balloon was collapsed (Table II).

Isolated intrapulmonary vessels. The effects of the analogs on contractile activity was studied in isolated helical segments of canine intrapulmonary lobar artery and vein 3–5 mm in diameter. Exposure of arterial and venous segments to 15-methyl-$PGF_{2\alpha}$ in the range of concentration of 10^{-7}–10^{-5} M caused a dose-related increase in isometric tension in both segments (Fig. 5). The increase in contractile activity in the venous segment was greater than in the artery at each concentration (Fig. 5). The elevation in tension in response to norepinephrine, 10^{-5} M, was 920±90 mg in arterial segments and 550±50 mg in venous segments. In another series of segments 15-methyl-PGE_2 in concentrations of 10^{-6}–10^{-5} M produced an increase in tension output in both arterial and venous segments (Fig. 5). The increase in tension in these segments in response to norepinephrine, 10^{-5} M, was 890±110 mg for arteries and 570±50 mg in the veins.

DISCUSSION

Present results show that intralobar infusion of the 15-methyl analogs of PGE_2 and $PGF_{2\alpha}$ increase lobar arterial pressure in the intact dog. Since blood flow to the left lower lobe was held constant by a pump and left atrial pressure did not change, the rise in pressure gradient across the lung reflects an increase in pulmonary vascular resistance. The pressor response was ac-

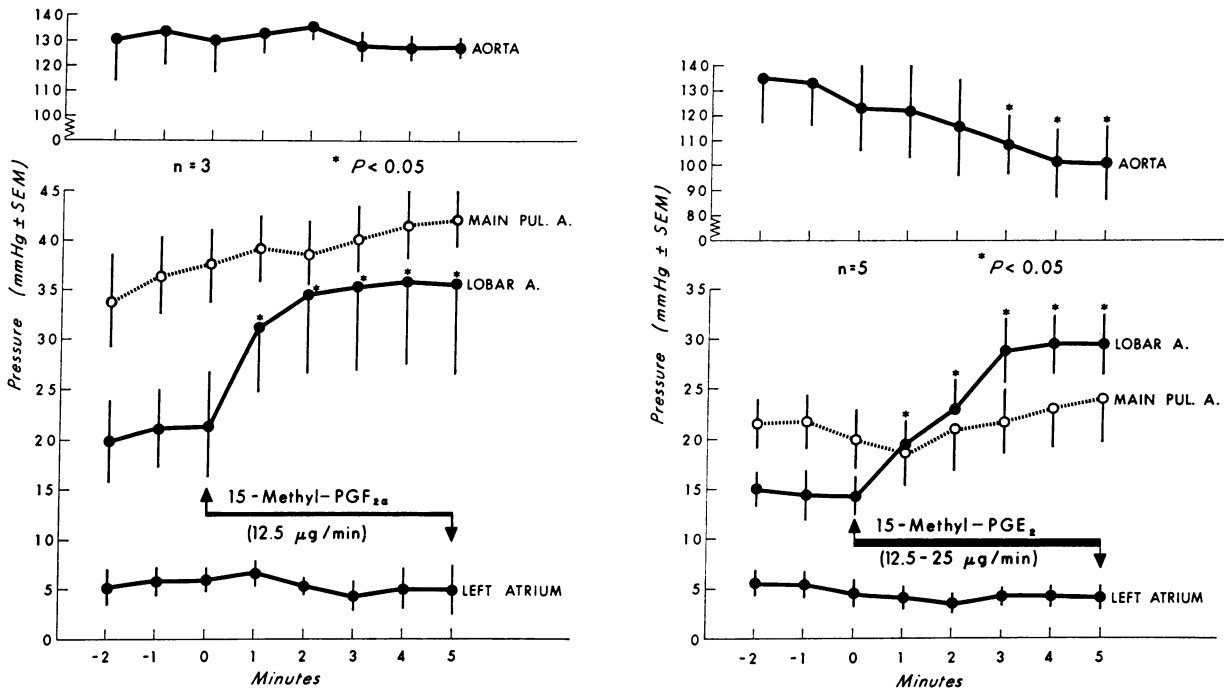

FIGURE 4 Influence of infusion of the 15-methyl analogs of $PGF_{2\alpha}$ and PGE_2 on mean vascular pressures in the dextran-perfused lung lobe. In these experiments the perfused dextran along with small amounts of blood was removed by way of a transeptally placed 18F withdrawal catheter in the lobar vein. *n* indicates number of dogs tested.

companied by an increase in pressure in small intrapulmonary veins and an increase in gradient from lobar artery to small vein. These data suggest that the analogs increase pulmonary vascular resistance by actively constricting pulmonary veins and vessels upstream to small veins presumed to be small arteries. In contrast to the effects of the analogs on venous segments and upstream vessels, passively induced increases in venous pressure decreased the pressure gradient from lobar artery to small vein. These data support the conclusion that the increase in upstream gradient in response to the analogs is the result of active vasoconstriction in upstream vessels. Data from experiments with isolated helical segments of canine intrapulmonary artery and vein are in agreement with studies in the intact dog and provide support for the postulated sites of action. The present data do not, however, allow a precise localization of the site of action of the analogs in upstream vessels and

TABLE II

Influence of Balloon Distension on Vascular Pressures in the Dog

	Control	Balloon distended	Balloon deflated
Pressure		*mm Hg±SEM*	
Lobar artery	20±1	25±2*	20±1
Lobar small vein	10±1	18±2*	9±1
Left atrium	1±1	1±1	1±1
Aorta	122±7	111±7	112±7
Main pulmonary artery	19±1	19±1	19±1
Gradient		*mm Hg±SEM*	
Lobar artery-lobar small vein	10±1	7±1*	9±1
Lobar small vein-left atrium	9±1	17±2*	8±1
Lobar artery-left atrium	19±1	24±2*	19±2

* Significantly different from corresponding control, $P < 0.05$.

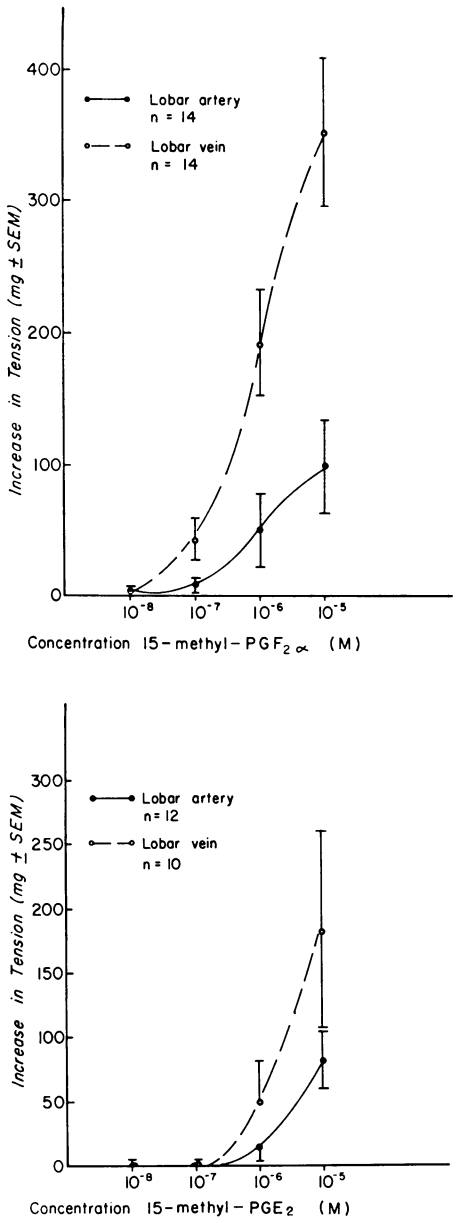

FIGURE 5 Dose-response curves showing the effects of 15-methyl-$PGF_{2\alpha}$ and 15-methyl-PGE_2 on isometric tension output in helical segments of isolated lobar artery and vein 3–5 mm in diameter. *n* indicates number of strips tested.

it is possible that segments of intrapulmonary artery smaller than those employed in the organ bath are responsive to these substances.

Prostaglandins have been reported to stimulate platelet aggregation (27, 28). However, it appears that platelet aggregation or interaction with blood-borne mediators contribute little if anything to the response to the analogs since comparable pressor responses were obtained in dextran- and blood-perfused lungs. The effects of PGE_2, $PGF_{2\alpha}$, and the methyl analogs on the canine pulmonary vascular bed are similar in that all four agents increase pulmonary vascular resistance (29–31). However, the analogs are much more potent in this respect. The major pathway for pulmonary inactivation of prostaglandins is dehydrogenation by the enzyme prostaglandin dehydrogenase. However, the 15-methyl analogs are not substrates for this enzyme (16–18). Therefore, methylation reduces the metabolism of these agents and greatly enhances their pressor activity in the lung. The present data demonstrate that the analogs are approximately 10 times more potent than the natural compounds as pulmonary pressor agents whereas they are reported to be 50–100 times more potent as abortifacient or antifertility agents (18–22). These results suggest that the analogs should have a higher therapeutic index than the natural compounds and would be expected to produce a lesser incidence of pulmonary hypertension when used for the induction of mid-trimester abortion.

Results of studies in the intact dog are in agreement with studies in the open chest dog in which the analogs were reported to increase calculated pulmonary vascular resistance (18). In the present experiments 15-methyl-PGE_2 produced a decrease in aortic pressure whereas 15-methyl-$PGF_{2\alpha}$ increased pressure in the main pulmonary artery. However, cardiac output was not measured so that the effects of these agents on systemic vascular resistance or resistance in the normally perfused lung lobes is unknown. In the intact dog under conditions of controlled flow, the relative contribution of venous segments and upstream vessels to total resistance is nearly equal since gradients across the two segments were of similar magnitude. These results are in agreement with previous studies in the dog (32). The contribution of the venous segments to the increase in resistance in response to the analogs was large and might be expected to cause leakage of fluid or formation of edema. However, evidence of lobar edema, including increased bronchopulmonary markings and X-ray opacity, were not observed. Although the experiments were not terminated until 30 min after the prostaglandin infusion, gross evidence of edema was not present at that time. These results are not unexpected in view of the findings of Guyton and Lindsey (33) that increases in left atrial pressure greater than 25 mm Hg were required to increase lung weight unless the plasma protein concentration was decreased. Their findings are in agreement with experiments in this laboratory in which increases in venous pressure greater than 30 mm Hg were required to produce pulmonary edema in the intact dog (34).

It is not known if the prostaglandins are involved in the regulation of the pulmonary circulation; however,

their great activity, natural occurrence, synthesis, and release may suggest such a role. The observation that prostaglandin-like substances are released during hypoxic ventilation in the cat and that inhibition of prostaglandin synthesis reduces the hypoxic pressor response suggests that these lipids may mediate the response to hypoxia in this species (6). Furthermore, several authors have provided evidence that hypoxia may constrict the pulmonary veins (35–37). However, the precise role of prostaglandins in the lung must await additional investigation and the development of specific prostaglandin antagonists.

The hypertensive effect of the prostaglandin analogs described in this study may have important therapeutic implications since these agents are undergoing clinical trial for use in terminating pregnancy. For example, shortness of breath and pulmonary hypertension have been observed in a clinical study when 15-methyl-$PGF_{2\alpha}$ was administered (23). The observation that 15-methyl-$PGF_{2\alpha}$ is 10 times as potent as $PGF_{2\alpha}$ as a pressor substance whereas it is 50–100 times more potent as an abortifacient suggests that the analog may be superior clinically to the natural substance.

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