

## Time Course and Responses of Sustained Hypoxic Pulmonary Vasoconstriction in the Dog

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The stability of the pulmonary blood pressure and flow response to alveolar hypoxia (hypoxic pulmonary vasoconstriction or HPV) was studied in six pentobarbital anesthetized, mechanically ventilated open-chested dogs. Aortic and left pulmonary artery blood flows; systemic and pulmonary arterial, central venous, left atrial, and airway pressures; hemoglobin; arterial and mixed venous blood gases were measured. The right lung was ventilated continuously with 100% oxygen, while the left lung was ventilated alternately with 100% O<sub>2</sub> (prehypoxia control phase), an hypoxic gas mixture containing 4% O<sub>2</sub>, 3% CO<sub>2</sub>, balance N<sub>2</sub> for 4 h, or 100% O<sub>2</sub> (post-hypoxia control phase). Hypoxic ventilation of the left lung resulted in an immediate and sustained decrease in left lung blood flow (Q<sub>L</sub>%) from 39.0 ± 1.8% (mean ± SE) to 9.9 ± 3.6% at 15 min of hypoxic ventilation. Q<sub>L</sub>% remained decreased and did not vary significantly during the 4 h of hypoxia. Venous admixture correspondingly was increased and Pa<sub>O</sub>, decreased by hypoxic ventilation and did not vary significantly during the 4 h of hypoxia. All variables returned to control levels upon reestablishing ventilation with 100% O<sub>2</sub>.

While the maximal reduction in Q<sub>L</sub>% with left lung hypoxic ventilation was identical to that observed during atelectasis previously in our laboratory, the time course of the response was different. The response to hypoxia was maximal by 15 min, however, Q<sub>L</sub>% decreased more slowly during atelectasis, where the maximal reduction was observed by 60 min. The present study therefore demonstrated that hypoxic ventilation of the left lung yielded an immediate and sustained decrease in left lung blood flow for 4 h. The stability of the HPV response probably was accounted for by the lack of such confounding factors as respiratory alkalosis, severe systemic hypoxemia, and increased cardiac output. (Key words: Lung: atelectasis; blood flow, hypoxic pulmonary vasoconstriction; shunting. Oxygen: blood levels.)

PULMONARY ARTERIOLES constrict in response to alveolar hypoxia and atelectasis (hypoxic pulmonary vasoconstriction or HPV), resulting in a dual response of blood flow diversion from hypoxic to normoxic regions

and increased pulmonary artery pressure.<sup>1</sup> There is uncertainty about the time course and stability of the HPV response, with transient responses reported by several investigators.<sup>2-6</sup> The purpose of this study was to assess the stability of the response to alveolar hypoxia and to contrast it with our previously observed pulmonary blood flow responses during atelectasis.<sup>7</sup>

### Methods

#### SURGICAL PREPARATION

Our experimental preparation has been described previously<sup>7</sup> and only will be summarized here. Six female mongrel dogs (mean weight 20.7 ± 1.1 kgs) were anesthetized with pentobarbital (30 mg/kg iv supplemented with 25-50 mg every 30 min), the trachea intubated, muscle paralysis secured with pancuronium (0.05 mg/kg iv, supplemented with 0.2-0.5 mg iv every 30 min), and the lungs ventilated with 100% O<sub>2</sub> by one side of a dual-piston Harvard ventilator. Following a median sternotomy and thoracotomy at the left fifth intercostal space, electromagnetic flow probes (Micron Instruments, Inc.) were placed around the ascending aorta and left pulmonary artery. Systemic arterial, central venous, pulmonary arterial (via Swan-Ganz catheter), and left atrial pressures were measured and thermodilution cardiac outputs were obtained. A Kottmeier double lumen endobronchial tube was placed via a subcricoid tracheostomy, and complete lung isolation was verified by direct vision. Both lungs then were ventilated synchronously with 100% O<sub>2</sub> by the dual-piston ventilator and with 5 cmH<sub>2</sub>O of PEEP. Tidal volumes were selected to produce equal peak airway pressures (15-20 cmH<sub>2</sub>O). Inspired CO<sub>2</sub> and/or the respiratory rate were adjusted to maintain equal end-tidal P<sub>CO2</sub> values of 32-35 mmHg, to achieve a Pa<sub>CO2</sub> close to 40 mmHg. The chest remained open throughout the experiment.

#### EXPERIMENTAL DESIGN

Prior to the experimental sequence, three 15-min trials of hypoxic (4% O<sub>2</sub>, 3% CO<sub>2</sub>, 93% N<sub>2</sub>) ventilation to the left lung were alternated with 100% O<sub>2</sub> ventilation to

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Received from the Department of Anesthesia, McNeil Center for Anesthesia Research, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania. Accepted for publication November 23, 1983. Supported in part by Research Project Grant GM 29628 from National Institutes of General Medical Sciences.

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insure stable, reproducible pulmonary blood flow and pressure responses to hypoxia.<sup>8,9</sup>

The experimental sequence consisted of three phases. In Phase 1 (prehypoxia control), both lungs were ventilated with 100% O<sub>2</sub> for 15 min. In Phase 2, the left lung was ventilated with the hypoxic mixture and the right lung ventilated with oxygen for 4 h. In Phase 3 (posthypoxia control), both lungs were ventilated again with 100% O<sub>2</sub> for 15 min. The lungs were hyperinflated every hour to prevent microatelectasis. At the end of the study, the animal was killed by simultaneously clamping both lung hila, and portions of right and left lungs were obtained for analysis of lung water content.

### MEASUREMENTS

At the end of Phases 1 and 3 and at 15, 30, 60, 120, 180, and 240 min during Phase 2, the following measurements were made: total cardiac output ( $\dot{Q}_T$ ) by thermodilution and aortic flow probe; left pulmonary artery blood flow ( $\dot{Q}_L$ ); airway, left atrial, central venous, pulmonary, and systemic arterial pressures; temperature; and inspired, mixed expired, and end-tidal O<sub>2</sub> and CO<sub>2</sub> tensions of both lungs. Arterial and mixed venous blood samples were collected for pH, P<sub>CO<sub>2</sub></sub>, P<sub>O<sub>2</sub></sub>, and hemoglobin concentration analysis.

### CALCULATIONS

The following calculations were made from the recorded data. The percentage of total cardiac output going to the left and right lungs ( $\dot{Q}_L\%$  and  $\dot{Q}_R\%$ , respectively) was calculated using the flow probe data. Absolute flows were based on thermodilution cardiac output data, with ratios determined by flow probes. Pulmonary perfusion pressure (PP) was calculated as mean PAP minus mean LAP in mmHg. Left, right, and total pulmonary vascular resistances in dyn · cm<sup>-5</sup> · s were calculated by (PP × 80) divided by the respective lung blood flow in l/min. With 100% oxygen ventilation to both lungs or to the right lung during hypoxia, alveolar oxygen tension was calculated as the barometric pressure minus the saturated water vapor pressure and the Pa<sub>CO<sub>2</sub></sub>. During hypoxic ventilation, left lung alveolar oxygen tension was calculated as the mean of the measured mixed expired P<sub>O<sub>2</sub></sub> and the mixed venous P<sub>O<sub>2</sub></sub>. Blood O<sub>2</sub> contents (C<sub>bO<sub>2</sub></sub>) were calculated from the measured O<sub>2</sub> tension and hemoglobin concentration using the equation:

$$C_{bO_2} = (1.34 \times \text{Hb} \times \% \text{ sat}) + (P_{bO_2} \times 0.0031)$$

where C<sub>bO<sub>2</sub></sub> = blood oxygen content in ml O<sub>2</sub>/dl blood, 1.34 = O<sub>2</sub> capacity of hemoglobin in ml O<sub>2</sub>/gHb,<sup>10</sup> Hb = hemoglobin in g/dl blood, % sat = per cent saturation, P<sub>bO<sub>2</sub></sub> = blood oxygen tension in mmHg, and 0.0031

= dissolved O<sub>2</sub> in ml O<sub>2</sub> · mmHg<sup>-1</sup> · dl<sup>-1</sup> blood. Per cent saturation, corrected for pH and temperature, was calculated from a nomogram for canine hemoglobin.<sup>11</sup> Calculated alveolar oxygen tension was used for end-capillary oxygen tension (PC<sub>O<sub>2</sub></sub>). The venous admixture ( $\dot{Q}_{VA}/\dot{Q}_T$ ) during the normoxic phases was calculated by the following equation:

$$\dot{Q}_{VA}/\dot{Q}_T = (CC'_{O_2} - C_{aO_2}) / (CC'_{O_2} - C\bar{v}_{O_2})$$

where CC<sub>O<sub>2</sub></sub>' = end-capillary O<sub>2</sub> content, C<sub>aO<sub>2</sub></sub> = arterial O<sub>2</sub> content, and C $\bar{v}_{O_2}$  = mixed venous O<sub>2</sub> content. For the hypoxic period (Phase 2), a variation of this shunt equation was used to allow for the difference between the alveolar oxygen tension of the hypoxic lung and that of the normoxic lung.<sup>7</sup> Lung water contents were calculated as (wet weight minus dry weight) divided by dry weight (value for normal resting dogs in our laboratory is 4.6 ± 0.016 ml H<sub>2</sub>O/g dry lung<sup>12</sup>).

### STATISTICS

The data were analyzed by a within-subjects analysis of variance (ANOVA) for repeated measurement, and the Duncan test was used for comparison of differences between means. The stability of the hypoxic response over time was assessed by determining the slope of the blood flow, pulmonary pressure, and venous admixture responses by linear regression analysis for each animal and comparing the mean slope to zero by a one-tailed *t* test. A paired comparison *t* test compared right and left lung water differences. *P* < 0.05 was deemed significant. Results are expressed as means ± standard errors.

### Results

The baseline experimental conditions remained essentially constant (mean Pa<sub>CO<sub>2</sub></sub> = 39.7 ± 0.6 mmHg, mean pH<sub>a</sub> = 7.360 ± 0.006, BE = -2.9 ± 0.3 mEq/l and temperature = 36.8 ± 0.1°C). Hemoglobin decreased from 12.3 ± 0.6 g/dl in the prehypoxia control phase to a low of 10.3 ± 0.6 g/dl in the posthypoxia control phase. Systemic blood pressure decreased significantly during the study (128 ± 9 mmHg in Phase 1 to 98 ± 4 mmHg in Phase 3), although neither systemic vascular resistance (3300 ± 100 dyn · cm<sup>-5</sup> · s), cardiac output (2.66 ± 0.07 l/min), left atrial pressure (4.4 ± 0.3 mmHg), central venous pressure (1.7 ± 0.2 mmHg), or heart rate (172 ± 4 beats/min) changed. Mean right and left airway pressures were equal (8.4 ± 0.1 cmH<sub>2</sub>O and 8.3 ± 0.1 cmH<sub>2</sub>O, respectively).

Ventilation of the left lung with the hypoxic gas mixture resulted in a significant and sustained decrease in blood flow to the left lung (*P* < 0.001, see fig. 1). The left lung blood flow expressed as percentage of total cardiac output

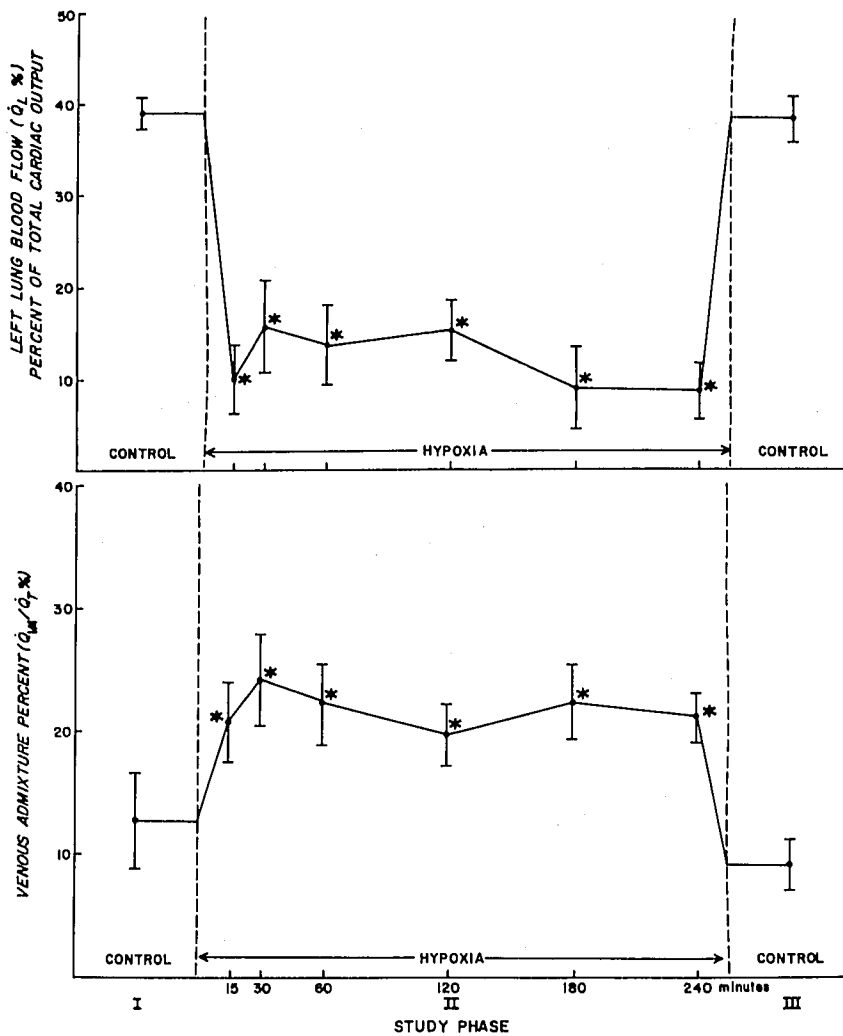


FIG. 1. Left lung blood flow as percentage of total cardiac output ( $\dot{Q}_L\%$ ) and venous admixture percent ( $\dot{Q}_{VA}/\dot{Q}_T\%$ ) for each study period. Phases I and 3 were normoxic controls (both lungs ventilated with 100%  $O_2$ ). Phase 2 (left lung hypoxic ventilation) is presented on a time scale of 0 to 240 min. Means  $\pm$  standard errors are plotted. Asterisk (\*) signifies values are significantly different from controls (Phases 1 and 3). Prehypoxic and posthypoxic control  $\dot{Q}_L\%$  and  $\dot{Q}_{VA}/\dot{Q}_T\%$  did not differ. Upper panel: Hypoxic ventilation resulted in a significant and sustained decrease in  $\dot{Q}_L\%$  ( $P < 0.01$  for all hypoxia  $\dot{Q}_L\%$  differing from controls). Lower panel: Venous admixture increased and remained constant during the 240 min of hypoxia ( $P < 0.01$  for all hypoxia  $\dot{Q}_{VA}/\dot{Q}_T\%$  differing from controls).

( $\dot{Q}_L\%$ ) decreased from  $39.0 \pm 1.8\%$  during 100%  $O_2$  ventilation to  $9.9 \pm 3.6\%$  at 15 min of hypoxic ventilation.  $\dot{Q}_L\%$  remained decreased and did not vary significantly during the 4 h of hypoxia (range =  $8.8 \pm 3.1\%$  to  $15.8 \pm 5.0\%$ ). The blood flow returned to control values when

the left lung again was ventilated with 100%  $O_2$  ( $38.7 \pm 2.6\%$ ).

The venous admixture increased significantly from  $12.7 \pm 3.9\%$  during the prehypoxia control period to  $20.8 \pm 3.3\%$  at 15 min of hypoxic ventilation ( $P < 0.001$ ,

TABLE 1. Selected Blood-Gas and Pulmonary Hemodynamic Data During 100%  $O_2$  Ventilation of Both Lungs (Phases 1 and 3) and 4 h of Hypoxic Ventilation of Left Lung (Phase 2)

	Phase 1 100% $O_2$	Phase 2—Left Lung Hypoxia			Phase 3 100% $O_2$
		15 min	120 min	240 min	
$Pa_{O_2}$ mmHg	$495 \pm 41$	$284 \pm 53^*$	$278 \pm 43^*$	$254 \pm 37^*$	$526 \pm 30$
$PV_{O_2}$ mmHg	$51 \pm 4$	$48 \pm 4$	$47 \pm 3$	$43 \pm 3$	$47 \pm 3$
$\overline{PAP}$ mmHg	$15.6 \pm 0.5$	$17.6 \pm 0.7^*$	$17.9 \pm 0.9^*$	$16.8 \pm 0.7$	$15.4 \pm 0.6$
LAP mmHg	$4.8 \pm 0.8$	$4.4 \pm 0.7$	$4.6 \pm 0.8$	$3.9 \pm 0.5$	$4.0 \pm 0.7$
$PVR_T$ dyn $\cdot$ cm <sup>-5</sup> $\cdot$ s	$310 \pm 30$	$410 \pm 30$	$420 \pm 30$	$400 \pm 30$	$360 \pm 20$
$PVR_L$ dyn $\cdot$ cm <sup>-5</sup> $\cdot$ s	$810 \pm 100$	$6,460 \pm 1,540^*$	$4,160 \pm 1,730^*$	$4,990 \pm 1,160^*$	$950 \pm 80$

Abbreviations:  $\overline{PAP}$  = mean pulmonary artery pressure; LAP = left atrial pressure;  $PVR_T$  = total pulmonary vascular resistance;  $PVR_L$  = left lung pulmonary vascular resistance.

\* Significantly different from Phases 1 and 3 using ANOVA and Duncan *post hoc* test. Mean  $Pa_{O_2}$ ,  $\overline{PAP}$ ,  $PVR_L$  did not differ significantly during the 4 h of hypoxia.

TABLE 2. Stability of the Pulmonary Vascular Response to Hypoxia: Summary of Previous Studies

Study	Species	Hypoxia	CO <sub>2</sub> in Hypoxic Gas	Ventilation	Flow Measurement	Stability
2	Dog	Generalized ( <i>in vitro</i> )	Yes	CV	PAP	Transient $\bar{p}$ 5 min
3	Dog	Generalized	No	SV	PVR	Transient $\bar{p}$ 9 min
			No	CV	PVR	Sustained 20 min
			Yes	SV	PVR	Sustained 20 min
4	Dog	Generalized	Yes	SV	PVR	Transient $\bar{p}$ 4 min
20	Dog	Regional (RL)	No	CV	<sup>133</sup> Xe	Sustained 30 min
13	Dog	Regional (LLL)	No	CV	Flow probes	Cyclic
			Yes	CV	Flow probes	Sustained 60 min
21	Sheep	Regional (RAL)	No	SV	<sup>85</sup> Kr	Sustained 138 min

Abbreviations: RL = right lung; LLL = left lower lobe; RAL = right apical lobe; CV = controlled ventilation; SV = spontaneous ventilation.

see fig. 1). It remained constant during the 4 h of hypoxia (range =  $20.8 \pm 3.3\%$  to  $24.2 \pm 3.8\%$ ) and returned to control values with oxygen ventilation during Phase 3 ( $9.4 \pm 2.0\%$ ).

PaO<sub>2</sub> decreased with hypoxic ventilation ( $P < 0.001$ , see table 1). Mean PaO<sub>2</sub> values during the 4 h of hypoxia did not differ significantly and ranged from  $237 \pm 50$  mmHg to  $284 \pm 53$  mmHg.

Mean pulmonary artery pressure ( $\bar{PAP}$ ) increased significantly during hypoxic ventilation ( $P < 0.05$ , see table 2). The control  $\bar{PAP}$  of  $15.6 \pm 0.5$  mmHg increased to  $17.6 \pm 0.7$  mmHg at 15 min of hypoxia. This increase in  $\bar{PAP}$  during hypoxic ventilation was persistent until 240 min when  $\bar{PAP}$  decreased slightly ( $16.8 \pm 0.7$  mmHg) to a value that was not statistically different from prehypoxic and posthypoxic controls. While total pulmonary vascular resistance (PVR<sub>T</sub>) did not change significantly, left lung PVR (PVR<sub>L</sub>) increased with hypoxic ventilation (table 1).

Postmortem analysis of lung water contents revealed that the right and left lung water contents did not differ (right =  $4.89 \pm 0.18$  ml H<sub>2</sub>O/g dry lung; left =  $4.73 \pm 0.06$  ml H<sub>2</sub>O/g dry lung).

### Discussion

This study demonstrates that hypoxic ventilation of the left lung in the open-chested dog resulted in a 70% flow diversion from the hypoxic to normoxic lung. The response was rapid in onset, sustained, and unchanged over 4 h. The decrease in blood flow to the hypoxic left lung was due to a regional increase in pulmonary vascular resistance of the left lung. This hypoxic pulmonary vasoconstriction (HPV) reduced the "expected" shunt from 50% (blood flow through the left lung and preexisting shunt during normoxic ventilation) to the 20% actually measured and systemic hypoxemia therefore was avoided.

The measured diversion of blood flow and increase in pulmonary artery pressure are consistent with previous predictions for hypoxic pulmonary vasoconstriction.<sup>1</sup> However, the duration and stability of the HPV response

has been uncertain (table 2). Transient HPV responses were observed in studies using severe hypoxemia in excised dog lobe preparations,<sup>2</sup> in dogs with whole lung hypoxia,<sup>3,4</sup> *in vitro* pig lungs,<sup>5,6</sup> and in studies complicated by alkalosis<sup>3,13</sup> and excessive sympathetic activity.<sup>3</sup> Respiratory alkalosis,<sup>13,14</sup> severe systemic hypoxemia,<sup>5,6</sup> low P<sub>v</sub>O<sub>2</sub>,<sup>15,16</sup> and increased cardiac output<sup>14,17-19</sup> all reduce the effectiveness of the HPV response. The transient response with severe hypoxemia may represent basic organ failure or release of a vasodilator. Our finding of a stable pressure and flow response to hypoxia is consistent with others using regional hypoxia in which alkalosis and hypoxemia<sup>13,20,21</sup> were avoided.

The time course of the pulmonary blood flow response with left lung hypoxia in the present study was compared with the results of left lung atelectasis<sup>7</sup> by a mixed-design ANOVA. While the maximal reduction in  $\dot{Q}_L\%$  with left lung hypoxic ventilation is identical to that observed during atelectasis, the time course of the response is different. The response to hypoxia was maximal by 15 min, however,  $\dot{Q}_L\%$  decreased more slowly during atelectasis, where the maximal reduction was observed by 60 min. Presumably, this was the time required for complete atelectasis to occur. While the data suggest that the role of any mechanical factors in reducing atelectatic lung blood flow must be small, their contribution cannot be evaluated convincingly because the experiments were performed at different times. The present study also showed that 4 h of hypoxia did not induce pulmonary edema, in contrast to the increased water content observed previously with lungs reinflated after 4 h of atelectasis.<sup>7,22</sup>

In summary, hypoxic ventilation of the left lung in open-chested, mechanically ventilated dogs resulted in an immediate and sustained decrease in left lung blood flow for 4 h. The HPV response is large and well sustained in the absence of respiratory alkalosis, severe systemic hypoxemia, and increased cardiac output.

The authors acknowledge the assistance of Barbara Ewing, B.S., in conducting the study and Amy Berdand and Judy Ayoub in preparation of the manuscript.

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