Influence of cyclo-oxygenase inhibition and of leukotriene receptor blockade on pulmonary vascular pressure/cardiac index relationships in hyperoxic and in hypoxic dogs

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Summary

1. Overall mean pulmonary arterial pressure (MPAP)/cardiac index (CI) relationships were investigated in 13 pentobarbital anaesthetized dogs ventilated consecutively with a fraction of inspired O₂ (F₁O₂) of 0.4 and with a F₁O₂ of 0.1. This sequence of alternated F₁O₂ 0.4 and F₁O₂ 0.1 was repeated (1) in the dogs with a strong pulmonary pressor response to hypoxia (more than 20% increase in pulmonary vascular resistance) (n = 6) under a continuous infusion of the leukotriene receptor blocker FPL 57231 (2 mg min⁻¹ kg⁻¹), and (2) in the dogs with a weak pressor response to hypoxia (n = 7) after cyclo-oxygenase inhibition by acetylsalicylic acid (1 g intravenously). Five-point MPAP/CI plots were constructed by opening a femoral arteriovenous fistula or by stepwise inflations of an inferior vena cava balloon catheter. The MPAP/CI plots were rectilinear in all experimental conditions.

2. In responders, hypoxia was associated with an increase in MPAP over the entire range of CI studied (1–5 litres min⁻¹ m⁻²). Infusion of FPL 57231 abolished the vasoconstricting effect of hypoxia. There is evidence implicating metabolites of arachidonic acid in the still unknown biochemical mechanism of hypoxic pulmonary vasoconstriction [1–3]. A current hypothesis is that the hypoxic pulmonary pressor response could be mediated by balanced actions of constricting leukotrienes (LT) and of vasodilating prostaglandins [4, 5]. We investigated this hypothesis in an intact anaesthetized and ventilated dog model using a LT receptor blocker FPL 57231 and a cyclo-oxygenase inhibitor, acetylsalicylic acid. Pulmonary vascular tone in intact animals and in man commonly is evaluated by the calculation of systemic capillary wedge pressure.

5. Stability of pulmonary vascular tone at F₁O₂ 0.4 and at F₁O₂ 0.1 and reproducibility of the hypoxic pressor response was ascertained in an additional group of five dogs with CI kept constant and MPAP measurements every 6 min during four consecutive periods of 30 min (i.e. maximum time needed to generate a MPAP/CI plot) alternately at F₁O₂ 0.4 and at F₁O₂ 0.1.

6. These results suggest that pulmonary vascular reactivity to hypoxia is regulated by balanced actions of vasoconstricting leukotrienes and vasodilating prostaglandins in anaesthetized dogs. They also indicate a vasodilating effect of FPL 57231 on systemic vessels.

Key words: acetylsalicylic acid, FPL 57231, hypoxic pulmonary vasoconstriction, leukotrienes, prostaglandins.

Abbreviations: CI, cardiac index; LT, leukotriene; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure.

Introduction

There is evidence implicating metabolites of arachidonic acid in the still unknown biochemical mechanism of hypoxic pulmonary vasoconstriction [1–3]. A current hypothesis is that the hypoxic pulmonary pressor response could be mediated by balanced actions of constricting leukotrienes (LT) and of vasodilating prostaglandins [4, 5]. We investigated this hypothesis in an intact anaesthetized and ventilated dog model using a LT receptor blocker FPL 57231 and a cyclo-oxygenase inhibitor, acetylsalicylic acid.
pulmonary vascular resistance, i.e., mean pulmonary artery pressure (MPAP) minus pulmonary capillary wedge pressure (PCWP) divided by cardiac output. This approach assumes that the pulmonary vascular gradient (MPAP–PCWP)/cardiac output relationship is linear and passes through the origin [6]. In isolated lung preparations [7, 8] the MPAP/flow relationship is linear over a wide range of flows, but becomes curvilinear when flow is low, so that the extrapolation of the linear part of the curve has a positive pressure intercept. This positive pressure intercept represents an averaged closing pressure of the pulmonary vessels [6-8]. In normoxic recumbent intact conscious dogs [9] and man [10] the extrapolation of the linear part of MPAP–PCWP/cardiac output relationships passes through the origin, suggesting that closing pressure is exceeded by left atrial pressure [7]. Hypoxia, a variety of diseases and pharmacological interventions are capable of affecting the slopes and increasing the extrapolated pressure intercepts of MPAP/cardiac output relationships [6-10]. As soon as closing pressure exceeds PCWP, calculation of pulmonary vascular resistance does not allow discrimination between active (i.e. changes in vascular tone) and passive (i.e. flow-dependent) modifications in pulmonary arterial pressures. A correct appreciation of pulmonary haemodynamics then obviously requires measurements of pulmonary arterial pressures at several levels of flow [6-10].

In the present experiments we manipulated cardiac output either by stepwise inflations of an inferior vena cava balloon or by opening an arteriovenous fistula in intact anaesthetized dogs, and so were able to characterize MPAP/flow relationships in hyperoxic and in hypoxic conditions before and after administration of drugs acting at different steps of the cyclo-oxygenase and the 5-lipoxygenase pathways of arachidonic acid metabolism.

Methods
Eighteen mongrel dogs (body weight 20-34 kg, mean 25 kg) were anaesthetized with sodium pentobarbital (25 mg/kg intravenously), paralysed with pancuronium bromide (0.2 mg/kg intravenously) and ventilated (Elema 900 B Servo-Ventilator, Siemens Elema, Solna, Sweden) via a cuffed endotracheal tube with an inspiratory fraction of O₂ (FIO₂) of 0.4, a respiratory rate of 12 breaths/min and a tidal volume of 15-20 ml/kg adjusted to maintain end-expiratory FIO₂ between 30 and 35 mmHg as measured with an infrared capnometer (model 47217, Hewlett Packard, Palo Alto, CA, U.S.A.). Pentobarbital (2 mg/kg intravenously) and pancuronium (0.2 mg/kg intravenously) were repeated hourly to maintain anaesthesia and prevent spontaneous respiratory efforts. Throughout the experiment, 0.9% NaCl was infused at 4 ml h⁻¹ kg⁻¹ into the left external jugular vein. Temperature was maintained at 37-38°C by use of a heating electric blanket. A thermistor-tipped Swan Ganz catheter (model 93A-131-7F, Edwards Laboratories, Santa Ana, CA, U.S.A.) was inserted via the right external jugular vein and positioned by means of pressure monitoring in a branch of the pulmonary artery, for measurement of pulmonary artery pressure, PCWP, right atrial pressure and mixed venous blood sampling. A polyethylene catheter was placed in the abdominal aorta via the right femoral artery for systemic blood pressure measurement and arterial blood sampling. A balloon catheter (Peri-Cor, 45, Datascop, Paramus, NJ, U.S.A.) was advanced into the inferior vena cava through a right femoral venotomy. Infusion of this balloon produced a measurable decrease in cardiac output by reducing venous return. A large-bore polyethylene cannula was inserted into the left femoral artery and vein to act as an arteriovenous fistula. Opening the fistula resulted in an increase in cardiac output. Thrombus formation along the catheters was prevented by intravenous infusion of 100 units of sodium heparin/kg just before insertion and 50 units/kg repeated every 2 hs thereafter. Pulmonary and systemic artery pressures were measured at end-expiration using Bentley transducers and the Heres computer system (ACEC, Charleroi, Belgium) and recorded on a four-channel Gould recorder (model 2400 S, Gould Inc., Instruments Division, Cleveland, OH, U.S.A.). The zero reference level was taken to be midway between the dorsal and the ventral margin of the thoracic cavity, measured at the caudal third of the sternum. Heart rate was determined from a continuously monitored electrocardiographic lead. Cardiac output was measured in triplicate by thermodilution with injection of 10 ml of 0.9% NaCl solution at 0°C, the 9520-A computer (Edwards Laboratories) and an automated pneumatic pump electronically synchronized on ventilatory cycle. Arterial and mixed venous haemoglobin, pH, PETO₂ and PO₂ were measured immediately after drawing the samples by an automated analyser (ABL-2, Radiometer, Copenhagen, Denmark) and corrected for temperature. Oxygen saturations were calculated from the nomogram of Rossing & Cain [11]. Body surface area (m²) was calculated as 0.112 × weight (kg)²/³. The following derived variables were calculated: O₂ transport (ml min⁻¹ m⁻²) = cardiac index (CI) × arterial O₂ content × 10; O₂ consumption (ml min⁻¹ m⁻²) = CI × arteriovenous O₂ content difference × 10.

After ensuring steady state conditions for 20 min at FIO₂ 0.4, the first five-point MPAP/CI plot was...
generated from haemodynamic determinations at baseline (one point), after opening the femoral arteriovenous fistula (one point) and after stepwise incremental inflations of the inferior vena cava balloon catheter with occluded fistula (three points). The same procedure was performed after 10 min of an acute hypoxic challenge at $F_{O_2}$ 0.1. When hypoxia induced a more than 20% increase in pulmonary vascular resistance at uncontrolled flow (responders, n=6) FPL 57231 (2 mg min$^{-1}$ kg$^{-1}$) was infused intravenously using a calibrated pump (Braun Melsungen AG, Melsungen, Germany). When hypoxia did not change pulmonary vascular resistance at uncontrolled flow by more than 20% (non-responders, n=7) a 1 g intravenous bolus of acetylsalicylic acid was given. After 45 min, two MPAP/CI plots were constructed as described above successively at $F_{O_2}$ 0.4 and at $F_{O_2}$ 0.1. The average time to generate a five-point MPAP/CI plot was 20–25 min.

The stability of hyperoxic and of hypoxic pulmonary vascular tone and the reproducibility of the hypoxic pressor response in our experimental model was ascertained in five additional dogs. Cardiac output was kept constant and MPAP was measured every 6 min during four consecutive 30 min periods alternately at $F_{O_2}$ 0.4 and at $F_{O_2}$ 0.1, starting at $F_{O_2}$ 0.4.

Inspection of the individual MPAP/CI plots showed them to be essentially rectilinear and thus a least squares regression analysis was used to compute slopes and extrapolated pressure intercepts for each MPAP/CI relationship. To obtain composite MPAP/CI plots for each experimental situation, MPAP interpolated from the regression analysis from individual dogs were averaged at 1 litre min$^{-1}$ m$^{-2}$ intervals of CI from 1 to 5 litres min$^{-1}$ m$^{-2}$ and presented as means ± SEM. A two-way analysis of variance with repeated measures was used to assess (1) the effects of reducing CI on haemodynamics and on blood gases, (2) the effects of hypoxia and/or drugs on haemodynamics and on blood gases at the highest and at the lowest CI, and (3) the effects of hypoxia and/or drugs on MPAP at CI levels from 1 to 5 litres min$^{-1}$ m$^{-2}$. Modified $t$-tests were used when the $F$-ratio of the analysis of variance reached a level of $P < 0.05$ to compare MPAP at a given level of flow in different experimental conditions [12].

Results

Haemodynamics and blood gases

Haemodynamic and blood gas determinations at the highest and at the lowest CI are shown in Table 1 and in Table 2. The presence, absence or restoration of hypoxic pulmonary vasoconstriction had no significant effect on blood gases. Reduction in cardiac output decreased $O_2$ transport, mixed venous $P_{O_2}$, mean systemic arterial pressure and MPAP with either no change or a slight decrease in right atrial pressure and in PCWP. Acetylsalicylic acid had no effect other than a restored hypoxic pulmonary pressor response (Table 2). FPL 57231 decreased systemic arterial pressure in addition to inhibition of hypoxic pulmonary vasoconstriction (Table 1).

Pulmonary arterial pressure/flow relationships

Fifty-two MPAP/CI plots (13 dogs in four different experimental conditions) were constructed. In all but one ($r=0.76$) the linear regression coefficients were above 0.95. Composite MPAP/CI plots are shown in Fig. 1 and in Fig. 2. In responders hypoxia increased MPAP over the entire range of CI studied (1 to 5 litres min$^{-1}$ m$^{-2}$) and this pressor response was abolished by FPL 57231 (Fig. 1). In non-responders hypoxia did not affect MPAP at any level of CI but acetylsalicylic acid restored a pressor response at all levels of CI studied except the lowest (Fig. 2).

Stability and reproducibility of hypoxic pulmonary vasoconstriction

As shown in Fig. 3, MPAP remained stable during 30 min periods at constant cardiac output in hyperoxic as well as in hypoxic conditions. The magnitude of increase in MPAP was not significantly different at two consecutive hypoxic challenges.

Discussion

The MPAP/CI relationships in these intact pentobarbital anaesthetized, paralysed and ventilated dogs were rectilinear in both hypoxic and hyperoxic conditions and remained so after pharmacological interventions. This is in agreement with studies on isolated lung preparations [7, 8, 13–15] and on intact conscious dogs [9, 16]. Individual pulmonary pressor responses to hypoxia consisted of variable increase of slopes and/or extrapolated pressure intercepts of MPAP/CI relationships, also in keeping with observations on isolated lungs [13, 14] or intact animals including man [9, 10]. The magnitude of hypoxia-induced increases in MPAP was comparable with previous observations on intact dogs [9] or man [10].

Repetition of hypoxic challenges has been reported either to enhance [17] or not to affect [18] hypoxic pulmonary vasoconstriction. The magni-
### Table 1. Effects of FPL 57231 on haemodynamics and blood gases

Values are means ± SEM (n = 6). Abbreviations: \( T_{O_2} \), \( O_2 \) transport; \( \dot{V}_O_2 \), \( O_2 \) consumption; HR, heart rate; SAP, mean systemic pressure; RAP, mean right atrial pressure. Statistical significance: †P < 0.05 vs baseline \( F_1O_2 \) 0.4 highest CI, ‡P < 0.001 vs baseline \( F_1O_2 \) 0.4 highest CI, ‡‡P < 0.001 vs baseline \( F_1O_2 \) 0.1 highest CI.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>FPL 57231 (2 mg min⁻¹ kg⁻¹)</th>
</tr>
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<tr>
<td></td>
<td>Highest CI</td>
<td>Lowest CI</td>
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<tr>
<td>Arterial pH</td>
<td>7.33 ± 0.02</td>
<td>7.33 ± 0.03</td>
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<td>( P_{A_0_2} ) (mmHg)</td>
<td>220 ± 8</td>
<td>213 ± 9</td>
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<td>( P_{A_CO_2} ) (mmHg)</td>
<td>36 ± 1</td>
<td>33 ± 1</td>
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<td>( P_{V_O_2} ) (mmHg)</td>
<td>58 ± 2</td>
<td>39 ± 2†</td>
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<tr>
<td>( T_{O_2} ) (ml min⁻¹ m⁻²)</td>
<td>799 ± 83</td>
<td>321 ± 39††</td>
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<tr>
<td>( V_O_2 ) (ml min⁻¹ m⁻²)</td>
<td>143 ± 8</td>
<td>117 ± 10</td>
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<td>HR (beats/min)</td>
<td>160 ± 3</td>
<td>169 ± 9</td>
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<td>CI (litres min⁻¹ m⁻²)</td>
<td>5.16 ± 0.32</td>
<td>2.02 ± 0.19††</td>
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<td>( S_A_P ) (mmHg)</td>
<td>115 ± 6</td>
<td>90 ± 10††</td>
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<tr>
<td>RAP (mmHg)</td>
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<td>MPAP (mmHg)</td>
<td>16 ± 1</td>
<td>10 ± 0††</td>
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<tr>
<td>PCWP (mmHg)</td>
<td>6 ± 1</td>
<td>4 ± 0††</td>
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### Table 2. Effects of acetylsalicylic acid on haemodynamics and blood gases

Results are means ± SEM (n = 7). For abbreviations, see legend to Table 1. Statistical significance: †P < 0.05 vs baseline \( F_1O_2 \) 0.4 highest CI, ‡P < 0.001 vs baseline \( F_1O_2 \) 0.4 highest CI, ‡‡P < 0.001 vs baseline \( F_1O_2 \) 0.1 highest CI.

<table>
<thead>
<tr>
<th>Variables</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Highest CI</td>
<td>Lowest CI</td>
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<tr>
<td>Arterial pH</td>
<td>7.34 ± 0.01</td>
<td>7.34 ± 0.02</td>
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<tr>
<td>( P_{A_0_2} ) (mmHg)</td>
<td>200 ± 8</td>
<td>190 ± 11</td>
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<td>( P_{A_CO_2} ) (mmHg)</td>
<td>38 ± 1</td>
<td>34 ± 1</td>
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<tr>
<td>( P_{V_O_2} ) (mmHg)</td>
<td>54 ± 2</td>
<td>40 ± 3†</td>
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<tr>
<td>( T_{O_2} ) (ml min⁻¹ m⁻²)</td>
<td>679 ± 72</td>
<td>318 ± 29††</td>
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<td>( V_O_2 ) (ml min⁻¹ m⁻²)</td>
<td>139 ± 16</td>
<td>110 ± 6</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>157 ± 7</td>
<td>167 ± 4</td>
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<tr>
<td>CI (litres min⁻¹ m⁻²)</td>
<td>4.36 ± 0.25</td>
<td>2.03 ± 0.08††</td>
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<tr>
<td>( S_A_P ) (mmHg)</td>
<td>120 ± 6</td>
<td>108 ± 5</td>
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<td>RAP (mmHg)</td>
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<td>3 ± 1</td>
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<tr>
<td>MPAP (mmHg)</td>
<td>15 ± 1</td>
<td>10 ± 1††</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>6 ± 1</td>
<td>4 ± 1††</td>
</tr>
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Eicosanoids and hypoxic pulmonary vasoconstriction

Fig. 1. Composite MPAP (mean ± SEM)/CI plots in six dogs with a strong pressor response to hypoxia, before (----) and after (-----) FPL 57231 (2 mg min⁻¹ kg⁻¹). ●, \( F_O_2 \) 0.4; ○, \( F_O_2 \) 0.1. Statistical significance: \( * P < 0.05 \) \( F_O_2 \) 0.1 (without drug) versus \( F_O_2 \) 0.1 (with drug).

Fig. 2. Composite MPAP (mean ± SEM)/CI plots in seven dogs with a weak pressor response to hypoxia, before (-----) and after (-----) acetylsalicylic acid (1 g intravenously). ●, \( F_O_2 \) 0.4; ○, \( F_O_2 \) 0.1. Statistical significance: \( * P < 0.05 \) \( F_O_2 \) 0.1 (without drug) versus \( F_O_2 \) 0.1 (with drug).

Fig. 3. Mean ± SEM of five successive measurements of MPAP at 6 min intervals in five dogs with cardiac output kept constant and exposed to two consecutive hypoxic challenges.

The magnitude of the hypoxic pressor response has also been observed to vary during time periods of 20–25 min [19]. It is thus noteworthy that in the present experimental model pulmonary vascular tone remained stable at both \( F_O_2 \) 0.4 and \( F_O_2 \) 0.1 during the time periods required to generate MPAP/CI plots and that two consecutive hypoxias induced the same increases in MPAP at identical flow.

The use of intact dogs allows the expression of many potential control mechanisms that contribute to the regulation of the pulmonary circulation. Changes in pH [20], mixed venous \( P_O_2 \) [21] and neurohumoral activity [16] may have influenced pulmonary vascular tone during cardiac output manipulations. Thus MPAP/CI plots probably represent an integrated response of the intact pulmonary circulation to multiple vasoactive stimuli rather than truly passive pressure/flow relationships [16]. Given these methodological limitations of the intact animal model, changes in MPAP were analysed at the different levels of flow instead of comparing slopes (taken as incremental vascular resistance) and extrapolated pressure intercepts (taken as averaged closing pressures) of the MPAP/CI plots.

Reduction of venous return by inflation of an inferior vena cava balloon is associated with an activation of the baroreflex to maintain systemic blood pressure [15]. Large changes in carotid sinus pressure, however, have little effect on pulmonary arterial pressure/flow relationships [15].

In the present experiments mechanical ventilation could have affected MPAP/CI relationships as a consequence of intermittent positive alveolar pressures. Although this was minimized by reading the vascular pressure tracings at end-expiration, when airway pressure was zero, such a mechanism might account for the somewhat higher extra-
polated pressure intercepts of MPAP/CI relationships than observed by others in spontaneously breathing dogs [9]. On the other hand, it was assumed that neither hypoxia nor the pharmacological interventions significantly affected pleural pressures nor bronchomotor tone. Pleural pressure has been shown to be unchanged after hypoxia or FPL 57231 infusion in sheep [4] or after inferior vena cava constriction in dogs [9]. Normal bronchial tone is low and it seems reasonable to consider that only very small changes would be expected after possibly bronchodilating pharmacological intervention.

This study shows that the cyclo-oxygenase inhibitor acetylsalicylic acid restores pulmonary reactivity in dogs with weak hypoxic pulmonary vasoconstrictor response. Recent evidence suggests that prostaglandins play a role in modulating pulmonary vascular tone. Acute administration of cyclo-oxygenase inhibitors raises basal pulmonary artery pressure in conscious dogs [22] and potentiates the pulmonary vasoconstrictor response to hypoxia in various species [1]. Repeated administration of indomethacin in sheep causes pulmonary hypertension and increases vasoreactivity to hypoxia [2]. The decay in pressor response to repeated hypoxic challenges in isolated dog lungs is abolished by cyclo-oxygenase inhibitors [23]. Sodium arachidonate administration in dogs during hypoxia results in pulmonary vasodilatation by being converted into prostacyclin [24]. These studies strongly suggest that vasodilating prostaglandins, presumably prostacyclin, contribute to low vascular tone in the pulmonary circulation, and are released during hypoxia, modulating its pressor effect. Other studies, however, show variable responses to cyclo-oxygenase inhibitors during normoxia or hypoxia, indicating that these drugs can influence the pulmonary circulation by mechanisms independent of prostaglandin metabolism [25]. At the high dose given in the present experiments acetylsalicylic acid could possibly exert vascular effects not related to cyclo-oxygenase inhibition, but this is unlikely since no vasoconstriction occurred in hyperoxic conditions. Some animals fail to respond to hypoxia with pulmonary vasoconstriction, possibly as the result of an increased basal production of vasodilating prostaglandins. Our results further support this hypothesis and are in agreement with previous studies showing that administration of cyclo-oxygenase inhibitors enhances the pulmonary vasoconstrictor response to hypoxia in ‘non-responder’ animals [5, 26].

More recently, evidence has been accumulated that some LT may be involved in the regulation of pulmonary vascular tone. LTC₄ and LTD₄ are potent smooth muscle constrictors that increase pulmonary vascular tone in vitro and produce pulmonary arterial hypertension in vivo [27–31]. During normoxic ventilation, the LT receptor antagonist FPL 57231 produces pulmonary vasodilatation in fetal [32] and newborn [33] lambs. Several structurally unrelated inhibitors of LT synthesis, release or action, such as diethylcarbamazine [3, 34], U-60257 [3], nordihydroguaiaretic acid [35], cromolyn sodium [4], FPL 57231 [4, 33, 36] and FPL 55712 [3], have been reported to block hypoxic pulmonary vasodilatation in conscious sheep [4], isolated perfused lungs from rats [3, 34] and ferrets [35], and newborn lambs [33, 36], but not in newborn piglets [28]. In the intact anaesthetized and ventilated dogs of the present study, the specific LT receptor antagonist FPL 57231 [37] abolished hypoxic pulmonary vasoconstriction in animals with vigorous pressor response to hypoxia. These results are in agreement with the hypothesis that LT may be involved in the mediation of hypoxic pulmonary vasoconstriction. It is suggested from recent studies that LTC₄ may be a major pulmonary vasoconstrictor [29] while LTD₄ may constrict pulmonary vessels by activation of the cyclo-oxygenase pathway with subsequent release of vasoconstricting prostaglandins and thromboxanes [28, 30]. On the other hand, prostacyclin is presumably the vasodilating prostaglandin released in response to the hypoxic stimulus [24] and modulating the LT vasoconstrictor effects.

Infusion of FPL 57231 results in a significant drop in systemic arterial pressure when compared with baseline values at similar cardiac output, during both hyperoxic and hypoxic ventilation. Whether this effect also recently observed by others [33] is related to LT receptor blockade needs further confirmation.

In summary, this study suggests that, in the intact anaesthetized dog, interactions between the cyclo-oxygenase and lipoxygenase pathways of arachidonic acid metabolism are involved in the control of hypoxic pulmonary vascular tone. The LT receptor blocker FPL 57231 induces systemic vasodilatation, possibility by a LT-related mechanism.

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References


10. Even, P., Duroux, P., Ruff, F., Cambarrera, I., de Morganroth, M.L., Reeves, J.T., Murphy, R.C. Methacin in sheep. Increased vasoreactivity caused by repeated indo- 


