HYPOXIA ENHANCES UNILATERAL LUNG INJURY BY INCREASING BLOOD FLOW TO THE INJURED LUNG

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Abbreviated Title: Hypoxia enchances unilateral lung injury

ABSTRACT

We hypothesized that in unilateral lung injury, bilateral hypoxic ventilation would induce vasoconstriction in the normal lung, redirect blood flow to the injured lung, and cause enhanced edema formation. Unilateral left lung injury was induced by intrabronchial instillation of 1.5 ml/kg of 0.1 N HCl. After HCl injury, blood flow to the injured left lung decreased progressively from .70±.04 to .37±.05 L/min and percent of flow to the injured left lung (Q_L/Q_T) decreased from 37.7±2.2 to 23.6±2.2% at 240 min. Exposure to hypoxia (12% O_2), for three 10-minute episodes did not affect Q_L/Q_T in normal animals, but after unilateral HCl injury, it caused blood flow to the injured left lung to increase significantly. A concomitant decrease in blood flow occurred to the non-injured right lung, resulting in a significant increase in $Q_{L/}Q_T$. The enhanced blood flow to the injured lung was associated with a significant increase in the wet-to-dry lung weight ratio in the dependent regions of the injured lung. These findings demonstrate that in unilateral HCl-induced lung injury, transient hypoxia can enhance blood flow to the areas of injury and increase lung edema formation.

Index Terms: Hypoxia, acid aspiration, unilateral lung injury, lung water, hypoxic pulmonary vasoconstriction.

INTRODUCTION

In experimental unilateral lung injury, blood flow to the injured lung has been reported to decrease (1). This physiological response is important in maintaining arterial oxygenation by shunting blood flow away from the injured to the normal lung. One of the mechanisms for this response is postulated to be hypoxic pulmonary vasoconstriction (HPV). HPV has been demonstrated to exist in areas of atelectasis as well as during hypoxic ventilation in animals and humans (2,3). In addition to maintaining arterial oxygenation, HPV may lessen the severity of lung injury by reducing blood flow to the lung with increased capillary permeability. Most experimental models of acute lung injury, including acid aspiration, involve endothelial damage and are characterized by an enhanced permeability type of edema (4,5). Bishop et al. reported that minoxidil, a potent HPV inhibitor, further increased the production of extravascular lung water during the early phase of acute lung injury in rabbits when it was given prior to oleic acid administration (6). These findings suggest that when blood flow increases to areas of injury and increased capillary permeability, edema formation increases. Clinically, patients with acute lung injury may be exposed to transient hypoxia during procedures such as endotracheal suctioning (7) and bronchoscopic examination (8). During the hypoxic period, the pulmonary vasculature in the normal lung may elicit HPV and shunt blood flow to injured areas of the lung, resulting in aggravation of injury.

The purposes of this study were 1) to observe serial physiological changes, including blood flow distribution, after unilateral lung injury; 2) to determine the effects of brief periods of bilateral hypoxic

ventilation on blood flow distribution; and 3) to measure the extent of edema formation in the injured lung following hypoxic ventilation by following wet-to-dry lung weight ratios (W/D).

METHODS AND MATERIALS

Animal Preparation

Twenty adult, male mongrel dogs screened for heart worm infestation and weighing 17 to 25 kg were anesthetized with intravenous pentobarbital sodium (30 mg/kg) and intubated with a cuffed endotracheal tube (9.0 mm ID). Mechanical ventilation with 100% oxygen was maintained with a Harvard animal ventilator to achieve a $PaCO_2$ of 32 to 38 torr by adjusting the tidal volume (20 ml/kg) and respiratory rate (10-13 cycles/min). Before sternotomy, 7.5 mg/kg of pentobarbital sodium and 0.15 mg/kg of pancuronium bromide were administered intravenously. After this, anesthesia was maintained with hourly administration of pentobarbital sodium (3 mg/kg) and pancuronium bromide (0.05 mg/kg). By using this regimen, no sign of light anesthesia was observed. To minimize the effects of these drugs, they were given 45 minutes prior to measurements.

After induction of anesthesia, a balloon-tipped Swan-Ganz catheter (7.5 Fr.) was advanced into the main pulmonary artery through the right external jugular vein to measure pulmonary arterial pressure (PAP). The position of the catheter was assured by direct palpation after thoracotomy. By cutdown of the right groin, a 14-G polyethylene catheter was placed in the femoral artery to measure arterial pressure (AP). Another catheter was advanced into the right atrium through the right femoral vein to measure right atrial pressure (RAP). After placement of catheters, the chest was opened via a median sternotomy and ventilation was maintained with an application of 5 cm H_2O end-expiratory pressure. A catheter was placed by a direct left atriotomy

for the purpose of left atrial pressure (LAP) measurement. A segmental branch of pulmonary vein draining from each lower lobe was canpulated with a thin polyethylene tube. The tube was advanced from the segmental branch into the lobar vein to obtain mixed pulmonary venous blood. An electromagnetic flow probe (5 or 6 mm in diameter, Micron Co.) with a nonocclusive zero function was placed around the left main pulmonary artery, and the mean blood flow to the left lung was recorded on a strip chart recorder (Hewlett-Packard Co., Model 7758A). The flowmeter was calibrated in vivo in every experiment. Blood flow to the right lung (Q_R) was calculated as the difference between Q_T and Q_L. A 36 Fr. Carlen's tube, designed for left endobronchial intubation, was placed via a tracheostomy to facilitate unilateral instillation of hydrochloric acid (HCl) and was kept in place during the rest of the study.

All surgical procedures were done under sterile conditions. Normal saline was infused at a rate of 50 ml/hr via a catheter in a peripheral vein during the study period. Intravascular pressures were measured with Statham pressure transducers (P 23 Db) and recorded on a strip chart recorder. The mid-point of the left atrium was used as zero reference. Q_T was determined using the thermal dilution technique and was done in triplicate using 10 ml of 5% dextrose solution at room temperature. Blood samples were withdrawn from femoral and pulmonary arteries and pulmonary veins and pH, PO_2 and PCO_2 were measured immediately using a blood gas analyzer (Radiometer, ABL-30). Total, left and right pulmonary vascular resistances (PVR_T, PVR_L and PVR_R, respectively) were calculated from the perfusion pressure (PAP-LAP) divided by the respective lung blood flow. Systemic

vascular resistance (SVR) was also calculated from systemic perfusion pressure (AP-RAP) divided by Q_T. Both PVR and SVR were expressed as mmHg/l/min. Body temperature was maintained at 37.0°C by using a heating pad.

Study Design (Figure 1)

After stabilization of hemodynamics following surgery, baseline hemodynamic and blood gas data were collected. Dogs were divided into four groups. A control group consisted of five dogs who underwent the same surgical procedure and placement of catheters as the injured animals. In the HCl group, five dogs had HCl instillation into the left lung after baseline measurements. A 10-Fr polyvinyl chloride tube was advanced into the left main bronchus through a left-sided orifice of a Carlen's double-lumen catheter and 1.5 ml/kg body weight of 0.1 N HCl was instilled slowly. In the supine position, intrabronchially injected HCl went preferentially into the lower lobe. To induce a more homogenous injury, HCl was instilled at four positions; supine, head down, head down + left side dependent recumbent and left side dependent recumbent positions. Distribution of HCl was confirmed by adding a small amount of 1% methylene blue as an indicator. Immediately after instillation of the HCl, intrabronchial suction of the right lung was performed to make sure that unilateral instillation into the left lung was achieved. After HCl administration, data were collected hourly for four hours. In the hypoxia group, 5 dogs were ventilated with a hypoxic gas mixture (12% O_2 + 88% N_2) for 10 minutes periodically at 60, 120 and 180 minutes after the baseline measurements. Hemodynamic and blood gas data were obtained at each pre- and post-hypoxic period.

The HCl + hypoxia group consisted of five dogs. They had both HCl instillation and hypoxic ventilation at the same times as the hypoxia group. After four hours of observation, the dogs were sacrificed with a fatal dose of pentobarbital sodium, and zero blood flow to the left lung was recorded in order to complete the in vivo calibration of the flow probe. Thereafter, both lower lobes were removed.

After the animals were sacrificed, the lungs and heart were removed en bloc by cutting the great vessels and allowing blood to drain freely into the chest. Next, the pericardium and heart were removed, and the lobes were individually separated. The identical procedure was carried out in all animals, so the wet-to-dry lung weight ratios (W/D) were not biased. After the lower lobes were removed, the dorsal (dependent) and ventral (non-dependent) parts of the lower lobes were identified in relation to the supine position of the dog over the six-hour experiment. The dorsal and ventral portions were separated by placing the lobes on a table in the exact anatomic relationship to the position of the animal and horizontally cutting the lobes in half.

Statistics

Analysis of variance followed by Duncan's multiple range test was used to compare physiologic data between and among groups. A two-sided, paired Student's t test was used to analyze data between pre- and post-hypoxia. A two-sided, unpaired Student's t test was used for comparison of W/D. Differences were considered statistically significant at P values of less than 0.05.

RESULTS

Effects of Acid Aspiration on Physiological Parameters

Hemodynamic changes following unilateral HCl administration are summarized in Table 1. In the control group, hemodynamics were stable during the study period. In the HCl-treated group, total pulmonary blood flow (Q_T) showed a tendency to decrease after HCl administration. At baseline blood flow to the left lung (Q_L) was .70±.04 L/min and percent of flow to the left lung (Q_L/Q_T) was 37.7±2.2%. However, following HCl administration, Q_L decreased progressively to .37±.05 L/min and Q_L/Q_T decreased to 23.6±2.2% at the end of a 4 hour study (Figure 2). On the other hand, blood flow to the right lung (Q_R) was stable during the study. A slight decrease was seen in mean systemic artery pressure; however, mean pulmonary artery pressure (PAP) did not change during the four-hour study period. Those changes were reflected in the vascular resistances. Total pulmonary vascular resistance (PVR_T) showed a tendency to increase after 120 minutes. Pulmonary vascular resistance in the right lung (PVR_R) did not change; however, pulmonary vascular resistance in the left lung (PVR_L) increased significantly and at the end of the experiment, it increased to 184% of the baseline (Figure 3). Systemic vascular resistance (SVR) increased significantly 180 minutes after HCl administration and stayed elevated thereafter. Heart rate (HR), left atrial pressure (LAP) and right atrial pressure (RAP) did not change throughout the study.

Table 2 summarizes blood gas data. In the control group, PO_2, PCO_2 and pH did not change during the study. Following HCl administration, the pulmonary venous PO_2 in the injured left lung decreased

significantly but the pulmonary venous PO_2 in the non-injured right lung was not affected. Arterial PO_2 decreased significantly during the first 2 hours after HCl; however, it showed a tendency to increase toward the baseline during the last 2 hours. Mixed venous PO_2 showed a time-related profile similar to the arterial PO_2. An increase of PCO_2 and a decrease of pH were observed in left pulmonary venous blood after HCl administration. On the other hand, right pulmonary venous PCO_2 decreased markedly after HCl administration. PCO_2 and pH did not change in arterial and mixed venous blood.

Effects of Bilateral Hypoxic Ventilation on Unilateral Lung Injury.

Hemodynamic and blood gas changes following bilateral hypoxic ventilation are summarized in Tables 3 and 4, respectively.

In both the hypoxia and HCl + hypoxia groups, bilateral hypoxic ventilation caused a significant elevation in pulmonary artery pressure (PAP). The PAP increase was greater after the second and third hypoxic ventilation than after the first hypoxic ventilation as previously reported (9). In the hypoxia group, total blood flow (Q_T) and blood flow to both the left (Q_L) and right (Q_R) lungs increased significantly following hypoxic ventilation (Table 3). Because the increase in blood flow was uniformly distributed, percent of flow to the left lung (Q_L/Q_T) did not change (open symbols, Fig. 4). In the presence of HCl induced unilateral lung injury, exposure to hypoxia caused an increase in blood flow to the injured left lung in conjunction with a decrease in blood flow to the normal right lung (Table 3). The result was a consistent increase in percent blood flow to the left lung (solid symbols, Fig. 4). In Figure 5, changes in pulmonary vascular resistance are depicted. In the hypoxia alone group, pulmonary vascular

resistances in both left and right lungs increased significantly after the second and third hypoxic ventilation, suggesting that the non-injured lung had a vasoconstrictive response to hypoxia. In the HCl + hypoxia group, the non-injured right lung had a vasoconstrictive response to hypoxia and PVR_R increased significantly. However, in the injured left lung, no vasoconstrictive response to hypoxia was observed (Fig. 5).

Hypoxic ventilation caused a significant decrease in PO_2 of the blood obtained from every sampling site in both groups. In the hypoxia group, the PO_2 decreased significantly; however, there was no difference between right and left pulmonary venous blood. Due to the low PO_2 caused by HCl injury, left pulmonary venous PO_2 was consistently lower than right pulmonary venous PO_2 after hypoxic ventilation in the HCl + hypoxia group. In general, PCO_2 and pH were not affected by 10 minutes of exposure to hypoxia.

Lung Water (Table 5)

In the control and hypoxia groups, there were no statistically significant difference in either the W/D ratios of the right and left lungs or in the W/D ratios of the dependent and non-dependent aspects of the right and left lung. In the HCL group, the W/D ratios of both the dependent and non-dependent portions of the injured left lower lobe increased significantly from that of the uninjured right lower lobe: 4.96±.13 to 6.83±.33, and 5.16±.07 to 7.08±.16 respectively. In the HCL-hypoxia group, the W/D ratios of the dependent and non-dependent regions of the injured left lower lobe also increased significantly over the corresponding right lower lobe: 5.02±.07 to 6.88±.22, and 5.12±.09 to 7.74±.17 respectively.

Next, we compared the W/D ratios of the HCl group to the HCl-hypoxia group. There was no statistical difference between the W/D ratios in the ventral or non-dependent regions of the injured left lower lobes in the two groups: 6.83±.33 to 6.88±.22. However, there was a statistically significant increase in the W/D ratio in the dorsal or dependent regions of the injured left lower lobe in the HCl-hypoxia group versus the HCl group: 7.08±.16 to 7.74±.17 (Table 5).

DISCUSSION

Acid aspiration is one of the major causes of acute lung injury and is characterized by increased alveolar-capillary membrane permeability (4,5). Clinically, it is often recognized as a localized injury such as unilateral lung injury. The physiological sequences of pulmonary acid aspiration have been extensively studied (10-14). In general, there are decreases in heart rate, blood pressure and cardiac index immediately after HCl administration followed by a progressive decrease in cardiac index and a progresive increase in systemic and pulmonary vascular resistances with or without an elevation of pulmonary artery pressure. Fabre et al. (11) compared these sequences to an early parasympathetic and successive hypovolemic syndrome. Following unilateral HCl administration, we observed a progressive decrease in cardiac output; however, pulmonary artery pressure did not change during the study. These findings are consistent with the study of Cameron et al. (13). They also found a progressive increase in hematocrit and suggested that the animals were sequesting fluid into the injured lung and were becoming hypovolemic even though they were hemodynamically stable.

We demonstrated that blood flow to the injured left lung progressively decreased with a concomitant increase in pulmonary vascular resistance in the injured lung following HCl administration. We also found a marked decrease in the pulmonary venous PO_2 in the injured lung from 552±22 to 70±8 torr; however, arterial PO_2 was affected less. Using differentially labeled microspheres, Fisher and Wood (15) investigated the effects of lobar acid injury on lobar and sublobar pulmonary perfusion. They sectioned the lobe into visibly injured and non-injured

segments and demonstrated that percent blood flow to the injured region decreased significantly three hours after HCl administration. However, percent flow to the non-injured region was not altered. They also studied the effect of their blood sampling technique on lobar venous PO_2 and demonstrated that blood from the ventral and dorsal part of pulmonary vein had oxygen tensions of 400 torr and 60 - 70 torr, respectively and mixed pulmonary venous blood had an intermediate PO_2. We collected mixed pulmonary venous blood with special attention to their findings; however, PO_2 was comparable to the PO_2 of blood from the dorsal (injured) part in their study. The lower PO_2 in our study may be attributed to a more severe injury since we used a larger amount of HCl. It is noteworthy that the percent decrease of flow to the injured segment in their study (-26.3%) is quite similar to our study (-27.1%) 3 hours after HCl administration.

Flow to the injured lung decreased because of a pulmonary vasoconstrictive response to acid injury. Local hypoxia induced by acid injury may elicit hypoxic pulmonary vasoconstriction (HPV) which, in turn, shunts blood to the normal region and maintains arterial oxygenation. The presence of HPV in acute lung injury is suggested by the fact that vasodilators can worsen gas exchange (16); however, this is still controversial. Vascular reactivity is reported to be increased in rat lungs injured with _-naphthylthiourea (17). On the other hand, HPV is reported to be altered or impaired in some lung injuries, such as bacterial pneumonia (18), endotoxemia (19,20), pulmonary oxygen toxicity (21,22), etc. Stephenson et al. (1) reported that in ethychlorvynol-induced unilateral lung injury, the percent flow to the injured right lung decreased by 10%; however, this reduction was

inadequate to prevent a decrease in arterial PO_2. It was suggested that, following acute lung injury, the reactivity of pulmonary vasculature was altered such that blood flow to hypoxic alveoli was maintained. In our study, percent flow to the injured left lung decreased by 37% 4 hours after HCl administration. Their study might be affected by a presence of systemic hypoxemia (PaO_2 60.7 torr). We found that arterial PO_2 decreased significantly, reaching its trough at 2 hours after HCl administration; however, it returned to pre-HCl level at 4 hours. This finding might be consistent with the study in which HPV is reported to be absent at one and two hours, but return by four hours after acid instillation in goats (23). Whatever the mechanism(s) is(are) to reduce the blood flow to the injured lung, this phenomenon is important to decrease the shunt and also to lessen the severity of injury which is characterized by permeability edema.

Another mechanism by which the flow to the injured lung decreases is mechanical. It has been suggested that perivascular cuffing during the early stage of pulmonary edema may cause a compression of small vasculature, resulting in a decreased blood flow to the edematous region (24). However, extensive edema is reported to be required to cause blood redistribution (25). By raising the pulmonary arterial and venous pressures, Bhattacharya et al. (26) induced edema in isolated perfused canine lobe. In edematous lobes, blood flow remained constant until lobe weight had doubled, suggesting that extensive edema is essential to reduce the blood flow to the edematous region. We observed alveolar flooding pathologically and a wet-to-dry lung weight ratio of 6.96, both of which suggest that severe pulmonary edema occurred. In addition, our preliminary study revealed that, at 4 hours

after HCl administration, the injured left lower lobe tripled its weight from a mean of 30.2 g to 87.6 g. If the HCl-induced edema occurred in a very short period of time, the blood flow decrease observed in our study might be explained by this mechanical factor.

In HCl-treated animals exposed to bilateral hypoxia, blood flow to the right non-injured lung decreased, but blood flow to the injured left lung increased (Fig. 4). This is explained by an increase in pulmonary vascular resistance in the non-injured lung without an increase in pulmonary vascular resistance in the injured lung which implies that either an impaired vascular reactivity to hypoxia or on-going vasoconstriction blocked the further response to hypoxia in the injured lung. It is plausible to postulate that an augmented blood flow to the injured lung can increase pulmonary shunt and aggravate the lung water accumulation. Bishop and Cheney (16) investigated effects of vasodilator treatment on gas exchange and lung water accumulation over a five-hour period in oleic acid-induced pulmonary edema. They found that minoxidil, which is a potent HPV inhibitor (27), increased venous admixture by 38%, whereas animals treated with hydralazine, which does not inhibit HPV (28), gave a smaller increase of 21%. Lung water accumulation was significantly accelerated by minoxidil; however, a smaller and non-significant increase was seen in the hydralazine group. Moreover, they observed a significantly higher mortality in minoxidil-treated dogs and concluded that vasodilators with a minimal effect on HPV might be preferable in the face of respiratory failure.

We hypothesized that the increase in blood flow secondary to bilateral hypoxia would increase intravascular pressure and, therefore, increase pulmonary edema in the injured lung. In our original protocol,

we sought to determine W/D ratios from both the dependent and non-dependent regions of the lung because we thought that injury may be increased in the dependent areas of the lung from conditions of this experiment. We found no increase in lung water accumulation in either the control group or in the hypoxia group alone, indicating no injury occurred secondary to manipulation and instrumentation of the animals. In both the HCl group and the HCl-hypoxia group, there were significant increases in W/D ratios in the injured lung. Also, in both of these injured groups, there was an increase in the W/D ratios in the dependent region versus the non-dependent region of the injured left lower lobe with the values in the HCl-hypoxia group achieving statistical significance. This is not surprising since gravity even in the normal human lung increases blood flow to the dependent areas of the lung in the upright position. In an injured capillary bed, this increase in blood flow would alter Starling's forces and increase edema formation. In the HCl-hypoxia group where blood flow was redirected from the normal lung to the injured lung by bilateral hypoxia, the W/D ratio from the dependent region was significantly greater than the corresponding region of the HCl group. These data indicate that local increases in pulmonary intravascular pressure either secondary to gravity or bilateral hypoxia will further increase W/D ratios and presumably lung water in an injured lung.

In clinical settings, patients with acute lung injury may be exposed to hypoxia during routine airway management procedures such as endotracheal suctioning (7), diagnostic bronchoscopy (8), ventilator circuit change (31), etc. Desaturation of arterial blood and hypoxia-induced arrhythmias have been reported during these procedures (32,

33). Our findings showed that hypoxia elicited a vasoconstrictive response in the normal lung and redistibuted the blood flow to the injured lung. If this effect is repetitive or prolonged, it may cause significant increases in lung water accumulation and aggravate the acute lung injury.

In summary, following unilateral HCl administration, blood flow to the injured lung decreased without any effect on the contralateral lung. This decrease in flow to the injured lung is a protective mechanism to maintain arterial oxygenation and lessen the severity of lung injury. If blood flow to the injured lung is increased either by blockade of HPV or by an elevation of pulmonary vascular pressure, intrapulmonary shunting and lung water accumulation may be accelerated, resulting in more severe injury, especially in the acute phase of lung injury.

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FIGURE LEGENDS

Figure 1: Scheme of experimental design. Arrows on the time line show when anesthetic drugs were given. Animals were ventilated with 100% O_2 after anesthesia was initiated except for the three 10-minute periods of hypoxia shown by the cross hatched areas on the third and fourth groups. The open circles with a solid center represent the times when physiologic data were collected.

Figure 2: Effect of HCl administration on percent of flow to the left lung (Q_L/Q_T).
In the control group (open circles), Q_L/Q_T did not change during the study. On the other hand, in the HCl group (solid circles), Q_L/Q_T decreased progressively.
* : $P < 0.05$ vs baseline

Figure 3: Effect of HCl administration on left and right pulmonary vascular resistances (PVR_L and PVR_R, respectively).
PVR_R in the non-injured right lung did not change, however, PVR_L in the injured left lung increased progressively after HCl administration.
* : $P < 0.05$ vs baseline

Figure 4: Effect of bilateral hypoxic ventilation on percent of flow to the left lung (Q_L/Q_T). The cross hatched regions represent the periods of hypoxic ventilation. There was no change in

Q_L/Q_T after bilateral hypoxic ventilation in the hypoxia group (open symbols). However, in the HCl + hypoxia group (solid symbols), hypoxic ventilation caused a significant increase in Q_L/Q_T, suggesting that a shift in blood flow toward the injured left lung occurred after hypoxia.

* : $P < 0.05$ vs comparable pre-hypoxia value.

Figure 5: Effects of bilateral hypoxic ventilation on left and right pulmonary vascular resistance (PVR_L and PVR_R, respectively). A. In the hypoxia group, bilateral hypoxic ventilation caused significant increases in PVR_L and PVR_R. B. In the HCl + hypoxia group, PVR_R in the non-injured right lung increased after hypoxic ventilation, however, in the injured left lung there was no increase in PVR_L after hypoxic ventilation.

In both A and B, the cross hatched regions represent the periods of hypoxic ventilation.

* : $P < 0.05$ vs the value immediately before that period of hypoxia.

TABLE 1. HEMODYNAMIC CHANGES AFTER HCl

		CONTROL		HCl				
		Baseline	240 min	Baseline	60 min	120 min	180 min	240 min
Q_T	l/min	2.02 ± .10	2.12 ± .06	1.88 ± .14	1.82 ± .17	1.59 ± .10	1.53 ± .09	1.56 ± .12
Q_R	l/min	1.33 ± .08	1.42 ± .06	1.18 ± .12	1.21 ± .11	1.09 ± .07	1.10 ± .04	1.19 ± .09
Q_L	l/min	.69 ± .02	.70 ± .03	.70 ± .04	.61 ± .07	.50 ± .06*	.43 ± .05*	.37 ± .05*
Q_L/Q_T	%	34.1 ± .8	33.0 ± 1.4	37.7 ± 2.2	33.5 ± 1.8	31.2 ± 2.8	27.5 ± 2.3*	23.6 ± 2.2*
HR	/min	162 ± 9	163 ± 10	148 ± 11	148 ± 6	155 ± 6	151 ± 7	159 ± 5
SAP	mmHg	117 ± 7	126 ± 2	103 ± 7	95 ± 8	98 ± 7	98 ± 7	99 ± 7
CVP	mmHg	3 ± 0	3 ± 1	2 ± 1	2 ± 1	2 ± 1	1 ± 1	1 ± 1
SVR	mmHg/l/min	57.2 ± 4.7	57.9 ± 1.9	53.8 ± 2.5	51.8 ± 3.3	60.3 ± 1.6	64.1 ± 4.2*	62.9 ± 2.5
PAP	mmHg	15 ± 1	15 ± 1	14 ± 1	15 ± 1	14 ± 1	15 ± 1	14 ± 1
LAP	mmHg	5 ± 1	4 ± 1	4 ± 1	4 ± 1	3 ± 1	4 ± 1	4 ± 1
PVR_T	mmHg/l/min	4.9 ± .4	5.4 ± .3	5.5 ± .5	5.7 ± 1.0	6.6 ± .6	7.1 ± .3	6.4 ± .7
PVR_R	mmHg/l/min	7.5 ± .6	8.0 ± .6	8.9 ± .9	8.6 ± 1.4	8.8 ± .9	9.8 ± .5	8.4 ± 1.0
PVR_L	mmHg/l/min	14.5 ± 1.3	16.1 ± 1.1	14.8 ± 1.5	17.5 ± 3.4	20.4 ± 3.4	26.4 ± 2.2*	27.2 ± 2.1*

Q_T : Total pulmonary blood flow
Q_R : Blood flow to right lung
Q_L : Blood flow to left lung
Q_L/Q_T : Percent of flow to the left lung
HR : Heart rate

SAP : Mean systemic artery pressure
PAP : Mean pulmonary artery pressure
CVP : Central venous pressure
LAP : Left atrial pressure

SVR : Systemic vascular resistance
PVR_T : Total pulmonary vascular resistance
PVR_R : Right pulmonary vascular resistance
PVR_L : Left pulmonary vascular resistance

Data are presented as mean ± SE.

* : $P < 0.05$ vs Baseline

TABLE 2. EFFECTS OF HCl ON GAS EXCHANGE

		CONTROL		HCl				
		Baseline	240 min	Baseline	60 min	120 min	180 min	240 min
Femoral Artery	PO_2†	500 ± 33	487 ± 42	558 ± 19	419 ± 40*	367 ± 50*	470 ± 22	471 ± 30
	PCO_2†	35 ± 1	36 ± 1	38 ± 1	37 ± 2	35 ± 2	34 ± 2	33 ± 1
	pH	7.38 ± .01	7.38 ± .03	7.35 ± 03	7.36 ± .03	7.36 ± .03	7.37 ± .02	7.38 ± .02
Pulmonary Artery	PO_2	46 ± 4	46 ± 3	44 ± 5	40 ± 3	40 ± 3	42 ± 3	41 ± 3
	PCO_2	43 ± 2	46 ± 2	48 ± 2	48 ± 1	45 ± 2	46 ± 3	48 ± 2
	pH	7.30 ± .01	7.31 ± .03	7.29 ± .01	7.29 ± .01	7.29 ± .01	7.27 ± .02	7.28 ± .02
Left Pulmonary Vein	PO_2	494 ± 14	517 ± 32	552 ± 22	110 ± 31*	129 ± 39*	70 ± 8*	106 ± 28*
	PCO_2	26 ± 2	31 ± 2	27 ± 2	39 ± 4	39 ± 6	42 ± 5	38 ± 6
	pH	7.44 ± .03	7.42 ± .03	7.44 ± .02	7.32 ± .03	7.32 ± .06	7.31 ± .04*	7.33 ± .05
Right Pulmonary Vein	PO_2	519 ± 46	543 ± 29	558 ± 27	524 ± 10	556 ± 14	570 ± 17	532 ± 29
	PCO_2	29 ± 2	31 ± 1	32 ± 4	26 ± 4	28 ± 4	28 ± 4	29 ± 3
	pH	7.44 ± .03	7.44 ± .05	7.40 ± .04	7.41 ± .04	7.40 ± .04	7.40 ± .04	7.38 ± .02

Data are presented as mean ± SE. * : $P < 0.05$ vs Baseline

† : torr

TABLE 3 EFFECTS OF BILATERAL HYPOXIC VENTILATION ON HEMODYNAMIC PARAMETERS

		Hypoxia Group						HCl + Hypoxia Group					
		1st		2nd		3rd		1st		2nd		3rd	
		Pre-Hypoxia	Post-Hypoxia	Pre-Hypoxia	Post-Hypoxia	Pre-Hypoxia	Post-Hypoxia	Pre-Hypoxia	Post-Hypoxia	Pre-Hypoxia	Post-Hypoxia	Pre-Hypoxia	Post-Hypoxia
Q_T	l/min	2.23±.12	2.64±.12*	2.16±.10	2.59±.14**	2.17±.09	2.42±.11*	1.94±.14	2.06±.16*	1.73±.17	1.84±.16	1.63±.20	1.71±.16
Q_R	l/min	1.42±.04	1.64±.18	1.43±.04	1.60±.09*	1.41±.04	1.52±.05*	1.34±.14	1.20±.14*	1.19±.17	.97±.09	1.15±.18	1.00±.09
Q_L	l/min	.79±.09	1.00±.15*	.73±.09	.99±.11**	.76±.10	.89±.08*	.61±.05	.86±.08**	.54±.05	.87±.08*	.48±.06	.71±.10*
Q_L/Q_T	%	34.9±2.1	38.0±5.6	34.0±2.7	37.5±2.9	34.7±3.2	36.8±1.7	31.7±3.2	42.3±4.1**	32.3±3.8	47.4±1.6**	30.2±3.9	41.2±3.0**
HR	/min	158±7	160±9	158±7	160±7	155±6	162±8	148±9	149±10	150±7	152±7	150±7	150±9
SAP	mmHg	130±10	130±10	128±10	131±11	126±10	129±10	105±7	102±8	99±7	93±9	96±9	90±13
CVP	mmHg	0±1	0±1	0±1	1±1	0±1	0±1	1±1	2±1	1±1	2±1	0±1	2±1
PAP	mmHg	15±1	23±1**	15±1	27±2**	15±1	27±2**	14±1	19±1**	13±0	21±1**	13±0	22±1**
LAP	mmHg	1±1	2±1	1±1	1±1	1±1	1±1	1±0	2±1	2±0	3±1	2±0	2±1

Data are presented as mean ± SE.

Abbreviations used are the same as Table 1

* : $p < 0.05$ vs comparable pre-hypoxia value

** : $p < 0.01$ vs comparable pre-hypoxia value

TABLE 4 BLOOD GAS CHANGES AFTER BILATERAL HYPOXIC VENTILATION

		Hypoxia Group						HCl + Hypoxia Group					
		1st		2nd		3rd		1st		2nd		3rd	
		Pre-Hypoxia	Post-Hypoxia	Pre-Hypoxia	Post-Hypoxia	Pre-Hypoxia	Post-Hypoxia	Pre-Hypoxia	Post-Hypoxia	Pre-Hypoxia	Post-Hypoxia	Pre-Hypoxia	Post-Hypoxia
Femoral Artery	PO_2†	523±30	40±3**	490±35	39±2**	505±34	38±1**	301±45	40±3**	333±58	37±3**	389±51	37±2**
	PCO_2†	35±1	32±1	31±1	31±2	33±1	31±2	34±2	34±1	34±2	33±2	33±2	34±3
	pH	7.35±.02	7.40±.03	7.38±.03	7.41±.04	7.37±.04	7.40±.03	7.39±.02	7.39±.01	7.39±.02	7.41±.03	7.39±.02	7.38±.03
Pulmonary Artery	PO_2	53±4	27±2**	51±3	26±2**	50±3	24±2**	39±1	24±1**	38±1	23±1**	37±1	20±2**
	PCO_2	40±1	38±1	40±1	35±3	41±2	37±2*	45±2	44±2	46±2	40±2	43±3	37±1
	pH	7.29±.03	7.34±.02	7.33±.02	7.34±.02	7.31±.02	7.34±.02*	7.31±.02	7.32±.01	7.30±.02	7.33±.01	7.29±.03	7.31±.02
Left Pulmonary Vein	PO_2	478±31	47±5**	470±19	44±3**	485±13	43±4**	66±16	31±4*	70±21	27±2	60±15	27±4
	PCO_2	27±2	27±1	26±2	27±1	27±3	26±2	39±2	34±3*	39±4	38±3	40±5	41±3
	pH	7.40±.04	7.41±.03	7.43±.04	7.42±.03	7.41±.04	7.41±.04	7.35±.03	7.39±.04	7.35±.04	7.37±.03	7.34±.03	7.35±.03
Right Pulmonary Vein	PO_2	534±29	49±2**	539±23	45±1**	547±33	43±3**	550±9	52±2**	533±22	49±4**	546±43	44±3**
	PCO_2	26±1	26±1	26±1	25±1	27±1	27±1	27±2	26±1	27±2	25±0	29±4	26±1
	pH	7.40±.02	7.42±.03	7.42±.02	7.43±.04	7.41±.02	7.43±.03	7.45±.04	7.44±.02	7.45±.02	7.45±.02	7.43±.01	7.43±.03

Data are presented as mean ± SE.

† : torr

* : $p < 0.05$ vs comparable pre-hypoxia value

** : $p < 0.01$ vs comparable pre-hypoxia value

TABLE 5

REGIONAL WET/DRY WEIGHT RATIOS

	Control Group	Hypoxia Group	HCl Group	HCl-Hypoxia Group
Left Lung				
Ventral or Non-Dependent Region	4.91 ± .11	4.99 ± .06	6.83 ± .33*	6.88 ± .22 *
Dorsal or Dependent Region	4.98 ± .11	5.03 ± .09	7.08 ± .16*	7.74 ± .17 * †‡
Right Lung				
Ventral or Non-Dependent Region	5.11 ± .13	5.11 ± .15	4.96 ± .13	5.02 ± .07
Dorsal or Dependent Region	5.15 ± .23	4.95 ± .07	5.16 ± .07	5.12 ± .09

All data are mean ± SE

* Significantly different from control ($p < .05$)

† Significantly different from HCl group ($p < .05$)

‡ Significantly different from HCl-hypoxia group, ventral or non-dependent region ($p < .05$)

Figure 1

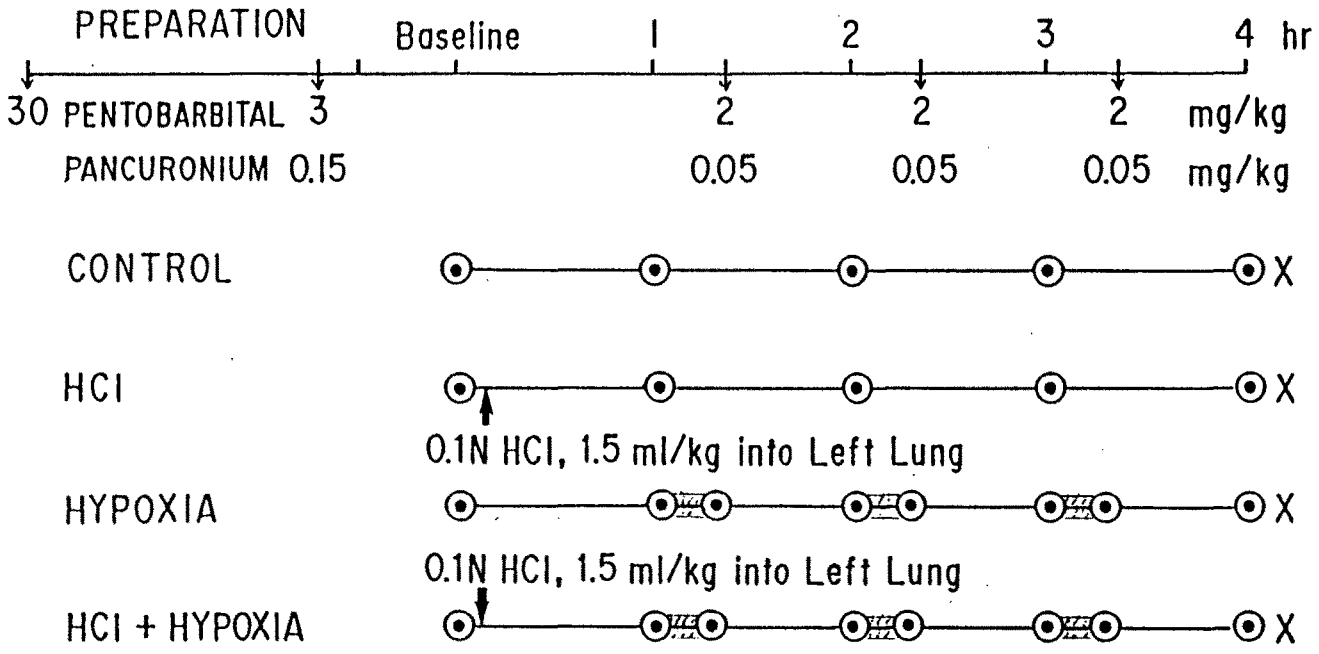

PREPARATION
Baseline
1
2
3
4 hr
30 PENTOBARBITAL 3
2
2
2 mg/kg
PANCURONIUM 0.15
0.05
0.05
0.05 mg/kg
CONTROL
X
HCl
X
0.1N HCl, 1.5 ml/kg into Left Lung
HYPOXIA
X
0.1N HCl, 1.5 ml/kg into Left Lung
HCl + HYPOXIA
X

Figure 2

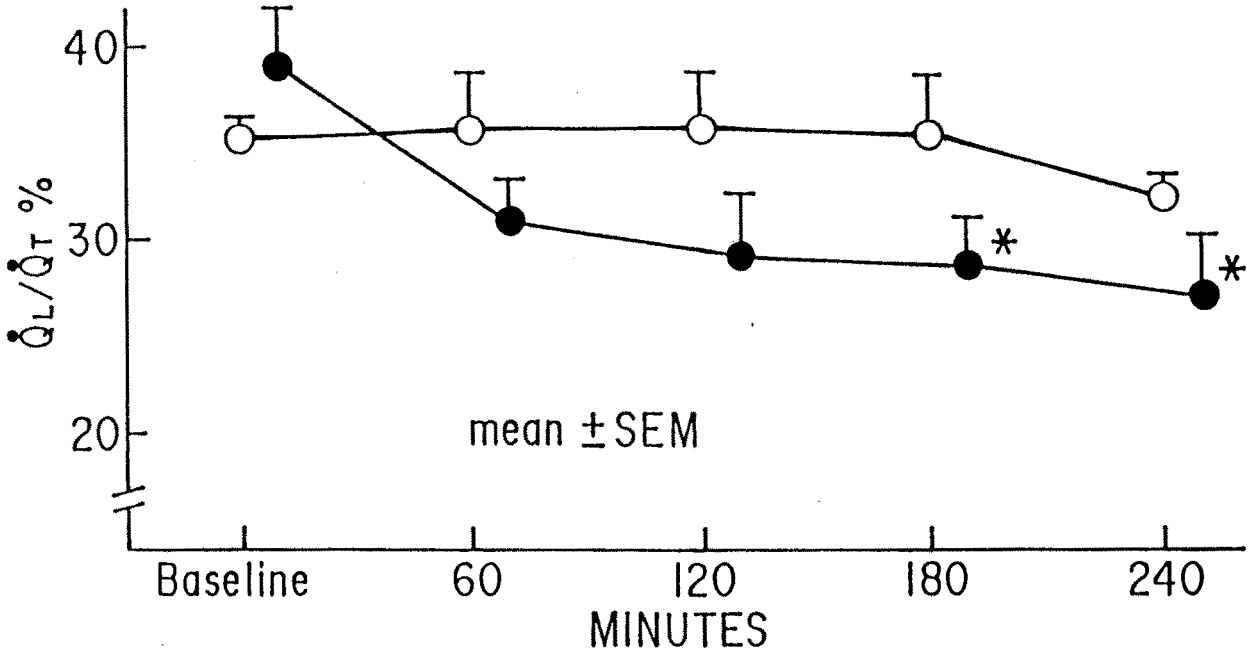


Figure 3

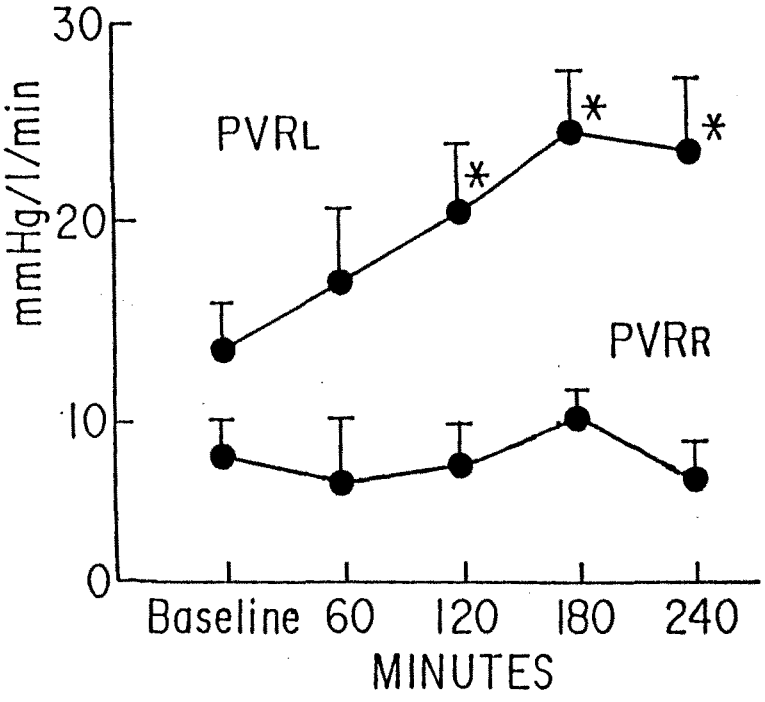


Figure 4

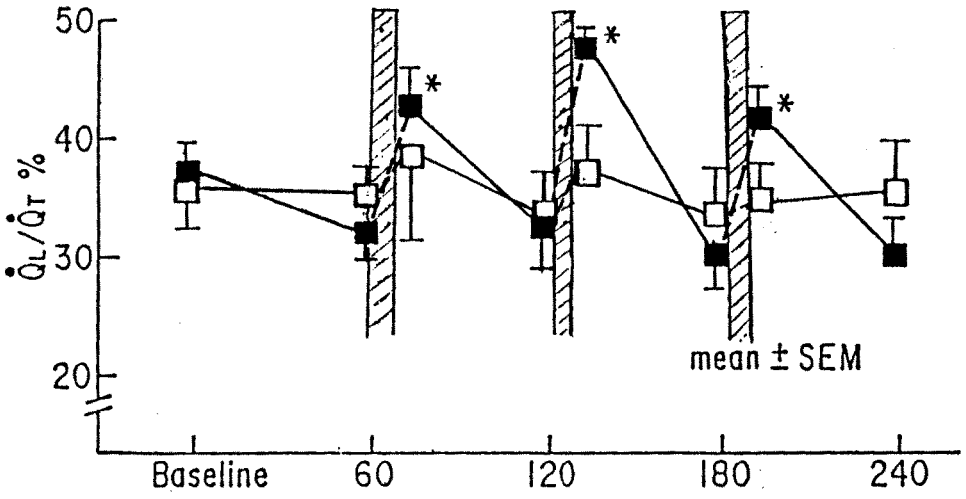
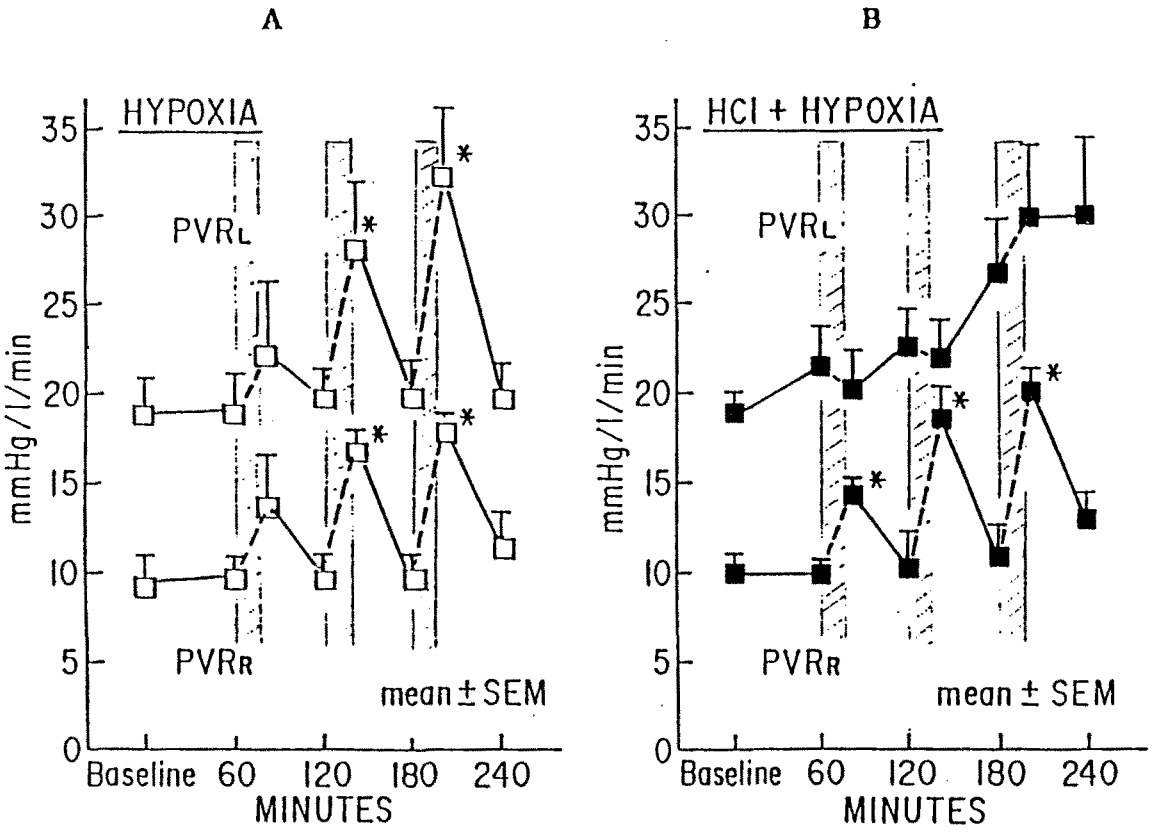


Figure 5


A
B
HYPOXIA
HCl + HYPOXIA
PVRL
PVRR
mean ± SEM
mmHg/l/min
0
5
10
15
20
25
30
35
Baseline
60
120
180
240
MINUTES