

Hypoxic Pulmonary Vasoconstriction Is Not Potentiated by Repeated Intermittent Hypoxia in Closed Chest Dogs

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Hypoxic pulmonary vasoconstrictor (HPV) responses were measured with repeated intermittent hypoxic challenges in eight non-traumatized closed chest dogs anesthetized with pentobarbital. The right lung was ventilated continuously with 100% O₂ while the left lung was either ventilated with 100% O₂ (control) or ventilated with a gas mixture containing 3-4% O₂ (hypoxia). Mean per cent left lung blood flow for all four normoxic periods was $43.1 \pm 1.5\%$ (mean \pm SE) of the total blood flow by the SF₆ excretion method and $40.8 \pm 1.1\%$ by the differential CO₂ excretion method, corrected for the Haldane effect. With hypoxic ventilation, flow diversion from the hypoxic lung was maximal with the first exposure and did not change subsequently with a total of four alternating exposures to normoxia and hypoxia. Flow diversion during hypoxia was approximately $50.5 \pm 2.4\%$ by the SF₆ method and $50.3 \pm 3.5\%$ by the \dot{V}_{CO_2} method. This result contrasts with the increasing flow diversion response with intermittent hypoxic exposure that has been reported in animals exposed first to thoracotomy and surgical dissection. It is concluded that in the absence of surgical trauma the initial response to hypoxia is maximal and is not potentiated by repeated hypoxic stimulation. (Key words: Hypoxia; pulmonary vasoconstriction. Lung; intermittent hypoxia; hypoxic pulmonary vasoconstriction; blood flow; vascular resistance; shunt. Oxygen.)

HYPOXIC PULMONARY VASOCONSTRICTION (HPV) reduces the severity of arterial hypoxemia by diverting blood flow away from hypoxic lung regions. Some investigators have suggested that a maximal response is only observed following repeated intermittent exposures.^{1,2} Others have hypothesized that the HPV response is affected by surgical vessel manipulation and instrumentation.³ The present study has examined the requirement for and effect of repeated intermittent hypoxic exposures in dogs with an intact thorax in the absence of surgical thoracotomy.

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Methods

ANESTHESIA AND SURGERY

Eight female dogs of mixed breed with mean weight of 16.6 ± 0.4 kg were anesthetized with 30 mg/kg intravenous pentobarbital supplemented with 25-50 mg/30 min. 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 intravenous pancuronium supplemented with 0.2-0.5 mg/30 min.

After subcricoid tracheostomy and placement of a double-lumen Kottmeier endobronchial tube (Rüsch, Inc.), the lungs were ventilated with 100% O₂ via a Harvard® dual-piston respirator with 5 cmH₂O of PEEP. Tidal volumes were selected to produce equal peak airway pressures of 15-20 cmH₂O. Inspired CO₂ and/or the respiratory rate were adjusted to keep end-tidal and arterial P_{CO₂} (Pa_{CO₂}) close to 35-40 mmHg.

In these closed chest dogs, complete separation of the right and left lungs was determined by auscultation and by adding inspired helium to one lung and demonstrating with a helium analyzer (Goddart #113®) that no contamination of the other lung occurred.

Effective blood flow to each lung was measured with a differential CO₂ elimination (\dot{V}_{CO_2}) method and an inert gas SF₆ method. A computerized system⁴ has been developed to measure continuously the CO₂ excretion from each lung and to calculate the relative fraction of the total pulmonary blood flow to each lung. The system links together a turbine spirometer with a digital electrical output (Boehringer Laboratories #8830) and a capnometer (Puritan-Bennett Corporation, Datex #CD-102-27-00®) through an interface (Boehringer Laboratories #9040C) to a small digital computer (Commodore® #4016). The apparatus calculates the CO₂ production continuously from the expired volume signals and from the difference between the inspired and mixed-expired CO₂ concentration.

A solution of the inert gas SF₆^{5,6} was infused into a peripheral vein. Simultaneous samples of mixed expired gas from both the right and left sides were collected and analyzed. From the mixed-expired SF₆ concentrations and the minute ventilation, the per cent left lung blood flow could be calculated.

STUDY DESIGN

The study was divided into eight phases, alternating normoxia and hypoxia to the left lung. The right lung was ventilated continuously with 100% O₂ throughout the study. The steady state normoxic control measurements were obtained while the left lung was ventilated with 100% O₂ (normoxia); then the ventilating gas mixture to the left lung was adjusted to maintain end-tidal gas concentrations constant at 4% O₂, 5% CO₂, balance N₂ (hypoxia). Measurements were made after 10–15 min when stable responses of pulmonary blood flow and pulmonary perfusion pressure were noted.

MEASUREMENTS

At each phase the following measurements were made: right and left peak and mean airway (P_{aw}), pulmonary (PAP) and systemic arterial (SAP), central venous (CVP), and pulmonary artery occlusion (PAOP) pressures; heart rate (HR); total cardiac output (CO) by thermodilution in triplicate; body temperature; inspired, end-tidal, and mixed expired O₂ and CO₂ of each lung by mass spectrometer (Perkin-Elmer® #MGA-1100). Arterial and mixed venous blood gas samples were collected to determine pH, P_{O₂}, P_{CO₂}, and hemoglobin (Hb) concentration.

CALCULATIONS

From the recorded data, blood flow, vascular resistance, and the per cent effective flow to the left lung (Q_L%) were calculated as either the ratio of the mixed expired SF₆ excretion or the ratio of the CO₂ excretion from the left side corrected for the Haldane effect⁷ to that of the left side plus right side.

Per cent flow diversion is calculated as the difference between the per cent left lung blood flow during normoxia and the per cent left lung blood flow during hypoxia divided by the per cent left lung blood flow during normoxia.⁸

Pulmonary perfusion pressure (PPP) in mmHg was calculated as mean PAP minus mean PAOP. Left, right, and total pulmonary vascular resistances in dyn · cm⁻⁵ · s were calculated from the perfusion pressure in mmHg (×80) divided by the respective lung blood flow in l/min.

Alveolar oxygen tension (PA_{O₂}) for the right lung was calculated from the barometric pressure minus the saturated water vapor pressure minus the Pa_{CO₂}. During hypoxic ventilation, the addition of CO₂ to the inspired gas was sufficient to introduce errors into the alveolar gas mixing equation.¹⁰ Therefore, left lung PA_{O₂} was calculated as the mean of the measured mixed expired P_{O₂} and the mixed venous P_{v̄O₂}. 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:

TABLE 1. General Hemodynamic and Blood Gas Values (n = 8, mean ± SE)

pH _a *	=	7.384 ± 0.016
Pa _{CO₂} †	=	37.3 ± 0.6 mmHg
Temperature	=	38.7 ± 0.4° C
Hb ‡	=	12.1 ± 0.5 g/dl
HR §	=	170 ± 8 beats/min
SAP ¶	=	117 ± 4 mmHg
SVR **	=	3547 ± 271 dyn · cm ⁻⁵ · s
CO ††	=	2.65 ± 0.14 l/min
PAOP †††	=	8.4 ± 0.6 mmHg
CVP	=	2.0 ± 0.4 mmHg
PawR §§	=	10.0 ± 0.1 cmH ₂ O
PawL ¶¶	=	10.1 ± 0.1 cmH ₂ O

- * Arterial pH.
- † Arterial PCO₂.
- ‡ Hemoglobin.
- § Heart rate.
- ¶ Systemic arterial pressure.
- ** Systemic vascular resistance.
- †† Cardiac output.
- ††† Pulmonary artery occlusion pressure.
- §§ Right mean airway pressure.
- ¶¶ Left mean airway pressure.

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

Per cent saturation (% Sat), corrected for pH and temperature, was calculated from a nomogram for canine hemoglobin.⁹ For the hypoxic periods a variation of the traditional shunt equation was used to allow for the difference between alveolar oxygen tension of the hypoxic versus normoxic lung; it assumes that the anatomic shunt flow (Q_S/Q_T) measured during normoxia remains constant during the hypoxia period.^{10,11} The errors associated with these assumptions are small compared with the changes that were observed.

STATISTICS

The data were analyzed by a one-way within-subjects analysis of variance (ANOVA) with Neuman-Keuls test for specific differences. A value of P < 0.05 was considered significant. Results are expressed as mean ± standard error.

Results

The initial baseline experimental conditions for pH_a, Pa_{CO₂}, temperature, Hb, HR, SAP, systemic vascular resistance (SVR), CO, PAOP, CVP, mean PawR, and PawL did not change significantly during the subsequent normoxic exposures (table 1).

The per cent left lung blood flows during all four normoxic phases were not significantly different from each other; the mean value was 43.1 ± 1.5% by the SF₆ excretion method and 40.8 ± 1.1% by the differential CO₂ elimination method. The per cent left lung blood flows during the four hypoxic phases were not significantly dif-

ferent from each other; the mean value was $21.0 \pm 1.2\%$ by the SF₆ excretion method and $15.5 \pm 1.2\%$ by the differential CO₂ elimination method corrected for the Haldane effect.

The per cent flow diversions away from the left lung during each of the successive hypoxic trials as measured by the SF₆ excretion method were 48.7 ± 6.3 ; 47.8 ± 4.8 ; 54.8 ± 3.8 ; and $50.9 \pm 4.8\%$, respectively. By the differential CO₂ elimination corrected for the Haldane effect, they were 53.4 ± 8.4 , 44.0 ± 5.8 , 48.7 ± 8.2 , and $55.0 \pm 5.8\%$, respectively. Flow diversion did not change significantly with successive trials with either measurement technique.

The difference between the normoxic and hypoxic phase was significant for each of the four trials. Between the first normoxic phase and the first hypoxic phase the pulmonary perfusion pressure increased significantly from 8.1 ± 1.0 to 11.1 ± 1.4 mmHg; the mean pulmonary arterial pressure changed from 16.4 ± 0.7 to 20.5 ± 0.8 mmHg; the per cent venous admixture increased from 5.5 ± 1.3 to $27.8 \pm 2.7\%$; the PaO₂ decreased from 587.0 ± 14.9 to 120.7 ± 11.7 mmHg. However, the values for each of the four normoxic exposures did not differ significantly from each other, nor did the values for each of the four hypoxic exposures differ significantly from each other.

Discussion

The suggestion that the normal response to HPV is systematically increased with intermittent hypoxic challenges has been a controversial one.^{1,2} All investigators have agreed that this phenomenon is observed consistently with lungs perfused *in vitro*,^{2,12} but reports *in vivo* have been more variable.^{1,2,13-15}

The present study has shown that ventilation of the left lung with an hypoxic gas mixture in mechanically ventilated normocarbic dogs stimulates hypoxic pulmonary vasoconstriction. Approximately 50% of the blood flow is diverted away from the hypoxic left lung to the normoxic right lung. The flow diversion reduces the pulmonary shunt and systemic hypoxemia.

These results are in contrast to those of Pirlo *et al.*¹ and Benumof,² where the HPV response and hence flow diversion was reported to increase with intermittent hypoxia toward a maximum value after three or four exposures. Their results with a left lower lobe lung preparation were confirmed with very similar results in our laboratory using a left lung preparation.¹⁵ However, in these three studies a thoracotomy was performed, and the left lung was dissected to allow placement of electro-

magnetic flow probes. Direct surgical manipulation of the lung was avoided in the present study.

It is therefore concluded that an increased HPV response with intermittent hypoxic exposures is a phenomenon observed when surgical or other trauma has reduced the initial response. In normal physiologic circumstances a maximal HPV response is to be expected in response to the initial hypoxic stimulus.

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