

Pulmonary Blood Pressure and Flow during Atelectasis in the Dog

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The purpose of the study was to measure the time course, direction, and magnitude of the hypoxic pulmonary vasoconstriction (HPV) response to atelectasis. Six dogs were anesthetized with pentobarbital. With the chest open, each lung was ventilated separately. Pulmonary blood flow was measured with electromagnetic flow probes. Pulmonary arterial, left atrial, and systemic arterial pressures were measured via indwelling catheters. The right lung was ventilated continuously with 100% O₂, while the left lung was either ventilated with 100% O₂ (control phase), unventilated (4 hours of atelectasis), or ventilated with a gas mixture containing 4% O₂, 3% CO₂, and 93% N₂ (hypoxia phase). Left lung atelectasis resulted in a reduction of the per cent left lung blood flow from 43 ± 4% (mean ± SE) to 25 ± 7% at 15 min and to 12 ± 1% at 60 min which persisted for the remaining four-hour period. The per cent left lung blood flow was significantly lower (8 ± 1%) and the PaO₂ significantly higher (356 ± 38 mmHg) during the maximal response to atelectasis as compared to 15 min of hypoxic ventilation (23 ± 5%; 211 ± 21 mmHg). With atelectasis or hypoxic ventilation, pulmonary perfusion pressure was increased significantly from the control value of 7.9 ± 0.8 mmHg to approximately 11 mmHg.

The present study demonstrated that in the open chest model without systemic hypoxemia, the response to acute atelectasis is a regional increase in pulmonary vascular resistance which develops quickly (15 min) and is maximal by 60 min and is maintained thereafter. As a result, there is a sustained diversion of blood flow away from the atelectatic lung and a generalized increase of pulmonary perfusion pressure. (Key words: Hypoxia. Lung: atelectasis; blood flow. Oxygen: blood levels.)

WHEN ALVEOLAR OXYGEN TENSION is reduced in regions of the lung, local vasoconstriction of small pulmonary arteries is induced. This phenomenon of hypoxic pulmonary vasoconstriction (HPV) results in a dual response¹ of increased pulmonary perfusion pressure and blood flow diversion from hypoxic regions to normoxic regions. The expected pulmonary shunt is thereby reduced and the arterial oxygen tension increased.

HPV also occurs in regional atelectasis² but there is uncertainty about its time course, magnitude, and even the direction of the pressure and flow responses during atelectasis. This present study is intended to characterize these responses when atelectasis is induced in open chest, mechanically ventilated, anesthetized dogs.

Materials and Methods

ANESTHESIA

Six female mongrel dogs weighing 19.4 ± 1.0 kg (mean ± SE) and free from heart and lung disease were anesthetized with intravenous pentobarbital (30 mg/kg). Their tracheas were intubated with 10-mm cuffed endotracheal tubes and the lungs ventilated with oxygen via one side of a dual-piston Harvard® respirator. Ventilation was begun with a tidal volume of 25 ml/kg at a rate of 10/min. Inspired CO₂ was added to keep end-tidal P_{CO₂} at 35–40 mmHg. Anesthesia was maintained throughout the subsequent surgery and experimental period with intravenous pentobarbital (12.5–25 mg/30 min). Muscular paralysis was secured and maintained with intravenous pancuronium (1 mg initially followed by 0.1–0.2 mg/30 min).

Fluid status was maintained by continuous intravenous administration of Normosol-R® (250–500 ml/h) and blood loss was replaced with stored blood from donor animals. The pH of arterial blood was measured at least hourly and base deficit corrected with intravenous NaHCO₃. Heating pads, lamps, and heated humidified inspired gas were utilized to maintain body temperature.

SURGERY

The dog was secured in the supine position and the chest was opened combining a mid-line sternotomy with a thoractomy at the left fifth intercostal space. Electromagnetic flow probes (Micron Instruments, Inc., Los Angeles, California), previously calibrated *in vitro*, were placed around the left pulmonary artery and the ascending aorta. Cannulae were placed in the main pulmonary artery through a right ventriculostomy, in the left atrium via the left auricle, in the superior vena cava via the right external jugular vein, and in the abdominal

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TABLE 1. Study Design

Study Phase	Right Lung	Left Lung	Time
I _A	100% O ₂	100% O ₂	15 min
II	100% O ₂	4% O ₂ , 3% CO ₂ , 93% N ₂	15 min
I _B	100% O ₂	100% O ₂	15 min
III	100% O ₂	Atelectasis	4 hrs
IV	100% O ₂	100% O ₂	15 min
V	100% O ₂	4% O ₂ , 3% CO ₂ , 93% N ₂	15 min

aorta via the right femoral artery. The positions of transducers were adjusted for zero pressure readings at mid-cardiac level. Body temperature was measured with a thermistor probe advanced into the vena cava from a femoral vein.

A subcricoid tracheostomy was performed and the endotracheal tube was replaced by a medium-sized left double-lumen Robertshaw® endobronchial tube. The endobronchial tube was secured in the left main bronchus under direct vision and ligatures placed to assure a gas-tight separation of the left and right lungs. The entire lung then was ventilated synchronously with the dual piston ventilator. One piston ventilated the right lung via the tracheal lumen of the Robertshaw tube while the other piston ventilated the left lung via the bronchial lumen. When surgery was complete the lungs were lightly covered with gauze moistened by normal saline.

VENTILATION

Each piston of the Harvard® respirator was part of a separate gas circuit. For each circuit, the composition of inspired oxygen, nitrogen, and carbon dioxide was selected and delivered to separate rubber reservoir bags before entering the appropriate piston inlet. Expired gases from each lung flowed through gas mixing cones before venting to atmosphere via an underwater seal providing 5 cmH₂O PEEP.

For each breathing circuit, inspired, end-tidal, and mixed expired carbon dioxide tensions (Goddart Capnograph) and inspired and mixed expired oxygen tensions (Instrumentation Laboratories IL-2) were measured. Analyzers were calibrated with gases of known composition and the recorded values were corrected for barometric pressure, temperature, and water vapor variations. Tidal volumes were adjusted to provide equal peak airway pressures (15–20 cmH₂O) and right and left end-tidal P_{CO₂} were equalized in the 35–40 mmHg range by adjusting the inspired P_{CO₂} and/or the respiratory rate.

STUDY DESIGN

The study period was divided into five phases (table 1). Throughout the study period, the right lung was

ventilated with oxygen, while the left lung ventilation was altered. Prior to Phase I, three short (15-min) trials of left lung ventilation with the hypoxic gas mixture (4% O₂, 3% CO₂, 93% N₂) were alternated with periods of oxygen ventilation until stable, reproducible responses of pulmonary blood flow and pulmonary perfusion pressure to hypoxia were noted.

In Phase I_A, both lungs were ventilated with oxygen. In Phase II, the right lung was ventilated with oxygen and the left lung was ventilated with the hypoxic gas mixture for 15 min. Both lungs were then ventilated again with oxygen in Phase I_B.

In Phase III, the left lung was made atelectatic by discontinuing ventilation to that lung, clamping the endobronchial tube, and allowing gas to be absorbed. This period lasted four hours with measurements at 15, 30, 60, 120, 180, and 240 min. The right lung was hyperinflated hourly during this phase. The left lung then was reinflated and ventilated with oxygen (Phase IV) for 15 min and then with the hypoxic gas mixture for 15 min (Phase V). Arterial and mixed venous blood samples were collected during Phases I, II, IV, V, and hourly (60, 120, 180, and 240 min) during Phase III.

At the conclusion of the study, cardiac arrest was induced by clamping the lung hila and portions of right and left lungs were obtained for lung water analysis.

MEASUREMENTS

At each phase, total cardiac output (Q_T), left pulmonary artery blood flow (Q_L), and airway, pulmonary artery, systemic artery, left atrial, and central venous pressures were recorded at the end-expiration phase of the respiratory cycle. Arterial and mixed venous blood samples were collected for determination of hemoglobin concentration, pH, P_{O₂}, and P_{CO₂}. All blood flows, vascular and airway pressures, and oxygen and carbon dioxide gas tensions were recorded on a Grass® 8-channel polygraph recorder.

CALCULATIONS

From the recorded data, the following calculations were made.

Alveolar Oxygen Tension. With 100% oxygen ventilation to both lungs or to the right lung during atelectasis, alveolar oxygen tensions (P_{AO₂}) were calculated as follows. P_{AO₂} equaled the barometric pressure minus the saturated water vapor pressure and the P_{aCO₂}. P_{aCO₂} was determined from blood-gas analysis when obtained during that phase, otherwise the end-tidal P_{CO₂} (P_{ETCO₂}) plus a correction factor (the average P_{aCO₂} - P_{ETCO₂} throughout the study) was substituted.

During hypoxic ventilation to the left side, the

PA_{O_2} for each lung was determined separately from the mixing equation:

$$PA_{O_2} = [PI_{O_2}] - \left[\frac{(PA_{CO_2} - PI_{CO_2})}{(PE_{CO_2} - PI_{CO_2})} \right] \times (PI_{O_2} - PE_{O_2})$$

Blood Flow Response. Right pulmonary artery flow (Q_R) was calculated as total cardiac output (Q_T) minus left pulmonary artery flow (Q_L). The per cent flow to each lung ($\%Q_L$ and $\%Q_R$) was calculated. During atelectasis, the flow at each time period was compared to the control normoxic period preceding the atelectatic period. For the initial hypoxic challenge, $\%Q_L$ was compared to the initial normoxic phase, while for the final hypoxic challenge it was compared to the final normoxic flow.

Pulmonary Perfusion Pressure Response. Pulmonary perfusion pressure (PP) was calculated as mean pulmonary artery pressure minus mean left atrial pressure.

$$PP = \overline{PAP} - \overline{LAP}$$

Venous Admixture. Per cent venous admixture ($\%VA$) was calculated for each normoxic or hypoxic period and hourly during atelectasis using the traditional shunt equation where the oxygen contents of end-capillary, arterial, and mixed venous blood were calculated from:

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

P_{O_2} and hemoglobin (Hb) were measured while per cent saturation ($\%Sat$), corrected for pH and temperature was calculated.³ Calculated alveolar oxygen tension was used for end-capillary oxygen tension. For the hypoxia periods (phases II and V), 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 (see Appendix 1).

Lung Water Content. Portions of right and left lung were weighed (wet weight) and the mixture homogenized. After lyophilization for 18 h, the dry weight was recorded. Lung water weight for each lung was calculated as (wet weight - dry weight)/(dry weight).

Statistics. A within subjects analysis of variance for repeated measures was used for all measured variables across all study periods. Those that showed a significant variance were tested further with Newman-Keuls test to determine specific significant differences. The effect of hypoxia versus the maximal effect of atelectasis and the difference in lung water content of the right versus the left lung were compared via a paired two-tailed t test. Comparison of the hypoxic challenges pre- and post-atelectasis were compared by a 2×2 within subjects analysis of variance. A $P < 0.05$ was deemed significant for all statistical measurements.

Results

During the initial control period the central venous pressure was 3.6 ± 0.6 mmHg, the left atrial pressure was 7.4 ± 1.0 mmHg, the total pulmonary vascular resistance was 416 ± 74 dyn \cdot cm⁻⁵ \cdot s, the heart rate was 168 ± 12 min⁻¹, the hemoglobin concentration was 11.9 ± 0.5 g/dl, the arterial pH was $7.39 \pm .03$, the Pa_{CO_2} was 36.4 ± 2.7 mmHg, the mixed venous P_{O_2} was 53.3 ± 2.2 mmHg, the body temperature was $37.0 \pm 0.4^\circ C$, and the total cardiac output $1,519 \pm 135$ ml/min. None of these variables changed significantly throughout the subsequent study periods, and they are not detailed further below.

The mean systemic arterial pressure was 113 ± 9 mmHg during the initial control period and decreased subsequently to 93 ± 5 mmHg at the end of four hours of atelectasis and 77 ± 3 mmHg at the conclusion of the study. This change was reflected in the total systemic vascular resistance which was $6,146 \pm 997$ dyn \cdot cm⁻⁵ \cdot s during the initial control period and decreased to $3,708 \pm 1,249$ dyn \cdot cm⁻⁵ \cdot s at the conclusion of the study.

INITIAL EFFECT OF HYPOXIA

Ventilation of the left lung with the hypoxic gas mixture resulted in a significant decrease in blood flow to the left lung (fig. 1). The blood flow returned to control level when the left lung was again ventilated with 100% oxygen. Pulmonary perfusion pressure significantly increased from control values during hypoxic ventilation of the left lung. This also returned to control level when the left lung was returned to 100% oxygen ventilation (fig. 1). Venous admixture increased from $8.2 \pm 2.6\%$ to $21.8 \pm 3.0\%$ during left lung hypoxia, while Pa_{O_2} decreased from 522 ± 43 mmHg to 211 ± 21 mmHg (table 2).

EFFECT OF ATELECTASIS

Left lung atelectasis resulted in a significant reduction in left lung blood flow at 15 and 30 min. A further significant decrease in left lung blood flow was evident at 60 min which did not change subsequently at 120, 180, and 240 min (fig. 1). Pulmonary perfusion pressure was increased significantly over control 15 min after initiation of left lung atelectasis and was sustained throughout the 240 min (fig. 1). Venous admixture ranged from $16.7 \pm 2.1\%$ to $21.5 \pm 1.8\%$ during the 240 min of left lung atelectasis (table 2). There were no significant differences among the four measurements. Mean Pa_{O_2} values ranged from 269 ± 34 to 356 ± 38 mmHg (table 2), and the four measurements did not differ significantly.

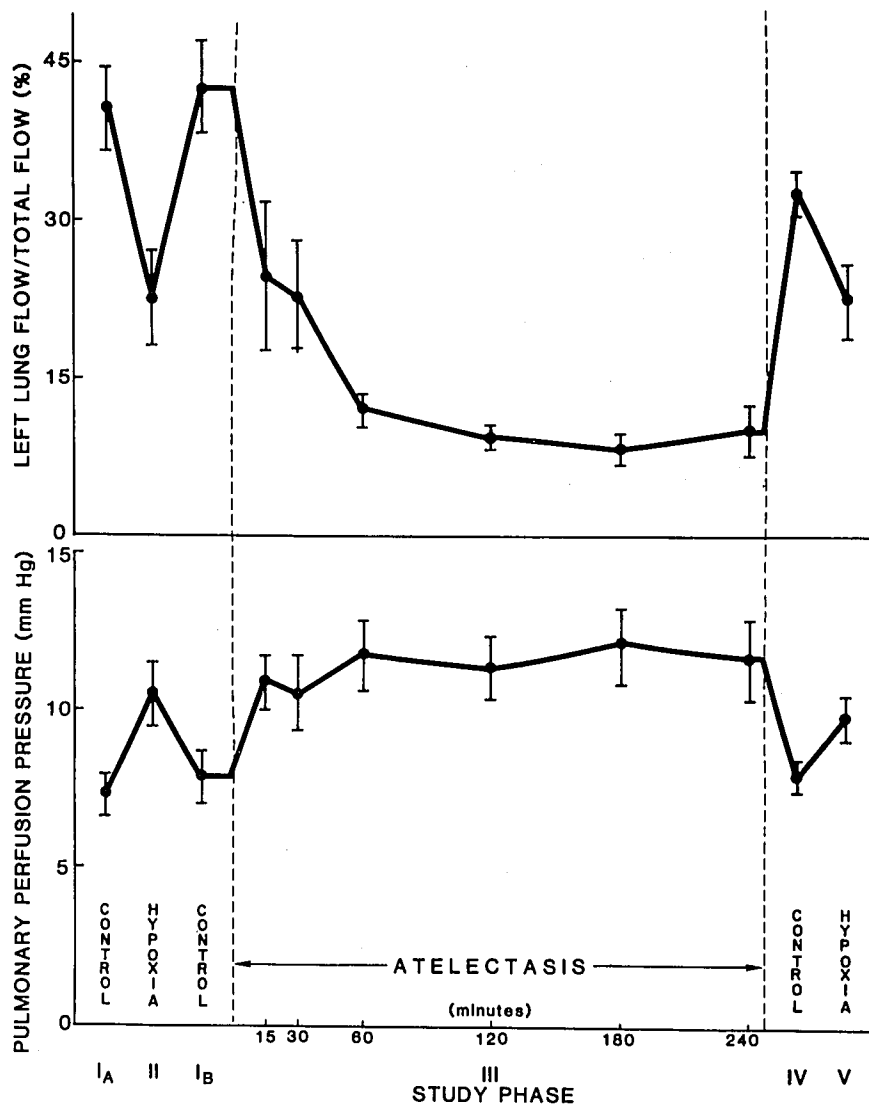


FIG. 1. Left lung blood flow as per cent of total blood flow (*upper*) and pulmonary perfusion pressure (mmHg) (*lower*) for each study period. Phase III, Atelectasis, is presented on a time scale of 0–240 min. The data are shown as means \pm standard errors from six dogs. (*Upper panel*). All measurements during hypoxia and atelectasis were significantly different from control. Measurements at 60, 120, 180, and 240 min of atelectasis were also significantly different from those at 15 and 30 min of atelectasis and during hypoxia. (*Lower panel*). All measurements during hypoxia and atelectasis were significantly different from control.

The maximal reduction of left lung blood flow with atelectasis was significantly greater than the response to hypoxic ventilation (fig. 1). Concomitantly, the P_{aO_2} at 120, 180, and 240 min of atelectasis were significantly greater than the P_{aO_2} during left lung hypoxia (table 2). However, there was no significant difference between the maximal effect of atelectasis and the effect of hypoxic ventilation on the pulmonary perfusion pressure (fig. 1).

EFFECT OF REINFLATION ON ATELECTATIC LUNG

After reinflation of the atelectatic left lung, the per cent blood flow to the left lung, (fig. 1), pulmonary perfusion pressure (fig. 1), per cent venous admixture, and P_{aO_2} (table 2) were not significantly different from pre-atelectatic control values.

The response to hypoxic ventilation appeared to be smaller after reinflation of the lung than that prior to atelectasis. However, analysis of variance of the effects

of hypoxia and time revealed no significant differences between the two responses separated by the four hours of atelectasis. The P_{aO_2} in the two periods were not significantly different, and of the three variables influencing it (vis P_{aO_2} , $P\bar{V}O_2$, and %VA) only the per cent venous admixture was significantly greater during the post-reinflation hypoxia phase than during the pre-atelectasis hypoxia period.

LUNG WATER

Postmortem analysis of wet-to-dry lung weights revealed that the left lung water (5.82 ± 0.80 ml H_2O/g dry lung) was significantly greater than that of the right lung (4.18 ± 0.60 ml H_2O/g dry lung).

Discussion

The present study has shown that left lung atelectasis induced in anesthetized, mechanically ventilated dogs

with open chests resulted in decrease of left lung blood flow as early as 15 min and a larger decrease by 60 min which was then sustained for four hours. Since the total cardiac output was unchanged, the blood flow decrease was a result of an increased pulmonary vascular resistance of the left lung, secondary to regional pulmonary vasoconstriction. This regional increase in PVR resulted in a maximal 75% diversion of blood from the atelectatic left lung to the ventilated right lung with a consequent reduction of the "expected" shunt from 42% (the blood flow through the left lung during bilateral normoxic ventilation) to the 16.7–21.5% range actually measured during the four hours of atelectasis. Systemic hypoxemia therefore was prevented. The expected dual response also was observed with the increase of pulmonary perfusion pressure evident at 15 min post-atelectasis and sustained for the four-hour study period.

The measured diversion of blood flow and increase of perfusion pressure with atelectasis are consistent with previous predictions for hypoxic pulmonary vasoconstriction.¹ However, previous studies have shown variability in the direction and magnitude of this response with atelectasis. The variety of results may be attributed to specific differences in study design,⁴ the type of ventilation (spontaneous *vs.* mechanical),⁵ whether the chest was open or closed,^{6,7} and whether systemic hypoxemia⁸ or respiratory alkalosis^{9,10} developed. In closed chest models, the development of greater negative pressures surrounding an acutely atelectatic lung segment may reduce the HPV response⁶. In any model, systemic hypoxemia and low mixed venous P_{O₂} reduce the effectiveness of the HPV response.^{11–13}

In the present study, the initial exposure to 15 min of hypoxic ventilation demonstrated that the form and magnitude of the responses were similar to those reported previously for this model.¹² The final period of hypoxic ventilation confirmed that the HPV responses were retained after the four hours of atelectasis. The flow diversion and perfusion pressure responses appear to reach a steady state during 15 min of hypoxic ventilation. It is therefore of interest that the responses measured 15 min after the onset of atelectasis were essentially identical to those after 15 min of hypoxic ventilation. The similarity of the responses with brief exposures has led to the conclusion that blood flow changes with atelectasis are attributable entirely to HPV.^{2,14}

Other investigators have concluded that lung volume reduction with atelectasis is associated with an additional mechanical increase in vascular resistance.^{15,16} The present observations of a maximal flow diversion response to atelectasis developing after one hour might be consistent with this thesis. However, this study was not designed to resolve the controversy, and the hypoxic ex-

TABLE 2. Pulmonary Shunt, Arterial, and Mixed Venous Oxygen Tensions and Arterial-Venous Oxygen Content Difference at Each Study Phase* (Mean ± SE)

	Study Phase						
	I _a Control	II Hypoxia	III Atelectasis (Minutes)			IV Reinflation Control	V Hypoxia
			60	120	180		
% VA	8.2 ± 2.6	21.8 ± 3.0*	21.5 ± 1.8*	16.7 ± 2.1*	18.3 ± 2.1*	17.8 ± 2.4*	27.6 ± 5.4*
PaO ₂ (mmHg)	522 ± 43	211 ± 21*	269 ± 34*	356 ± 38*	323 ± 39*	314 ± 55*	170 ± 39*
P _v O ₂ (mmHg)	53.3 ± 2.2	50.7 ± 3.4	53.0 ± 1.9	50.0 ± 3.1	49.8 ± 3.6	48.7 ± 2.9	44.1 ± 4.2
C (a - v) O ₂ (ml/dl)	4.49 ± 0.6	4.43 ± 0.7	4.53 ± 0.9	4.90 ± 0.7	4.85 ± 0.8	4.99 ± 1.0	4.59 ± 0.9

* Indicates significantly (*P* < 0.05) differs from Phase I_a control by analysis of variance.

TABLE 3. Magnitude and Time Course of HPV Response to Atelectasis; Summary of Four Previously Published Studies

Reference	Species	Atelectatic Lung Segment	Chest	Ventilation	Anesthesia	Estimated % Change of Blood Flow to Atelectatic Lung Segment
21	Dog	LLL	Closed	MV	Pentobarbital	20% decrease at one hour 70% decrease at four hours*
22	Dog	LLL	Closed	SV	Halothane N ₂ O	20% decrease at 15, 30 and 120 minutes
23	Dog	LLL	Closed	MV	Pentobarbital	54% decrease at 30 minutes 95% decrease at two hours* Sustained for six hours
24	Man	RL or LL	Open	MV	Halothane 1% Innovar Thiamylal	54% decrease at 15 minutes 85% decrease at two hours*

LLL = left lower lobe; RL = right lung; LL = left lung; MV = mechanical ventilation; SV = spontaneous ventilation.

* Per cent blood flow change estimates derived from respective authors' pulmonary shunt data.

posures were included only to demonstrate that normal HPV reactivity was present. Although HPV appears to be the important mechanism in atelectasis, contribution of mechanical factors has not been convincingly evaluated.

Several investigators using hypoxic ventilation have reported a transient (less than 30 min) HPV response,^{17,18} but interpretation of these results are complicated by the occurrence of systemic hypoxemia¹⁹ and/or alkalosis,²⁰ which alters the response to HPV. Table 3 summarizes several previously published investigations in which the time course of the response to atelectasis can be approximated.²¹⁻²⁴ These studies used a variety of models, ventilation methods, and anesthetic agents. They generally found that after an initial variable period, acute atelectasis resulted in a sustained decrease in blood flow to the nonventilated region. The techniques by which blood flow was estimated (shunt equation^{21,23,24} or radioactive microsphere injections²²) were neither direct nor continuous, but the results are consistent with the present observations.

The greater venous admixture observed during post-reinflation hypoxic ventilation of the left lung may have been the result of the increased water content of the left lung. Kersten *et al.*²³ noted a regional increase in PVR for at least four hours following expansion of atelectatic left lower lobes of dogs. Unilateral pulmonary edema following abrupt reexpansion of collapsed lung has been demonstrated in rabbits,²⁵ monkeys,²⁶ and humans.²⁷ Lung collapsed for at least three days, large negative or positive pressure applications, and rapid reexpansion have been implicated as causative factors, but the precise circumstances remain ill-defined. Recent evidence suggests that the edema is due to increased pulmonary vascular permeability caused by mechanical stress applied to the lung during reexpansion.²⁵

In the present study, an open chest preparation without systemic hypoxemia, the response to acute atelec-

tasis included diversion of blood flow from the atelectatic lung to the ventilated lung and a generalized increase in pulmonary perfusion pressure because of an increase of PVR in the atelectatic region. These responses developed quickly (15 min), were maximal by 60 min, and were sustained for four hours.

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APPENDIX

Derivation of Hypoxic Shunt Equation

Systemic arterial blood ($\dot{Q}T$) consists of three components: mixed venous blood not perfusing ventilated alveoli from either lung ($\dot{Q}S$), blood perfusing the hypoxic left lung ($\dot{Q}H$), and blood perfusing the normoxic right lung ($\dot{Q}T$) - $\dot{Q}S$ - $\dot{Q}H$.

Therefore, the total oxygen flow out of the lung is:

$$\dot{Q}T \cdot Ca_{O_2} = \dot{Q}H \cdot CH_{O_2} + \dot{Q}S \cdot C\bar{v}_{O_2} + (\dot{Q}T - \dot{Q}S - \dot{Q}H) \cdot C\dot{c}_{O_2}$$

and rearranging:

$$\dot{Q}H/\dot{Q}T = [(C\dot{c}_{O_2} - Ca_{O_2}) - \dot{Q}S/\dot{Q}T(C\dot{c}_{O_2} - C\bar{v}_{O_2})]/(C\dot{c}_{O_2} - CH_{O_2})$$

Assuming that the anatomic shunt flow ($\dot{Q}S/\dot{Q}T$) measured during normoxia remains constant during the other phases then this equation is soluble and the final calculated admixture is:

$$VA = \dot{Q}H/\dot{Q}T + \dot{Q}S/\dot{Q}T$$