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Prostaglandin $F_{2\alpha}$ Improves Oxygen Tension and Reduces Venous Admixture during One-lung Ventilation in Anesthetized Paralyzed Dogs

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The authors investigated the effect of prostaglandin $F_{2\alpha}$ infused into the pulmonary artery of an acutely atelectatic lung in dogs. Seven dogs were anesthetized with piritramid and pentobarbital and intubated with a Kottmeier canine endobronchial tube. Cardiac output, pulmonary arterial, capillary wedge, and systemic arterial pressure were measured via indwelling catheters. Ventilating both lungs with 66% O_2, Pa_{O_2} was 327 ± 15 mmHg (mean ± SD) and venous admixture ($\dot{Q}_{sp}/\dot{Q}_t$) was 11 ± 3%. One-lung atelectasis reduced Pa_{O_2} to 91 ± 12 mmHg and increased $\dot{Q}_{sp}/\dot{Q}_t$ to 40 ± 4%. Prostaglandin $F_{2\alpha}$ in doses of 0.4, 0.6, 1.2, and 1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was infused into the pulmonary artery of the atelectatic lung through a second pulmonary artery catheter. Up to a dose of 1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ there was a dose-dependent reduction in $\dot{Q}_{sp}/\dot{Q}_t$ to a minimum of 25 ± 4% and an increase in Pa_{O_2} to 168 ± 25 mmHg, which could be explained by enhanced pulmonary vasoconstriction in the atelectatic lung with increased blood flow diversion toward the ventilated lung. Infusion of 1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ decreased Pa_{O_2} to 156 ± 32 mmHg and increased $\dot{Q}_{sp}/\dot{Q}_t$ to 32 ± 9%. Increased systemic effects of prostaglandin $F_{2\alpha}$ were observed and presumably were related to saturation of prostaglandin-dehydrogenase leading to vasoconstriction in both lungs and thus reduced blood flow diversion toward the ventilated lung. (Key words: Lung: hypoxic pulmonary vasoconstriction; shunting. Pharmacology: Prostaglandin $F_{2\alpha}$. Ventilation: one lung.)

IN A RECENT CLINICAL INVESTIGATION very low levels of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) were reported during two- and one-lung ventilation.[1] This experimental study was devised to test the hypothesis that exogenous $PGF_{2\alpha}$ infused into the pulmonary artery of an atelectatic lung will potentiate hypoxic pulmonary vasoconstriction (HPV) of that lung and improve oxygenation by redistribution of blood flow to the ventilated lung. Although $PGF_{2\alpha}$ is not a direct mediator of HPV,[2–4] being a potent pulmonary vasoconstrictor[5–7] it seems to be a suitable drug to elicit this response.

As 70–98% of $PGF_{2\alpha}$ is inactivated within one passage through the lung,[8,9] it is assumed that careful dosage of $PGF_{2\alpha}$ would prevent saturation of the inactivation mechanism and would limit the effect to the atelectatic lung.

Materials and Methods

Seven mongrel dogs weighing 23.4 ± 2.3 kg (mean ± SD) and free from overt heart and lung disease were anesthetized with intravenous piritramid 15 mg**, pancuronium bromide 4 mg, and atropine 0.25 mg; thereafter with 66 ± 1.2% oxygen (mean ± SD) in nitrogen. Anesthesia was maintained with piritramid 15 mg/h and pancuronium bromide 2 mg/h. Because piritramid is only an analgesic agent, pentobarbital 25 mg/h was added as an hypnotic agent. The animals were ventilated mechanically with a Dräger ventilator UV-1 at constant rate (10 breaths/min), adjusting tidal volume between 12 and 15 ml/kg to maintain arterial P_{CO_2} at 35 ± 4 mmHg. Fluid status was maintained by continuous intravenous infusion of 5% dextrose in water containing sodium chloride 20 mmol/l and potassium chloride 40 mmol/l (250–500 ml/h). A heating lamp and humidified inspired gas were utilized to maintain body temperature at 36.8 ± 0.6°C (mean ± SD). After the dog was secured in the supine position, a cannula and a 5F catheter incorporating a Clark-type polarographic oxygen electrode (Fresenius) were placed into the right and left femoral artery to measure the time course of changes in Pa_{O_2}, induced by $PGF_{2\alpha}$ infusion. Under fluoroscopic control, balloon-tipped 7F triple lumen Swan–Ganz® thermodilution catheters were introduced into the right and left main pulmonary artery through the external jugular veins.

A subcricoid tracheostomy was performed and the endotracheal tube was replaced by a Rüsch®–Kottmeier tube. By its design this divided airway with two short tubes protruding from a common cuff does not obstruct ventilation of both upper lobes of the lungs. Complete separation of the two lungs was assured by statically inflating one lung to 50 mmHg pressure through one lumen while the other was attached to a tube submerged a few millimeters in a beaker of water with no air bubbles escaping.

Following baseline measurements during two-lung

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** Piritramid is a tertiary amine of the diphenyl prophylamine group; 20 mg piritramid are equianalgesic to 15 mg of morphine, causing less cardiovascular depression than morphine.[10]

TABLE 1. Hemodynamic and Respiratory Parameters in Seven Dogs before, during, and after One-lung Ventilation and PGF_{α} Infusion (Mean Values ± SD)

Type of Ventilation (Phase)	TLV 1	OLV 2	OLV 3a	OLV 3b	OLV 3c	OLV 3d	OLV 4	TLV 5	Significance
$PGF_{2\alpha}$ infusion ($\mu g \cdot kg \cdot min$)	—	—	0.4	0.6	1.2	1.8	—	—	
Pa_{O_2} (mmHg)	327 ± 15	91 ± 12	108 ± 20	140 ± 15	168 ± 25	156 ± 32	99 ± 14	312 ± 30	$P \leq 0.001$
$P\bar{v}_{O_2}$ (mmHg)	55 ± 6	46 ± 6	47 ± 3	47 ± 4	49 ± 4	55 ± 7	48 ± 5	56 ± 6	$P \leq 0.001$
$\dot{Q}_{sp}/\dot{Q}_t$ (%)	11 ± 3	40 ± 4	35 ± 7	27 ± 3	25 ± 4	32 ± 9	39 ± 5	12 ± 3	$P \leq 0.001$
HR (beats/min)	79 ± 9	85 ± 13	91 ± 16	91 ± 17	103 ± 18	109 ± 18	103 ± 11	89 ± 12	$P \leq 0.001$
CO (l/min)	4.1 ± 8	4.5 ± 1.2	4.2 ± 9	4.5 ± 1.2	4.7 ± 1.2	5.2 ± 1.1	4.6 ± 6	4.4 ± 7	$P \leq 0.01$
MAP (mmHg)	94 ± 14	94 ± 10	99 ± 8	101 ± 9	106 ± 10	113 ± 11	99 ± 8	90 ± 11	$P < 0.001$
MPAP (mmHg)	9 ± 2	11 ± 3	11 ± 3	12 ± 4	15 ± 4	16 ± 4	13 ± 2	9 ± 2	$P \leq 0.001$
PCWP (mmHg)	4 ± 1	4 ± 1	5 ± 1	4 ± 1	5 ± 1	5 ± 1	5 ± 1	4 ± 1	ns
PVR ($dyn \cdot s \cdot cm^{-5}$)	85 ± 23	120 ± 44	126 ± 50	145 ± 65	163 ± 70	170 ± 56	126 ± 57	91 ± 33	$P \leq 0.001$
AWP_{peak} (mmHg)	20 ± 2	31 ± 2	31 ± 2	32 ± 3	32 ± 2	32 ± 3	31 ± 2	2 ± 1	*ns*
$AWP_{plateau}$ (mmHg)	9 ± 1	13 ± 2	12 ± 2	13 ± 2	14 ± 2	14 ± 2	13 ± 1	9 ± 1	*ns*

* Significance related to analysis of variance, considering the block of phase 2, 3a, 3b, 3c, 3d. For analysis of blocks 1, 2 and 1, 2, 4, 5 and multiple comparisons see text.

ventilation (TLV) (phase 1) nitrogen was washed out by ventilating the right lung in four animals and the left lung in three animals with 100% oxygen for 15 min prior to discontinuing ventilation to that lung. Atelectasis was induced by clamping the endobronchial tube and allowing the oxygen to be absorbed. The other lung was ventilated with 66 ± 1.2% oxygen. One lung atelectasis was verified by chest roentgenogram. After 60 min of one-lung ventilation (OLV) (phase 2), $PGF_{2\alpha}$ was infused into the pulmonary artery of the nonventilated lung via an electronic infusion pump (Braun, West Germany). The initial dose of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ gradually was increased every 15 min to 0.6, 1.2, and 1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (phase 3a–3d). OLV control measurements were taken 30 min after prostaglandin infusion was stopped (phase 4); the atelectatic lung then was hyperinflated manually. Following 30 min of TLV (phase 5), a final set of baseline measurements was taken and cardiac arrest was induced by an intravenous injection of 20 mmol potassium chloride. At each phase, cardiac output (CO), mean pulmonary artery (MPAP), and pulmonary capillary wedge (PCWP) pressures were determined using the pulmonary artery catheter in the ventilated lung. Heart rate (HR), airway pressure (AWP), mean arterial (MAP), and central venous pressure were measured at end-expiration and recorded on a five-channel polygraph recorder. Arterial and mixed venous blood gas analysis and determinations of oxygen concentration in the inspired gas were done immediately using a Radiometer® ABL-2. All measurements were made following two-point calibration.

Venous admixture ($\dot{Q}_{sp}/\dot{Q}_t$) was calculated using the traditional shunt equation.[11] Canine blood oxyhemoglobin saturation was derived from the dissociation curve corrected for *p*H and temperature.[12] Hemoglobin was determined with an Eppendorf® Digital Photometer 6114 S. Alveolar oxygen tension was calculated. Pulmonary vascular resistance (PVR) was calculated using standard formulas.

Statistical Method

To test the global influence of treatments, analysis of variance was used for each variable.

The main effects on the factor treatment were tested on the 0.05, 0.01, or 0.001 level of significance. If global differences of treatments were significant, multiple comparisons were performed with a posteriori probability of 0.05 based on the Bonferroni α-adjustment procedure.[13] Statistical calculations were made using program INSTAT.[14]

Results

The results of the hemodynamic and respiratory measurements are shown in table 1.

Effect of One-lung Atelectasis

With the changeover from TLV to OLV the arterial PO_2 decreased significantly ($P \leq 0.001$). Mixed venous PO_2 also decreased ($P \leq 0.01$), while venous admixture ($\dot{Q}_{sp}/\dot{Q}_t$) increased ($P \leq 0.001$). Heart rate, cardiac output, MAP, and PCWP did not change, while MPAP and PVR increased ($P \leq 0.05$). With the beginning of OLV peak airway pressure increased ($P \leq 0.001$) and so did end-inspiratory plateau pressure ($P \leq 0.01$).

Effect of Prostaglandin Infusion

Prostaglandin infusion had a significant effect on Pa_{O_2}. Infusion of 0.4, 0.6, 1.2, and 1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of $PGF_{2\alpha}$ increased Pa_{O_2} significantly ($P \leq 0.05$) when compared with the preinfusion OLV period (phase 2). Multiple comparisons showed that there was a significant ($P \leq 0.05$) increase in Pa_{O_2} following each successive dose increment up to a dosage of 1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of $PGF_{2\alpha}$. Pa_{O_2} reached 168 ± 25 mmHg in phase 3c (fig. 1). The increase in Pa_{O_2} following infusion of $PGF_{2\alpha}$ occurred rapidly reaching a new equilibrium within 62 ± 24 s (mean ± SD) (fig. 2). Mixed venous PO_2 did not increase significantly before 1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of $PGF_{2\alpha}$ was given. $PGF_{2\alpha}$ significantly reduced $\dot{Q}_{sp}/\dot{Q}_t$ ($P \leq 0.001$). When compared with phase 2, significant reductions in $\dot{Q}_{sp}/\dot{Q}_t$ occurred at 0.6 and 1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ $PGF_{2\alpha}$, maximum reduction was observed at 1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. With infusion of 1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, Pa_{O_2} decreased slightly and $\dot{Q}_{sp}/\dot{Q}_t$ increased when compared with phase 3c (fig. 1). Heart rate and cardiac output were significantly influenced by $PGF_{2\alpha}$ infusion, but in multiple comparisons a significant increase was observed only between phases 2 and 3d (table 1).

MAP increased significantly during $PGF_{2\alpha}$ infusion, but there were no significant differences between the four dosages given. MPAP was significantly ($P \leq 0.05$) increased during phase 3c and 3d when compared with the preinfusion period and 0.4 and 0.6 $\mu \cdot kg^{-1} \cdot min^{-1}$ of $PGF_{2\alpha}$.

Likewise, PVR increased significantly when phase 2 and 3a were compared with 3d. The increase in peak airway pressure and end-inspiratory plateau pressure was not significant.

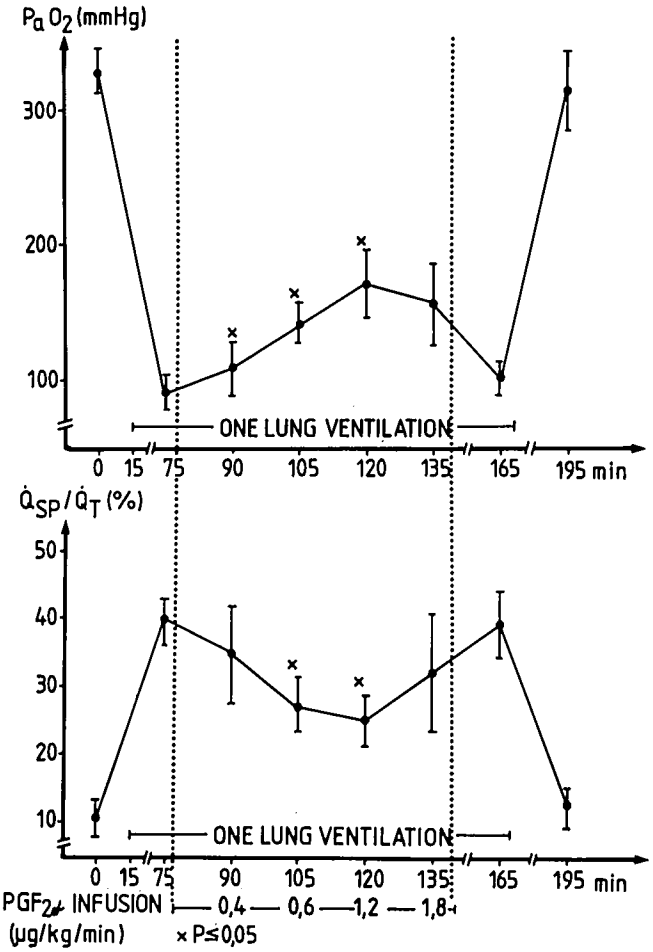

FIG. 1. Changes of arterial P_{O_2} and venous admixture ($\dot{Q}_{sp}/\dot{Q}_t$) during two-lung ventilation and one-lung ventilation and the effect of prostaglandin $F_{2\alpha}$ infusion in seven dogs (mean values ± SD). During prostaglandin infusion, Pa_{O_2} increased significantly ($P \leq 0.05$) when compared with each preceding step; $\dot{Q}_{sp}/\dot{Q}_t$ decreased ($P \leq 0.05$) when compared with step 2 at 75 min.

Control Measurements after $PGF_{2\alpha}$ Infusion

Thirty minutes after $PGF_{2\alpha}$ infusion was stopped, Pa_{O_2} $P\bar{v}_{O_2}$, $\dot{Q}_{sp}/\dot{Q}_t$, cardiac output, MAP, MPAP, PCWP, PVR, and AWP were not significantly different from their respective preinfusion levels. Heart rate still was significantly above preinfusion levels.

With reexpansion of the atelectatic lung, all measured variables returned to preatelectatic control values.

During the entire 3-h study period, arterial *p*H was 7.39 ± 0.03 and hemoglobin decreased from 12.1 ± 1.6 g/dl to 11.1 ± 0.9 g/dl. Central venous pressure was 2.6 ± 0.4 mmHg.

Discussion

The major findings in the present study show that arterial and mixed venous oxygen tension and calculated venous admixture during stable one-lung atelectasis in mechanically ventilated dogs can be improved by infusion of $PGF_{2\alpha}$ into the pulmonary artery of the atelectatic lung. These findings are discussed in detail, after some methodologic considerations.

Induction of atelectasis resulted in a small but consistent increase in mean pulmonary artery pressure and an increase in venous admixture, comparable with results of other investigators.[15,17] The increase in MPAP is typical for HPV in a large hypoxic segment, resulting in limited blood flow redistribution to the ventilated lung.[18] Intermittent challenges with hypoxic gas mixtures potentiated HPV in an open-chest preparation of the left lower lobe in the dog.[19,20] In the open chest the increase in pulmonary vascular resistance in response to acute atelectasis is maximal after 60 min and stable thereafter.[21] In a closed-chest preparation, flow diver-

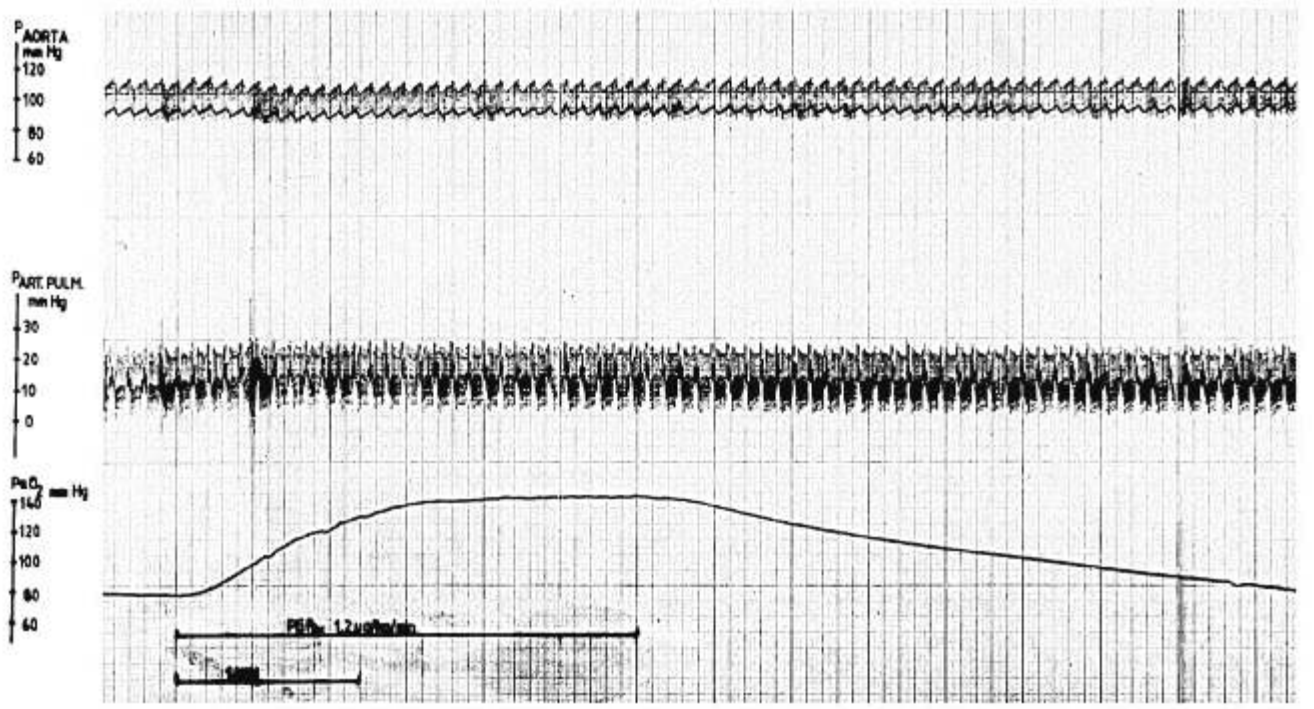

FIG. 2. Original, recording of aortic pressure, pulmonary artery pressure, and arterial oxygen tension measured by indwelling intraarterial oxygen probe. In little more than 1 min after $PGF_{2\alpha}$ infusion ($1.2\,\mu g \cdot kg^{-1} \cdot min^{-1}$) was started, Pa_{O_2} reached a new stable level. There was a small increase in pulmonary artery pressure.

sion was maximal after the first hypoxic exposure compared with the fourth hypoxic trial in an open-chest experiment.[22]

Therefore, in the present study repeated challanges of the pulmonary vasculature were not performed in this closed-chest model before HPV of the atelectatic lung was considered to have reached near steady state conditions.

In contrast to other studies,[17,20,21] the nonatelectatic lung was ventilated with 66% instead of 100% oxygen. Using an FI_{O_2} of 0.66, no severe hypoxemia occurred during OLV in a previous human study[1] nor in the present study. Severe hypoxemia can induce HPV in the ventilated lung counteracting blood flow redistribution from the atelectatic lung.[15] Increasing FI_{O_2} to 95 or 100% may result in a release of HPV in regions of the ventilated lung with critically low $\dot{V}_A/Q$ ratios and increase venous admixture.[23]

The effect of $PGF_{2\alpha}$ on arterial and mixed venous oxygen tension and shunt only can be explained by an increase in HPV in the atelectatic lung, resulting in increased blood flow redistribution toward the ventilated lung. Pa_{O_2} was improved despite significant increases in pulmonary perfusion pressure, estimated by MPAP – PCWP, and cardiac output. Increased pulmonary blood volume and increased intraluminal vascular pressures normally are considered an important factor inhibiting effective blood flow redistribution by HPV.[18,24]

The largest increase in Pa_{O_2} and associated decrease in $\dot{Q}_{sp}/\dot{Q}_t$ was observed at a PGF infusion rate of $1.2\,\mu g \cdot kg^{-1} \cdot min^{-1}$. The oxygen content was estimated only by oxygen tension and hemoglobin, assuming a carboxyhemoglobin of zero and using the hemoglobin saturation derived from the Rossing nomogram for dogs,[11] therefore, the calculated venous admixture likely yielded falsely high shunt values.[25] However, the errors attributable to the common clinical practice of neglecting carboxyhemoglobin and methemoglobin measurements are smaller when saturation is calculated than when it is directly measured by an oxygen analyzer.[26]

There was a slight decrease in Pa_{O_2} and increase in $\dot{Q}_{sp}/\dot{Q}_t$ at $PGF_{2\alpha}$ infusion rate of $1.8\,\mu g \cdot kg^{-1} \cdot min^{-1}$. This decrease in response to $PGF_{2\alpha}$ presumably can be related to saturation of PG dehydrogenase, the enzyme responsible for PG metabolism.[9] $PGF_{2\alpha}$ is inactivated almost completely during one passage through the lung,[8,9] however, if PG infusion rate surpasses enzyme capacity, $PGF_{2\alpha}$ will reach the systemic circulation. Systemic effects of $PGF_{2\alpha}$ include an increase in mean arterial pressure, cardiac output, and heart rate.[6,7] The

significant increases in heart rate and cardiac output in phase 3d, when compared with phase 2, coincide with the maximum increase in MPAP and PVR.

$PGF_{2\alpha}$ escaping hepatic metabolism[3,4,6] will affect pulmonary vessels in both the ventilated and atelectatic lung. A slight vasoconstricting effect in the ventilated lung would diminish blood flow diversion away from the atelectatic lung.

In contrast to other investigators,[27,28] PG doses given in the present study did not produce any major bronchoconstriction, as there was a nonsignificant increase in airway peak pressure and no significant increase in end-inspiratory plateau pressure. The latter could be attributed to decreased compliance caused by small airway constriction as normal PCWP values exclude pulmonary venous hypertension.[28]

A few minutes after the PG infusion was stopped, all variables except heart rate returned to base line values (phase 2). The persisting moderately increased heart rate may be in large measure a reflex consequence of a decrease in blood pressure. Higher doses of $PGF_{2\alpha}$ in the systemic circulation may induce a persisting increase in sympathic outflow from the central nervous system.[6] However, the effects of $PGF_{2\alpha}$ are not mediated by sympathic stimulation, because of the reported complete resistance of its pulmonary vasoconstricting effect to enhancement or blunting by alpha- and beta-adrenergic blocking agents.[29,30] An activation of histamine receptors or the release of histamine does not mediate this action of $PGF_{2\alpha}$ as well.[30]

Norepinephrine and histamine are unlikely to provide the same selective pulmonary vasoconstriction in the atelectatic lung as $PGF_{2\alpha}$; both produce variable degrees of pulmonary vasoconstriction, but histamine, like epinephrine and dopamine, is not eliminated from the pulmonary circulation to any appreciable extent, and only 20–35% of exogenously administered norepinephrine is metabolized on passage through the lung.[31]

Experimental evidence in animals is difficult to apply to humans because of considerable species differences in response to PGs, but $PGF_{2\alpha}$ is a pulmonary vasoconstrictor in humans[32] as well, and human pulmonary circulation metabolizes $PGF_{2\alpha}$ in much the same way as other mammalian lungs.[33] Therefore, $PGF_{2\alpha}$ infusion into the pulmonary artery of an acutely atelectatic lung also may prove to be a practical and safe method to improve oxygenation during one-lung ventilation in humans. $PGF_{2\alpha}$ can be titrated to achieve an optimal effect without causing major systemic reactions. There was no persisting PG action or cardiopulmonary dysfunction at the end of the study period.

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