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Intravenous $PGF_{2\alpha}$ Infusion Does Not Enhance Hypoxic Pulmonary Vasoconstriction during Canine One-lung Hypoxia

Linda Chen, M.D., Francis L. Miller, M.D., Ph.D.,* Gunnar Malmkvist, M.D.,† Randahl Cooley, M.D.,‡ Carol Marshall, Ph.D.,§ Bryan E. Marshall, M.D., F.R.C.P.¶*

The effect of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) on the hypoxic pulmonary vasoconstrictor (HPV) response was studied in 12 closed-chest dogs anesthetized with pentobarbital and paralyzed with pancuronium. The right lung was ventilated continuously with 100% O_2, while the left lung was either ventilated with 100% O_2 ("hyperoxia") or ventilated with an hypoxic gas mixture ("hypoxia:" end-tidal $P_{O_2} \cong 50.0 \pm 0.1$ mmHg). Cardiac output (CO) was altered from a "normal" value of 2.89 ± 0.26 l·min^{-1} to a "high" value of 3.55 ± 0.26 l·min^{-1} by opening arteriovenous fistulae which allowed measurements of two points along a pressure-flow line. These four phases of left lung hypoxia or hyperoxia with normal and high cardiac output were performed in the absence of, and in the presence of, $PGF_{2\alpha}$ administered as a constant peripheral intravenous infusion of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. During left lung hypoxia, mean pulmonary artery pressure (PAP) increased significantly when compared to hyperoxia. With $PGF_{2\alpha}$ administration, mean PAP increased significantly during both hyperoxia and hypoxia. The presence or absence of $PGF_{2\alpha}$ had no effect on cardiac output or Pa_{O_2} during hypoxia. Relative blood flow to each lung was measured with a differential CO_2 excretion ($\dot{V}CO_2$) method corrected for the Haldane effect. With both lungs hyperoxic, the percent left lung blood flow ($\%\dot{Q}_{L\text{-}\dot{V}CO_2}$) was 45 ± 1%. When the left lung was exposed to hypoxia, the $\%\dot{Q}_{L\text{-}\dot{V}CO_2}$ decreased significantly to 29 ± 3%. However, with the administration of $PGF_{2\alpha}$, the $\%\dot{Q}_{L\text{-}\dot{V}CO_2}$ during left lung hypoxia did not change significantly 26 ± 3%. Pulmonary vascular conductance (G) is the slope of the pressure-flow line. The pulmonary vascular conductance of the hyperoxic right lung (G_R) remained unchanged with hypoxia, but decreased with $PGF_{2\alpha}$ administration during both hyperoxia and hypoxia. The pulmonary vascular conductance of the left lung (G_L) also decreased significantly between hyperoxia and hypoxia. With the addition of $PGF_{2\alpha}$, G_L decreased significantly during hyperoxia. However, with the administration of $PGF_{2\alpha}$ during hypoxia, G_L decreased further than with hypoxia alone; this occurred at the normal cardiac output, but not at the high cardiac output. In this study, $PGF_{2\alpha}$ behaved differently from other pulmonary vasoconstrictors, in that it induced the same proportionate constriction in both the hypoxic segment and the rest of the lung. Although there was a rightward shift in the pressure-flow line due to major increases in mean PAP and minimal decreases in blood flow, no enhancement of HPV was detected with the vasoconstriction that occurred. (Key words: Hypoxia: pulmonary vascular response. Lung: blood flow; hypoxic pulmonary vasoconstriction; shunting; vascular conductance. Oxygen: blood levels. Pharmacology: $PGF_{2\alpha}$.)

PROSTAGLANDIN $F_{2\alpha}$ ($PGF_{2\alpha}$) is a naturally occurring acidic lipid which is synthesized in the lung from several fatty acid precursors.[1,2] In addition to synthesis and release, the lung is an important organ for metabolism of these lipids,[3,4] and $PGF_{2\alpha}$ is largely inactivated in one passage through the lung.[5] Their natural occurrence in and release from the lung suggest that these substances may be important in the regulation of the pulmonary vascular bed in normal and disease states.

When the pulmonary vasoconstrictor $PGF_{2\alpha}$ was infused selectively into one canine pulmonary artery of an atelectatic lung at doses of 0.4–1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, the reduction in venous admixture suggested enhancement of hypoxic pulmonary vasoconstriction (HPV).[6] The present study examined the hypothesis that $PGF_{2\alpha}$ infused peripherally enhances the HPV response in closed chest dogs during left lung hypoxia.

Materials and Methods

Anesthesia and Surgery

Twelve female dogs of mixed breed with mean weight of 20.7 ± 1.0 kg were anesthetized with a bolus of 30 mg·kg^{-1} intravenous pentobarbital (Abbott® Lab) followed by an infusion at 0.82–4.08 mg·min^{-1} (Harvard® Infusion Pump model #902). The trachea was intubated initially with a 10-mm cuffed endotracheal tube, and mechanical ventilation was begun. Muscle paralysis was established with 0.05 mg·kg^{-1} intravenous pancuronium (Organon® Inc.) supplemented with 0.2–0.5 mg every 30 min.

After subcricoid tracheostomy, a double-lumen Kottmeier® endobronchial tube (Rüsch Inc.) was placed. Complete lung isolation was verified by auscultation and the demonstration that cross-contamination did not occur when the left lung was ventilated with an hypoxic gas mixture. The lungs were ventilated synchronously with 100% O_2 *via* a Harvard® dual-piston respirator with 5 cm H_2O of PEEP applied by water seal to prevent

* Assistant Professor of Anesthesia.

† Assistant Professor of Anesthesia, Department of Anesthesia, University Hospital, University of Lund, Lund, Sweden.

‡ Medical Student.

§ Assistant Research Professor of Anesthesia.

¶ Horatio C. Wood Professor of Anesthesia.

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Address reprint requests to Dr. Chen: Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Dulles 788, Philadelphia, Pennsylvania 19104.

atelectasis. Tidal volumes were selected to produce equal driving pressures, *i.e.*, equal peak airway pressures of 15–20 cm H_2O. Inspired CO_2 and/or the respiratory rate were adjusted to keep right and left end-tidal P_{CO_2} close to 35–40 mmHg. Each piston of the Harvard® ventilator was part of a separate gas circuit, with its gas composition determined by separate flow meters. Right and left lung inspired, end-tidal, and mixed expired P_{O_2} and P_{CO_2} were measured by a mass spectrometer (Perkin-Elmer® model #1100 Medical Gas Analyzer), which was calibrated daily with gases of known composition and corrected for barometric pressure, temperature, and water vapor.

Peripheral veins were cannulated for intravenous fluid administration (approximately 5.8 ± 0.5 $ml \cdot min^{-1}$ Normosol® and/or 0.9% saline) and for infusion of $PGF_{2\alpha}$. Based on a study by Scherer *et al.*,[6] $PGF_{2\alpha}$ was administered at a constant infusion of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (Harvard® Infusion Pump model #600-910/920). Body temperature, measured by an esophageal temperature probe, was maintained at 38 ± 0.2° C with heating lamps, pads, and heated humidifier. Sodium bicarbonate ($NaHCO_3$) was available to correct metabolic acidosis. Urine was collected from a Foley catheter.

Arterial pressure (*via* femoral artery) and central venous pressure (*via* an external jugular vein) were measured. Pulmonary arterial and pulmonary arterial occlusion pressures were measured with a flow-directed Swan-Ganz catheter (American Edwards® #93A-131H-7F) inserted percutaneously (*via* a femoral vein). Pressures were measured continuously on an eight-channel Grass® polygraph (Model #7WC16PA Serial #791W3). The transducers (Statham® model #P23BB and Gould-Statham® model P23Db) were zeroed at the mid-cardiac level and calibrated to mmHg or cm H_2O as appropriate. Thermodilution cardiac outputs (Edwards® cardiac output computer model #9510-A) were obtained in triplicate using an injection of 5 ml of ice-cold 5% dextrose in water.

Since the dual responses of HPV are flow diversion and a change in pulmonary artery pressure (PAP), two points were collected using normal and high cardiac outputs to generate the pressure-flow line. For the manipulation of cardiac output, two arteriovenous (AV) fistulae (4 mm ID arterial end, 6 mm ID venous end) were constructed, one between a femoral artery and vein and the other between an internal carotid artery and external jugular vein. The cardiac output was "normal" when the shunts were closed and "high" when the shunts were open. The dog was anticoagulated with approximately 300 $units \cdot kg^{-1}$ of heparin iv followed by 50 $units \cdot kg^{-1}$ every 30 min.

Blood flow to each lung was measured with a differential carbon dioxide elimination ($\dot{V}CO_2$) method.[7]** For each lung, the expired gas was directed through a turbine spirometer with a digital electronic output (Boehringer® Labs #8830) and a capnometer (Puritan-Bennett Corporation, Datex #CD-102-27-00) linked through an interface (Boehringer Labs #9040C) to a small digital computer (Commodore® #4016). Carbon dioxide (CO_2) production was calculated continuously from the expired volume signals and from the difference between the inspired and mixed-expired CO_2 concentration. When one lung was ventilated with an hypoxic gas mixture, the excretion was corrected for the Haldane effect based on the coefficients published by Grønlund and Garby.[8] An experimental confirmation of this correction has also appeared.[9] The percent left lung blood flow ($\%\dot{Q}_{L\text{-}\dot{V}CO_2}$) was calculated as the CO_2 excretion of the left lung divided by the total CO_2 excretion for both lungs.

Study Design

Prior to the experimental sequence, three 15-min trials of hypoxic (approximately P_{ETO_2} = 30 mmHg, P_{ETCO_2} = 35–40 mmHg, balance N_2) ventilation to the left lung were alternated with 100% O_2 ventilation to determine the presence of stable reproducible pulmonary blood flow and pressure responses to hypoxia.[10]

The study was divided into halves with a 90-min waiting period between the no $PGF_{2\alpha}$/$PGF_{2\alpha}$ periods. Each half consisted of four phases with the left lung either hyperoxic or hypoxic and with the cardiac output either normal or high. To obtain steady-state conditions and to record measurements required approximately 30–50 min for each phase. Whether the $PGF_{2\alpha}$ or the no $PGF_{2\alpha}$ period was examined first was randomized, as were each of the four phases within each group.

The right lung was ventilated continuously with 100% O_2, while the left lung was ventilated either with 100% O_2 (hyperoxia) or with an hypoxic gas mixture (hypoxia). The left lung end-tidal P_{O_2} during hypoxia was maintained at 50.0 ± 0.1 mmHg; this was chosen to yield an oxygen tension at the sensor site for HPV (P_{SO_2}) that would be approximately a half maximal hypoxic stimulus.[11]

$PGF_{2\alpha}$, diluted with 0.9% normal saline solution (Abbott® Lab), was administered as a constant peripheral intravenous infusion of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ which was the highest infusion rate which decreased venous admixture in a study by Scherer *et al.*[6]

** Williams JJ, Chen L, Aukburg SJ, Alexander CM, Domino KB, Marshall BE: Computerized measure of CO_2 production to determine differential pulmonary blood flow (abstract). ANESTHESIOLOGY 59:A496, 1983.

Measurements

At each phase, the following measurements were obtained: peak and mean airway (P_{aw}), pulmonary (PAP), and systemic arterial (SAP), central venous (CVP), and pulmonary artery occlusion pressures (PAOP); total cardiac output (CO) by thermodilution in triplicate; body temperature (temp); and inspired, end-tidal, and mixed-expired O_2 and CO_2 of each lung by mass spectrometer. Arterial and mixed venous blood gas samples were collected to determine *p*H, P_{O_2}, P_{CO_2} (Corning® *p*H/Blood Gas Analyzer model #168); and hemoglobin concentration (Sigma® Kit #525). Right and left tidal volume (TV), respiratory rate (RR), and minute ventilation ($\dot{V}_E$) were recorded.

Calculations

From the recorded data, blood flow, vascular conductance, and the percent blood flow to the left lung were calculated.

Pulmonary perfusion pressure (PPP) in mmHg was calculated as mean PAP minus mean PAOP. Left and right pulmonary vascular conductances ($dyn^{-1} \cdot cm^5 \cdot s^{-1}$) were calculated from the respective lung blood flow in $l \cdot min^{-1}$ divided by the perfusion pressure in mmHg (×80).

Alveolar oxygen tension (PA_{O_2}) for the right lung ventilated with 100% O_2 was calculated from the barometric pressure minus the saturated water vapor pressure minus the Pa_{CO_2}. During hypoxic ventilation, the addition of CO_2 to the inspired gas was sufficient to introduce errors into the alveolar gas mixing equation.[12] Therefore, left lung PA_{O_2} was calculated as the mean of the measured mixed-expired P_{O_2} and the mixed venous $P\bar{v}_{O_2}$. End-capillary oxygen tension was assumed to be equal to the calculated alveolar oxygen tension. The oxygen contents of end-capillary, arterial, and mixed venous blood were then calculated from:

$$CO_2 = (1.34 \times Hb \times \% \text{ Sat}) + (P_{O_2} \times 0.0031)$$

Percent saturation (% Sat), corrected for *p*H and temperature, was calculated from a nomogram for canine hemoglobin.[13]

Venous admixture (%VA) was calculated from the traditional shunt equation.[14] Calculation of left lung blood flow was made by two methods. The first method, based on differential CO_2 excretion of each lung, was described above as $\%\dot{Q}_{L\text{-}\bar{v}CO_2}$. The second method for estimation of left lung blood flow during the hypoxic periods ($\%\dot{Q}_{L\text{-}VA}$) was based on a variation of the traditional shunt equation which allowed for the difference between alveolar oxygen tension of the hypoxic *versus* hyperoxic lung.[12,15] This equation assumed: 1) that the total anatomic shunt flow ($\dot{Q}_S/\dot{Q}_T$) measured during 100% O_2 ventilation remained unchanged during hypoxic ventilation for corresponding experimental conditions; and 2) that the apportionment of anatomic shunt flow, whether to the right lung or the left lung, also remained unchanged during hypoxic ventilation. The errors associated with these assumptions regarding the anatomic shunt flow during 100% O_2 ventilation were small compared to the variations in left lung flow during the experimental conditions. The stimulus for HPV, the P_{SO_2}[11] was calculated from:

$$P_{SO_2} = (P\bar{v}_{O_2})^{0.32} \times (PA_{O_2})^{0.68}$$

Statistics

The system variables were analyzed by a one-way within-subjects analysis of variance (ANOVA) for repeated measurements with Neuman-Keuls test for specific differences between means. The experimental variables were analyzed by a three-way ANOVA of repeated measures/randomized blocks with the three factors being gas mixture (hyperoxia/hypoxia), cardiac output (normal/high), and drug (absence/presence). A value of $P < 0.05$ was considered significant. Results are expressed as mean ± standard error.

Results

The general experimental conditions for *p*Ha, HR, Pa_{CO_2}, temperature, Hb, SAP, CVP, airway pressure of the right lung (P_{awR}), airway pressure of the left lung (P_{awL}), tidal volume of the right lung (TV_R), tidal volume of the left lung (TV_L), minute ventilation of the right lung ($\dot{V}_{ER}$), and minute ventilation of the left lung ($\dot{V}_{EL}$) were measured at each phase of the study; since the mean values were not significantly different between the eight phases of the study, only the control measurements for the 100% O_2-normal cardiac output-no $PGF_{2\alpha}$ phase are reported (table 1). The mean systemic vascular resistance (SVR) decreased significantly between each normal/high cardiac output pair (4160 ± 377 to 3189 ± 284 $dyn \cdot cm^{-5} \cdot s$), but otherwise was not affected by gas mixture or $PGF_{2\alpha}$ administration.

The results from each phase for the following variables are presented in table 2. The normal and high cardiac outputs were significantly different from each other; however, neither the gas mixture nor the drug affected cardiac output.

The arterial oxygen tension (Pa_{O_2}) decreased significantly between hyperoxia and hypoxia, but, during hypoxia, the Pa_{O_2} remained unchanged with the addition of $PGF_{2\alpha}$. Mixed venous oxygen tension ($P\bar{v}_{O_2}$) decreased significantly between hyperoxia and hypoxia, but was not affected by $PGF_{2\alpha}$; $P\bar{v}_{O_2}$ increased significantly between the normal and high cardiac outputs

during both hyperoxia and hypoxia. During hypoxia, the P_{ETO_2} were not significantly different. During hypoxia, the stimulus for HPV decreased (*i.e.*, the P_{SO_2} increased) significantly when the cardiac output was increased; however, at each cardiac output level, the P_{SO_2} was not affected when $PGF_{2\alpha}$ was administered.

During hypoxia, mean PAP increased significantly compared with hyperoxia and increased even further with the addition of $PGF_{2\alpha}$. Mean PAP also increased significantly between normal and high cardiac outputs during both hyperoxia and hypoxia. During both hyperoxia and hypoxia, the PAOP did not change with the addition of $PGF_{2\alpha}$.

The pulmonary vascular conductance (G) is the reciprocal of pulmonary vascular resistance and is the slope of the pressure-flow line. The pulmonary vascular conductance of the right lung (G_R) was not affected by the type of gas mixture (hyperoxia/hypoxia) administered to the left lung, since the right lung was always hyperoxic. However, with $PGF_{2\alpha}$ administration, G_R of the right lung decreased.

The pulmonary vascular conductance of the left lung (G_L) decreased significantly with hypoxia. With the addition of $PGF_{2\alpha}$, the hypoxic left lung showed a further decrease in G_L during the normal cardiac output phase, but not during the high cardiac output phase.

There were no changes in percent venous admixture

TABLE 1. General Hemodynamic and Blood Gas Values During the 100% O_2—Normal Cardiac Output—No $PGF_{2\alpha}$ Condition (n = 12, Mean ± Standard Error)

*p*Ha	7.345 ± 0.002
HR (bpm)	191 ± 2
Pa_{CO_2} (mmHg)	37.9 ± 0.2
temp (°C)	37.7 ± 0.1
Hb (g/dl)	12.7 ± 0.2
SAP (mmHg)	140.0 ± 1.6
CVP (mmHg)	4.5 ± 0.1
P_{awR} (cm H_2O)	11.3 ± 0.1
P_{awL} (cm H_2O)	11.3 ± 0.1
TV_R (ml)	219.8 ± 10.2
TV_L (ml)	216.6 ± 11.6
$\dot{V}_{ER}$ ($l \cdot min^{-1}$)	3.90 ± 0.08
$\dot{V}_{EL}$ ($l \cdot min^{-1}$)	3.94 ± 0.10

*p*Ha = arterial *p*H; HR = mean heart rate; Pa_{CO_2} = arterial carbon dioxide tension; temp = temperature; Hb = hemoglobin; SAP = mean systemic arterial pressure; CVP = mean central venous pressure; P_{awR} = mean right airway pressure; P_{awL} = mean left airway pressure; TV_R = mean tidal volume right lung; TV_L = mean tidal volume left lung; $\dot{V}_{ER}$ = mean minute ventilation right lung; $\dot{V}_{EL}$ = mean minute ventilation left lung.

TABLE 2. Effect of $PGF_{2\alpha}$ on Various Hemodynamic and Blood Gas Parameters during Left Lung 100% O_2/hypoxia and Normal (Nl)/high (Hi) Cardiac Outputs (n = 12, Mean ± Standard error)

	100% O_2				Hypoxia			
	No $PGF_{2\alpha}$		$PGF_{2\alpha}$		No $PGF_{2\alpha}$		$PGF_{2\alpha}$	
	Nl	Hi	Nl	Hi	Nl	Hi	Nl	Hi
CO ($l \cdot min^{-1}$)	2.89 0.26	3.55* 0.26	2.72 0.31	3.46* 0.30	2.91 0.29	3.80* 0.29	2.70 0.30	3.50* 0.34
Pa_{O_2} (mmHg)	599 8	598 9	603 4	598 5	237 31	239 36	275 32	252 27
$P\bar{v}_{O_2}$ (mmHg)	70.1 2.5	78.8* 2.4	66.1 2.8	79.1* 2.0	57.7 1.8	62.7* 1.8	58.4 2.3	64.4* 1.7
$P_{ETO_2\text{-}L}$ (mmHg)					50.0 0.2	50.0 0.1	49.8 0.2	50.3 0.2
P_{SO_2} (mmHg)					52.6 0.6	54.6* 0.7	53.0 0.7	55.1* 0.6
PAP (mmHg)	20.8 0.7	22.8* 0.8	24.4† 0.7	27.3*† 0.7	24.2 1.0	27.3* 1.3	28.6† 0.9	31.4*† 1.1
PAOP (mmHg)	9.0 0.6	9.2 0.8	8.9 0.8	8.9 0.7	8.5 0.8	9.6 0.7	8.9 0.9	9.4 0.8
G_R ($10^{-3} \cdot dyn^{-1} \cdot cm^5 \cdot s^{-1}$)	1.77 0.17	1.83 0.14	1.20† 0.13	1.30† 0.11	1.67 0.14	1.97 0.17	1.27† 0.12	1.47† 0.14
G_L ($10^{-3} \cdot dyn^{-1} \cdot cm^5 \cdot s^{-1}$)	1.43 0.10	1.55 0.13	1.01† 0.11	1.08† 0.09	0.73 0.11	0.87 0.13	0.44† 0.07	0.56 0.08
%VA	6.24 0.01	7.44 0.01	5.41 0.003	6.98 0.003				
$\%\dot{Q}_{L\text{-}VA}$					20.72 2.34	22.13 2.26	17.85 2.13	19.27 1.71
$\%\dot{Q}_{L\text{-}\dot{V}CO_2}$	45.2 1.3	45.7 1.4	45.4 1.7	45.4 1.8	28.8 3.4	29.2 3.1	25.6 3.3	27.4 2.8

* Indicates a significant difference ($P < 0.05$) between normal/high cardiac output; †between no $PGF_{2\alpha}$/$PGF_{2\alpha}$ values.

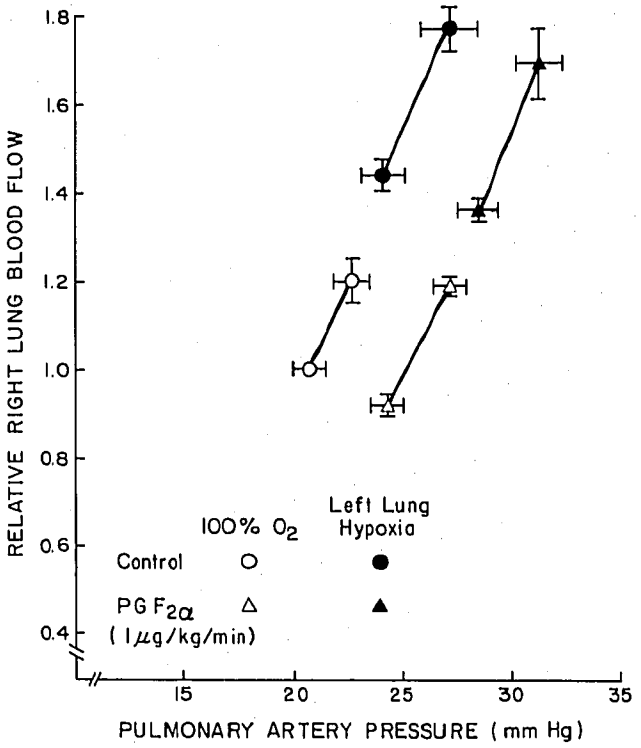

FIG. 1. Pressure-flow relationship for the right lung. The blood flow to the right lung was calculated relative to the 100% oxygen, normal cardiac output phase. Compared to the control state when $PGF_{2\alpha}$ was absent (circles), the addition of $PGF_{2\alpha}$ (triangles) caused vasoconstriction in the right lung which was represented by a shift of the points to the right. The right lung always received 100% oxygen, and this shift of the points to the right occurred when the left lung was ventilated with 100% oxygen (open symbols) and when the left lung was hypoxic (filled symbols).

(%VA) during hyperoxia. The percent left lung blood flow during hypoxia ($\%\dot{Q}_{L\text{-}VA}$) did not change with the administration of $PGF_{2\alpha}$.

During hyperoxia, there were no changes in percent left lung blood flow ($\%\dot{Q}_{L\text{-}\dot{V}CO_2}$) at either cardiac output or with $PGF_{2\alpha}$ administration. During hypoxia, there was a significant decrease in $\%\dot{Q}_{L\text{-}\dot{V}CO_2}$, which did not change after $PGF_{2\alpha}$ administration.

Since the dual responses of HPV are a change in pulmonary artery pressure and diversion of blood flow from the hypoxic lung, the data are presented as pressure-flow lines. The blood flow for each lung under each experimental condition is calculated "relative" to the 100% O_2 ventilation-normal cardiac output-no $PGF_{2\alpha}$ control phase to facilitate analysis and discussion of the right *versus* left lung data. For the right lung (fig. 1), which was always ventilated with 100% oxygen, the infusion of $PGF_{2\alpha}$ caused vasoconstriction regardless of whether the left lung was being exposed to 100% O_2 or hypoxia. For the left lung (fig. 2), $PGF_{2\alpha}$ caused vasoconstriction both during 100% O_2 and hypoxia.

Discussion

This study describes the effect of $PGF_{2\alpha}$ on the right and left lungs during conditions of bilateral hyperoxia and unilateral hypoxia. $PGF_{2\alpha}$ at a dose of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ administered *via* a continuous peripheral intravenous infusion caused vasoconstriction in both the right lung receiving 100% O_2 and the left lung receiving an hypoxic gas mixture without significantly changing blood flow to either lung.

$PGF_{2\alpha}$ is a potent pulmonary vasoconstrictor.[16-19] Kadowitz *et al.*[18] infused $PGF_{2\alpha}$ (20 $\mu g \cdot ml^{-1} \times 10$ min) into the lobar artery of intact anesthetized swine, lambs, and dogs spontaneously breathing room air enriched with O_2 and with a roller pump controlling blood flow to the left lower lobe lung. $PGF_{2\alpha}$ increased the PVR in all species. In the dogs (n = 6), both lobar veins and upstream vessels, presumed to be small arteries, were constricted, but, in the swine and lamb, apparently only arterial segments were constricted.[20-23]

Scherer *et al.*†† measured endogenous arterial levels of $PGF_{2\alpha}$ in nine male patients undergoing resection of carcinoma of the esophagus. They found that the level of $PGF_{2\alpha}$ measured during two- and one-lung ventilation was significantly lower than normal values for a ten-subject age-matched control group, whereas the pulmonary vasodilator $PGE_{2\alpha}$ was significantly elevated. They suggested that the "high levels of $PGE_{2\alpha}$ in the absence of adequate counter balance by $PGF_{2\alpha}$ may have reduced the effectiveness of HPV in these patients."

In the present study, $PGF_{2\alpha}$ was administered *via* a continuous peripheral intravenous infusion, whereas, in another study by Scherer *et al.*,[6] the $PGF_{2\alpha}$ was infused directly into the right or left pulmonary artery confined to an acutely atelectatic lung. They interpreted their observations as an enhancement of HPV. This present work suggests rather that $PGF_{2\alpha}$ exerts a direct non-specific vasoconstriction which resulted in the improved Pa_{O_2} and $\dot{Q}_{VA}/\dot{Q}_T$ in the study of Scherer *et al.*[6] only because the infusion of low dose was confined to the atelectatic lung. When the infusion rate in the study by Scherer *et al.*[6] was increased from 1.2 to 1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, the worsening of $\dot{Q}_{VA}/\dot{Q}_T$ which occurred may have been due to: 1) tachyphylaxis of the atelectatic pulmonary vessels to $PGF_{2\alpha}$; and 2) saturation of the enzyme system so that the $PGF_{2\alpha}$ activity appeared not only in the pulmonary, but also the systemic, circulation; *i.e.*, spill-over of $PGF_{2\alpha}$ from the atelectatic to the ventilated lung so that vasoconstriction in the ventilated lung diverted blood back into the atelec-

†† Scherer RW, Van Aken H, Schlegel W, Lawin P: Prostaglandins during one-lung ventilation in esophageal surgery (abstract). ANESTHESIOLOGY 59:A502, 1983.

tatic lung. If we assume that, during two-lung ventilation, their $\dot{Q}_{VA}/\dot{Q}_T$ was equally divided between the right and left lung, then estimates of left lung blood flow ($\%\dot{Q}_{L\text{-}VA}$) and pulmonary vascular conductance of the left lung (G_L) are as shown in table 3. Comparing the 100% O_2 ventilation *versus* atelectasis-no drug phase, the G_L decreased by 46% due to vasoconstriction and the G_R increased by 3% due to receiving the diverted blood flow. However, comparing the 100% O_2 ventilation *versus* the atelectasis with 1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ $PGF_{2\alpha}$ phase, the G_L decreased by 69%, but the G_R decreased by 15%, suggesting that spill-over of $PGF_{2\alpha}$ caused additional vasoconstriction in the right lung. Scherer *et al.*[6] did report systemic effects with their dose of $PGF_{2\alpha}$, including an increase in heart rate, mean arterial pressure, and cardiac output.

Neither the present nor the Scherer *et al.*[6] study measured the pulmonary arterial or the systemic arterial levels of either $PGF_{2\alpha}$ or its metabolites. Since the active constrictor is metabolized in a single pass by the mixed oxidase, 15-hydroxy prostaglandin dehydrogenase system of pulmonary endothelial cells,[3,4] systemic vasoconstriction is believed not to occur during a low dose of $PGF_{2\alpha}$ infusion. Also, the 13,14-dihydro 15-keto metabolite of $PGF_{2\alpha}$ is inactive as a vasoconstrictor. However, if the $PGF_{2\alpha}$ infusion rate surpassed enzyme capacity, then $PGF_{2\alpha}$ should have reached the systemic circulation resulting in an increase in heart rate, systemic arterial pressure, systemic vascular resistance, and cardiac output,[17,18,24] none of which were observed to change significantly in the present study but did occur in the study of Scherer *et al.*[6] Interestingly, the effects of

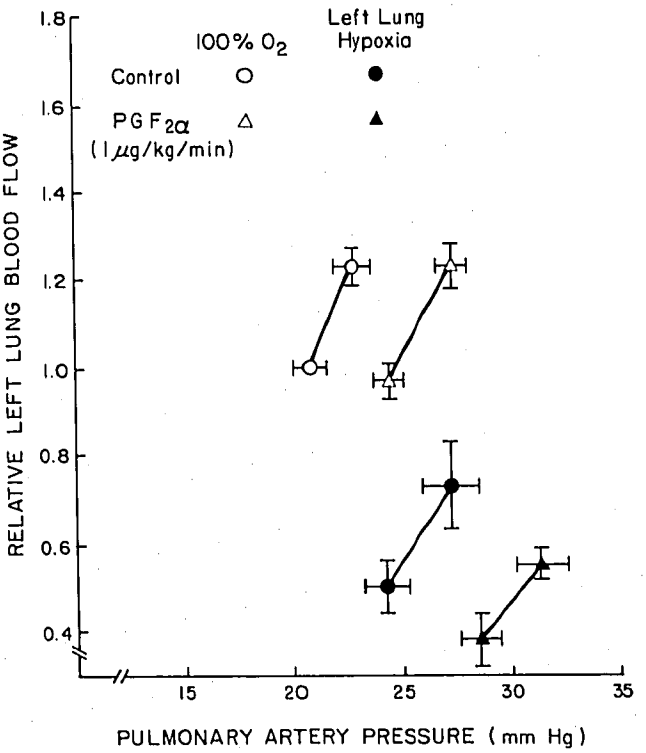

FIG. 2. Pressure-flow relationship for the left lung. The blood flow to the left lung was calculated relative to the 100% O_2-normal cardiac output phase. In the absence of $PGF_{2\alpha}$ (circles), active HPV was represented by a rightward and downward shift of the points from 100% oxygen (open circles) to hypoxia (filled circles). With the addition of $PGF_{2\alpha}$ (triangles), there was constriction of the hyperoxic left lung (open triangles); however, during hypoxia (filled triangles), a slight but not significant rightward and downward shift of points for the left lung was observed.

TABLE 3. Comparison of HPV Responses during Hypoxia or Atelectasis in the Absence and Presence of $PGF_{2\alpha}$

	Present Study			Scherer et al. (6)				
Condition	Closed chest			closed chest				
Anesthesia	Na Pentobarbital, pancuronium			Na Pentobarbital, pancuronium, piritramid				
Hypoxic stimulus	Left lung hypoxia			One-lung atelectasis				
$PGF_{2\alpha}$ infusion								
Site	Peripheral			Directly into PA				
Rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)			1.0			1.2		1.8
	No $PGF_{2\alpha}$		$PGF_{2\alpha}$	No $PGF_{2\alpha}$		$PGF_{2\alpha}$		$PGF_{2\alpha}$
Pa_{O_2} (mmHg)	237	→	275	91	→	168*		
$P\bar{v}_{O_2}$ (mmHg)	58	→	58	46	→	49		
P_{SO_2} (mmHg)	53	→	53	46	→	49		
HR (beats · min^{-1})	190	→	193	85	→	103*		
CO ($l \cdot min^{-1}$)	2.9	→	2.7	4.5	→	4.7		
$\%\dot{Q}_{L\text{-}VA}$	21	→	18	34.5	→	19.5	→	26.5
$\dot{Q}_{VA}/\dot{Q}_T$ (%)				40	→	25*		
PAP (mmHg)	24	→	29*	11	→	15*		
PVR_T (dyn · cm^{-5} · s)	462	→	646*	120	→	163*		
G_R ($10^{-3} \cdot dyn^{-1} \cdot cm^5 \cdot s^{-1}$)	1.67	→	1.27*	5.26	→	4.73	→	4.34
G_L ($10^{-3} \cdot dyn^{-1} \cdot cm^5 \cdot s^{-1}$)	0.73	→	0.44*	2.77	→	1.15	→	1.57

* Indicates a significant difference ($P < 0.05$) between the no $PGF_{2\alpha}$ *versus* the $PGF_{2\alpha}$ group.

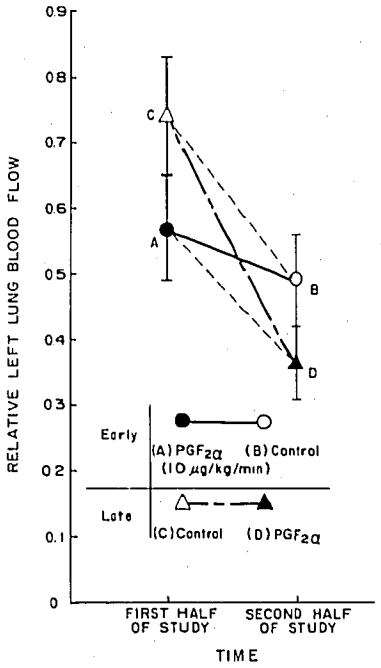

FIG. 3. The effect of time on the HPV response. The effect of $PGF_{2\alpha}$ was less evident when given in the first half of the study (early; point A) when compared to its paired control (point B) *versus* when given in the second half of the study (late; point D) compared to its paired control (point C). Point A was significantly different from B and point D from C ($P < 0.01$); and point C was significantly different from B and point A from D ($P < 0.05$). However, point C was not significantly different from A, nor point B from D, although the data suggested that the relative left lung blood flow in the absence of $PGF_{2\alpha}$ (line CB) was greater than in the presence of $PGF_{2\alpha}$ (line AD).

$PGF_{2\alpha}$ are not mediated by sympathetic stimulation, since its pulmonary vasoconstrictor effect is reported to be completely resistant to enhancement or blunting by alpha- and beta-adrenergic blocking agents.[25,26]

There are several other differences between the present study and the study by Scherer *et al.*[6] (table 3), but they do not affect the interpretation or conclusion of the studies. Scherer *et al.*[6] measured the change in venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) rather than the more specific HPV response of atelectatic lung blood flow.[27] Although hypoxia was used in the present study and atelectasis in the study by Scherer *et al.*,[6] the stimulus for HPV (P_{SO_2})[11] were similar for the two studies. P_{SO_2} is the oxygen tension at the sensor for HPV and is related to both the alveolar oxygen tension (PA_{O_2}) and the mixed venous oxygen tension ($P\bar{v}_{O_2}$) during hypoxia and to the $P\bar{v}_{O_2}$ during atelectasis. During the hypoxia-no $PGF_{2\alpha}$ phase, the venous admixture was smaller and the Pa_{O_2} and the $P\bar{v}_{O_2}$ greater in the present study; however, in the present study, the ventilated lung received an FI_{O_2} of 100% *versus* their FI_{O_2} of 66 ± 1.2%. In the present study, the HR was greater and the CO smaller; however, these are consistent with the general hemodynamic conditions previously reported for this dog model.[7,9,12,15,28,29] In both studies, mean PAP and total pulmonary vascular resistance (PVR_T) increased with $PGF_{2\alpha}$ infusion, which is consistent with the action of $PGF_{2\alpha}$ as a pulmonary vasoconstrictor. Although other investigators[30,31] have reported major bronchoconstriction, $PGF_{2\alpha}$ infusion did not produce any significant increase in peak airway pressure in the present study.

During previous studies employing a similar study design,[27,28] the effect of time was confounded by randomization. However, in this study (fig. 3), the data suggested that the effect of $PGF_{2\alpha}$ during hypoxia was less evident when $PGF_{2\alpha}$ was given in the first half of the study (early; point A) compared to its paired control (point B) than when $PGF_{2\alpha}$ was given during the second half of the study (late; point D) compared to its paired control (point C). Although point C was not significantly different from A nor point B from D, the data suggested that the relative left lung blood flow in the absence of $PGF_{2\alpha}$ (line CB) was greater than in the presence of $PGF_{2\alpha}$ (line AD). For each group of six animals during hypoxia, the $PGF_{2\alpha}$ group was significantly different from the no $PGF_{2\alpha}$ control group; point A was significantly different from point B and point C from point D ($P < 0.01$). Also, point A was significantly different from point D and point C from point B ($P < 0.05$). Therefore, further studies may be necessary to determine whether $PGF_{2\alpha}$ actually causes such an enhancement of HPV, but, in any event, the effect is a subtle one.

The present study showed the ability of $PGF_{2\alpha}$ to stimulate vasoconstriction in both the 100% O_2 ventilated lung and hypoxic lung proportionately. HPV was not specifically enhanced by this increase in vasoconstriction. If $PGF_{2\alpha}$ is to be used to enhance oxygenation during one-lung anesthesia, the present results support the suggestion of Scherer *et al.*[6] that the infusion of $PGF_{2\alpha}$ should be confined to the atelectatic lung.

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