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Hypocapnia Worsens Arterial Blood Oxygenation and Increases \dot{V}_A/\dot{Q} Heterogeneity in Canine Pulmonary Edema

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Background: Hyperventilation frequently is employed to reduce carbon dioxide partial pressure in patients in the operating room and intensive care unit. However the effect of hypocapnia on oxygenation is complex and may result in worsening in patients with preexisting intrapulmonary shunt. To better define the interplay between hypocapnia and oxygenation, the effects of hypocapnia and hypercapnia on the matching of ventilation (\dot{V}_A) and perfusion (\dot{Q}) were studied in dogs with oleic acid-induced pulmonary edema, using the multiple inert gas elimination technique.

Methods: Eight pentobarbital-anesthetized, closed-chested dogs were administered 0.06 ml/kg of oleic acid at least 150 min prior to study. Ventilation was set with an FiO_2 of 0.90, a tidal volume of 20 ml/kg, and a respiratory rate of 35 breaths/min. The arterial carbon dioxide tension (Pa_{CO_2}) was varied in a randomized order to three levels (26, 38, and 50 mmHg) by altering the amount of CO_2 in the inspired gas mixture. Gas exchange was assessed by true shunt, dead space, the log standard deviation of the perfusion (log $\text{SD}_\dot{Q}$) and the ventilation (log $\text{SD}_\dot{V}$) distributions, and the tracer inert gas arterial-alveolar difference ([a-A]D) area.

Results: Cardiac output (4.1 ± 0.4 L/min), mean pulmonary artery pressure (25 ± 1 mmHg), inert gas shunt ($22 \pm 3\%$), and dead space ($38 \pm 4\%$) during normocapnia were not different from that during hypocapnia and hypercapnia. Hypocapnia increased ($P < .05$) the alveolar-arterial oxygen tension difference ($\text{P}[A-a]_{\text{O}_2}$) and decreased ($P < .05$) the arterial blood

oxygen tension (Pa_{O_2} , 181 ± 33 mmHg vs. 221 ± 35 mmHg with normocapnia). $\text{P}[A-a]_{\text{O}_2}$ and Pa_{O_2} were unaffected by hypercapnia. During hypocapnia, \dot{V}_A/\dot{Q} inequality increased, demonstrated by an increase ($P < .05$) in log $\text{SD}_\dot{Q}$ (1.60 ± 0.15 vs. 1.35 ± 0.19 with normocapnia) and in the [a-A]D area (0.63 ± 0.09 vs. 0.50 ± 0.09 with normocapnia) indexes of \dot{V}_A/\dot{Q} heterogeneity. During hypercapnia, the [a-A]D area (0.63 ± 0.11) and log $\text{SD}_\dot{V}$ (1.13 ± 0.10 compared to 0.97 ± 0.12 with normocapnia) also were increased ($P < .05$). With hypocapnia, there was a small but insignificant increase in blood flow to shunt and low \dot{V}_A/\dot{Q} areas ($29 \pm 4\%$ compared to $26 \pm 4\%$ with normocapnia). In the presence of a high FiO_2 , this small increase in shunt and low \dot{V}_A/\dot{Q} may result in a significant decrease in Pa_{O_2} .

Conclusions: Both hypocapnia and hypercapnia were associated with an increased \dot{V}_A/\dot{Q} inequality. However, Pa_{O_2} decreased and $\text{P}[A-a]_{\text{O}_2}$ increased with only hypocapnia. These results suggest that hyperventilation to reduce Pa_{CO_2} may be detrimental to arterial P_{O_2} in some patients with lung disease. (Key words: Lung: gas exchange; hyperventilation; hypocapnia; oleic acid injury; pulmonary edema. Measurement technique: multiple inert gas exchange.)

HYPERVENTILATION to reduce arterial carbon dioxide tension (Pa_{CO_2}) frequently is employed in the operating room and in the intensive care unit. Hyperventilation traditionally has been thought to improve arterial oxygen tension (Pa_{O_2}) by increasing the alveolar oxygen tension (Pa_{O_2}).¹ However, the increased ventilation in patients with adult respiratory distress syndrome (ARDS) may be detrimental to the patient by producing barotrauma and additional lung injury. Additionally, hypocapnia may adversely affect arterial blood oxygenation in patients with a preexisting intrapulmonary shunt, such as some patients undergoing general anesthesia. The alveolar-arterial O_2 tension difference ($\text{P}[A-a]_{\text{O}_2}$) was increased with hypocapnia in anesthetized patients.^{2,3,||} However, the resultant effect of hypocapnia on Pa_{O_2} and intrapulmonary shunt was complex, because changes in minute ventilation, cardiac output, body metabolism, or the Bohr effect may influence the measured Pa_{O_2} and intrapulmonary shunt.

A significant advance in the understanding and mea-

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|| In-nami H, Kikuta Y, Nagai H, Okada K: The increase in pulmonary venous admixture by hypocapnia is enhanced in obese patients (abstract). ANESTHESIOLOGY 63:A520, 1985.

surement of pulmonary gas exchange is the development of the multiple inert gas elimination technique.⁴⁻⁶ Classically, gas exchange has been assessed by measurements of the inefficiency of O₂ exchange (e.g., intrapulmonary shunt or venous admixture) and inefficiency of CO₂ exchange (e.g., physiologic and anatomic dead space). In contrast, the multiple inert gas elimination technique can provide information about the actual pattern of ventilation/perfusion (\dot{V}_A/\dot{Q}) relationships in the lung, as well as specifically determine intrapulmonary shunt and dead space. By measuring the mixed venous, arterial, and mixed expired concentrations of six inert gases, a range of \dot{V}_A/\dot{Q} distributions can be determined. The theoretical basis for the model is that, when the blood gas partition coefficient for the gas is equal to the \dot{V}_A/\dot{Q} of the alveolus, half of the inert gas will be retained in the blood and half eliminated in the exhaled gas.

P_{aCO_2} may affect \dot{V}_A/\dot{Q} heterogeneity by affecting the adaptive processes that preserve \dot{V}_A/\dot{Q} matching in the lung. Hypoxic pulmonary vasoconstriction (HPV) is attenuated by hypocapnia.⁷⁻¹⁰ Hypocapnia also causes bronchoconstriction of airways of all sizes and reduces collateral ventilation.^{11,12} Using the multiple inert gas elimination technique, we found that hypocapnia, induced by hyperventilation with a tidal volume of 18 ml/kg and respiratory rate of 35 breaths/min, increased \dot{V}_A/\dot{Q} mismatch but did not affect P_{aO_2} in dogs with normal lungs.¹³ Because of the greater importance of HPV in preserving \dot{V}_A/\dot{Q} matching and oxygenation in diseased than in normal lungs, we investigated the effects of changes in P_{aCO_2} on gas exchange in dogs with noncardiogenic pulmonary edema, induced by the intravenous administration of oleic acid. Oleic acid immediately increases pulmonary vascular permeability, resulting in hemorrhagic pulmonary edema, which has been used as an animal model of ARDS.¹⁴ We hypothesized that hypocapnia would increase \dot{V}_A/\dot{Q} heterogeneity and worsen arterial oxygenation in dogs with pulmonary edema.

Methods and Materials

Instrumentation

The study was approved by the Animal Care Committee of the authors' institution. Eight mongrel dogs of both sexes (21–25 kg) were anesthetized with pentobarbital sodium (30 mg/kg iv, supplemented with 30–90 mg/h). After tracheal intubation, their lungs were ventilated with an Fi_{O_2} of 0.50, at a tidal volume

and respiratory rate adjusted to maintain normocapnia. Diaphragmatic paralysis was assured with succinylcholine (100 mg im, supplemented with 20–40 mg/h iv). Carotid and pulmonary arterial catheters were placed *via* peripheral cut-down. At the completion of the surgical preparation, the endotracheal tube was replaced through a tracheostomy. Oleic acid (0.06 ml/kg) was administered into the right atrium by infusion pump over 10 min. The lungs were hyperinflated hourly to a peak airway pressure of 40 cmH₂O to prevent atelectasis. Sodium chloride (0.9%) and Hespan[®] (6% hetastarch in 0.9% sodium chloride; Dupont Pharmaceuticals, Wilmington, DE) were administered to maintain the pre-injury cardiac output of approximately 4 L/min.

Inert Gas Measurements

The multiple inert gas elimination technique was used to assess gas exchange.^{4,5} A dilute solution of six inert gases (sulfur hexafluoride, ethane, cyclopropane, halothane, diethyl ether, and acetone) dissolved in 5% dextrose was infused into a peripheral vein for at least 60 min before the first samples were drawn. Inert gas partial pressures were measured in duplicate in blood simultaneously collected from the pulmonary artery ($P_{\bar{V}}$) and the carotid artery (P_a), and in mixed expired gas (P_E). Exhaled gas specimens were maintained at >40° C before analysis to avoid condensation and loss of highly soluble gases. The concentrations of inert gases were measured on a gas chromatograph (Varian 3300, Walnut Creek, CA), equipped with a flame ionization detector and an electron capture detector. The gas extraction method of Wagner *et al.*¹⁵ was used to determine the concentration of inert gases in the blood samples.

Experimental Protocol

As the oleic acid injury stabilizes after 90–120 min, after which further increases in lung water and gas exchange abnormalities are minimal,^{16,17} we waited to begin experimental manipulations for at least 120 min following the administration of oleic acid. After this rest period, the experimental protocol was begun after demonstration of stability of the arterial blood gases over an additional 30-min period. Ventilation was then increased to a tidal volume of 20 ml/kg, a respiratory rate of 35 breaths/min, and an Fi_{O_2} of 0.90. These parameters were chosen after pilot data revealed an inability to lower P_{aCO_2} to 26 mmHg with lower tidal volumes and respiratory rates in dogs with pulmonary

edema. The high F_{IO_2} was chosen on the basis of pilot data to prevent systemic hypoxemia. The P_{aCO_2} was varied to three levels (26, 38, and 50 mmHg) in a randomized order, by altering the amount of CO_2 in the inspired gas mixture.

Measurements

After 20 min of stable P_{aCO_2} in each phase, hemodynamic, blood gas, and inert gas measurements were made. These included systemic arterial (P_{sa}), pulmonary arterial (P_{pa}), pulmonary capillary wedge (P_{pcw}), and peak airway (P_{aw}) pressures; heart rate (HR); and cardiac output (QT) by thermodilution using 5% dextrose in water (American Laboratory Edwards Cardiac Output Computer, Santa Ana, CA). Tidal volume was measured by spirometer (Warren E. Collins, Braintree, MA), and minute ventilation was calculated. Temperature-corrected arterial and mixed venous blood gases (P_{O_2} , P_{CO_2} , and pH; Instrumentation Laboratory 813, Lexington, MA) and hemoglobin concentration (Hb) and oxyhemoglobin saturation (S_{O_2} , Instrumentation Laboratory 282 co-oximeter) were measured. Although the rationale for and physiologic significance of the temperature correction is controversial,¹⁸ the corrections were small because of the maintenance of constant temperature close to 37° C ($36.9 \pm 0.1^\circ$ C). Inert gases in arterial and mixed venous blood and in mixed expired gas were measured. Following completion of the experiment, the dogs were killed by an overdose of sodium thiopental and KCl. The right and left lower lobes were removed for gravimetric analysis.¹⁹

Data Analysis

Gas exchange was assessed by changes in the perfusion and ventilation distributions predicted by the 50-compartment model of Evans and Wagner^{4,5} and by the arterial-alveolar difference ($[a-A]D$) area derived from retention and excretion data of the tracer inert gases.^{6,20} Inert gas shunt (\dot{Q}_S/\dot{Q}_T), dead space (V_D/V_T), mean \dot{V}_A/\dot{Q} ratio of the perfusion (mean \dot{V}_A/\dot{Q} of \dot{Q}) and ventilation distributions (mean \dot{V}_A/\dot{Q} of \dot{V}), log standard deviations of the perfusion ($\log SD_{\dot{Q}}$) and ventilation ($\log SD_{\dot{V}}$) distributions, percentage of perfusion to low \dot{V}_A/\dot{Q} units (\dot{V}_A/\dot{Q} ratio of 0.001–0.1), and percentage of perfusion and ventilation to high \dot{V}_A/\dot{Q} units (\dot{V}_A/\dot{Q} ratio of 10–100) were calculated from the 50-compartment model.

The retention and excretion data of each of the six inert gases were also analyzed to derive the tracer inert gas $[a-A]D$ area.²⁰ The $[a-A]D$ area can be subdivided into

a retention (R) component (difference between the measured retention curve plotted against inert gas solubility and the predicted retention curve for an ideal homogeneous lung with the same shunt and dead space) and an excretion (E) component (difference between the measured excretion curve plotted against inert gas solubility and the predicted excretion curve for an homogeneous lung plotted against inert gas solubility). The $R[a-A]D$ area increases more in the presence of low \dot{V}_A/\dot{Q} regions (as in pulmonary edema), and the $E[a-A]D$ area increases more in the presence of high \dot{V}_A/\dot{Q} regions (as with pulmonary embolism).²⁰ The $[a-A]D$ area is derived by adding the retention and excretion components. This measure of \dot{V}_A/\dot{Q} heterogeneity is useful in that it provides an assessment of the inert gas data that is independent of the 50-compartment model. Increases in $\log SD_{\dot{Q}}$, $\log SD_{\dot{V}}$, and $[a-A]D$ area are all indicative of increases in \dot{V}_A/\dot{Q} mismatch or heterogeneity. While the $\log SD_{\dot{Q}}$ is most sensitive to changes in the perfusion distribution and $\log SD_{\dot{V}}$ is most sensitive to changes in the ventilation distribution, the $[a-A]D$ area reflects changes in both distributions. The alveolar-arterial oxygen tension difference ($P[a-a]_{O_2}$) was also calculated, correcting for inspired CO_2 .^{1,21}

Statistical Analysis

The cardiopulmonary and gas exchange data were analyzed by a within-factor analysis of variance and further differences were compared by the Duncan *post hoc* test. Because of a lack of normal distribution, the $\log SD_{\dot{Q}}$ and $\log SD_{\dot{V}}$ data were analyzed by the Friedman test, with *post hoc* comparison by Wilcoxon's signed rank test with *P* adjusted for multiple comparisons. Multiple regression analysis of the relationship of P_{aCO_2} to P_{aO_2} and $P[a-a]_{O_2}$ was performed. Multiple regression analysis of the relationship of blood flow to shunt and low \dot{V}_A/\dot{Q} units, cardiac output, mixed venous S_{O_2} , and P_{pa} to P_{aO_2} also was performed. *P* < .05 was deemed significant. Results are presented as mean \pm SE.

Results

The experimental preparation was stable, as \dot{Q}_T , P_{pcw} , HR, P_{aw} , and Hb did not change throughout the protocol (table 1). P_{sa} and P_{pa} during hypocapnia and normocapnia were not different. Hypercapnia resulted in a small reduction in P_{sa} and a small increase in P_{pa} compared to hypocapnia. $P\bar{V}_{O_2}$ was decreased with hy-

Table 1. Cardiopulmonary Data

	Hypocapnia	Normocapnia	Hypercapnia
Psa (mmHg)	141 ± 8	140 ± 10	128 ± 9*†
Ppa (mmHg)	24.1 ± 0.9	25.1 ± 0.9	27.4 ± 1.5†
Ppcw (mmHg)	10.2 ± 1.0	9.6 ± 0.7	10.2 ± 1.2
HR (beats/min)	139 ± 16	142 ± 12	132 ± 8
Q _T (L/min)	3.8 ± 0.3	4.1 ± 0.4	4.2 ± 0.4
Paw (cmH ₂ O)	23 ± 2	22 ± 2	22 ± 2
PiCO ₂ (mmHg)	0 ± 0*	16 ± 1	33 ± 1*†
PaCO ₂ (mmHg)	26 ± 1*	38 ± 1	50 ± 1*†
pH (units)	7.53 ± 0.02*	7.39 ± 0.01	7.29 ± 0.01*†
PvO ₂ (mmHg)	40 ± 2*	50 ± 3	58 ± 4*†
Hb (g/dl)	10.8 ± 0.5	11.1 ± 0.5	10.6 ± 0.4

Values are mean ± SE. Psa = mean systemic arterial pressure; Ppa = mean pulmonary arterial pressure; Ppcw = pulmonary capillary wedge pressure; HR = heart rate; Q_T = cardiac output; Paw = peak airway pressure; PiCO₂ = inspired CO₂ tension, corrected for inspired CO₂; PaCO₂ = arterial CO₂ tension; PvO₂ = mixed venous O₂ tension; Hb = arterial hemoglobin.

* $P < .05$ versus normocapnia.

† $P < .05$ hypercapnia versus hypocapnia.

pocapnia and \bar{PvO}_2 was increased with hypercapnia (table 1). However, mixed venous oxyhemoglobin saturation (\bar{SvO}_2) was unchanged with hypercapnia, and it was reduced only slightly with hypocapnia ($72 \pm 4\%$ vs. $75 \pm 4\%$ with normocapnia). The differences in \bar{PvO}_2 were within the range expected by the Bohr effect ($\bar{PvO}_2 = 41$ mmHg calculated for hypocapnia and $\bar{PvO}_2 = 57$ mmHg calculated for hypercapnia).²²

Both Pa_{O_2} and $P[A-a]_{O_2}$ had a significant relationship ($P < .001$) with Pa_{CO_2} (fig. 1). Compared to normocapnia, Pa_{O_2} was reduced and $P[A-a]_{O_2}$ was increased during hypocapnia compared to normocapnia. In contrast, hypercapnia did not significantly affect Pa_{O_2} and $P[A-a]_{O_2}$.

The effect of Pa_{CO_2} on gas exchange measured by the multiple inert gas elimination technique is illustrated in a representative dog in figures 2 and 3. During hypocapnia, the perfusion and ventilation distributions were broader than during normocapnia (fig. 2), reflected by a significant (18%) increase in $\log SD_{\dot{Q}}$ and an insignificant (15%) increase in $\log SD_{\dot{V}}$ (table 2). The [a-A]D area measurement of \dot{V}_A/\dot{Q} heterogeneity was increased by 26% with hypocapnia (table 2). Further analysis demonstrated that hypocapnia increased both the retention and the excretion components of the [a-A]D area (figs. 2 and 4). In contrast, inert gas shunt and dead space were unaffected by hypocapnia (table 2).

During hypercapnia, the ventilation and perfusion distributions also became broader, accompanied by a

small, insignificant decrease in both inert gas shunt and dead space (fig. 2). $\log SD_{\dot{V}}$ was significantly increased by 16% with hypercapnia. The [a-A]D area was increased by 26%, with similar increases occurring in both the retention and the elimination components (figs. 3 and 4).

Multiple regression analysis revealed a significant ($P < .05$) relationship between the blood flow to shunt and low \dot{V}_A/\dot{Q} units and Pa_{O_2} . There was no additional effect of \dot{Q}_T , \bar{SvO}_2 , or Ppa on Pa_{O_2} . Further examination of the data revealed one dog with severe pulmonary edema, in which we were unable to lower Pa_{CO_2} below 30 mmHg. If this dog was excluded from the analysis (because it did not meet our desired experimental parameters), a statistically significant increase in blood flow to shunt and low \dot{V}_A/\dot{Q} units was observed with

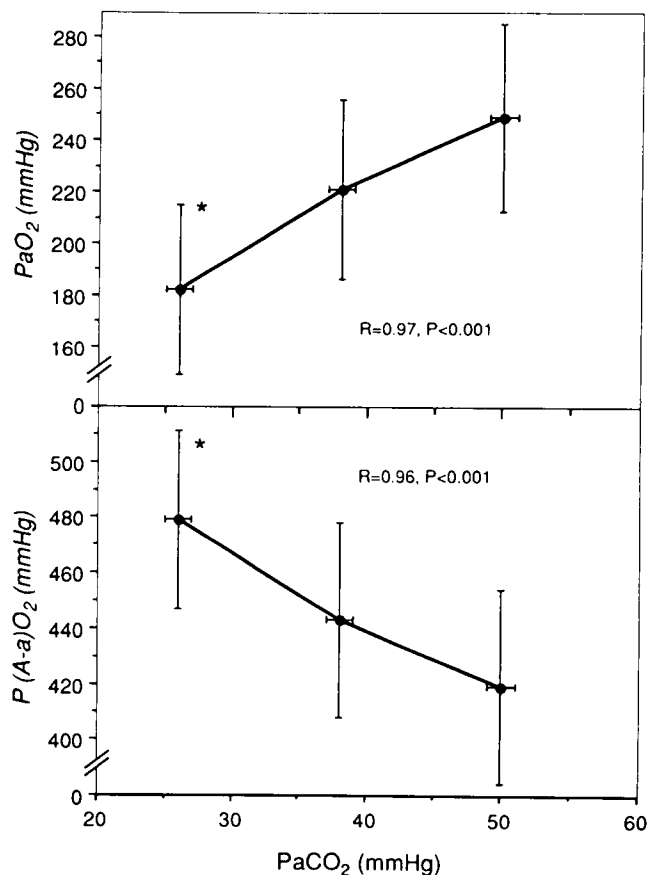


Fig. 1. Effect of inspired CO₂ on arterial blood oxygen tension (Pa_{O_2} , top) and the alveolar-arterial oxygen tension difference ($P[A-a]_{O_2}$, bottom). Pa_{CO_2} had a significant linear relationship with Pa_{O_2} and $P[A-a]_{O_2}$. Pa_{O_2} was reduced and $P[A-a]_{O_2}$ was increased with hypocapnia. Hypercapnia did not significantly affect Pa_{O_2} or $P[A-a]_{O_2}$. * $P < .05$ compared to normocapnia.

P_{aCO_2} , PULMONARY EDEMA, AND \dot{V}_A/\dot{Q} MISMATCH

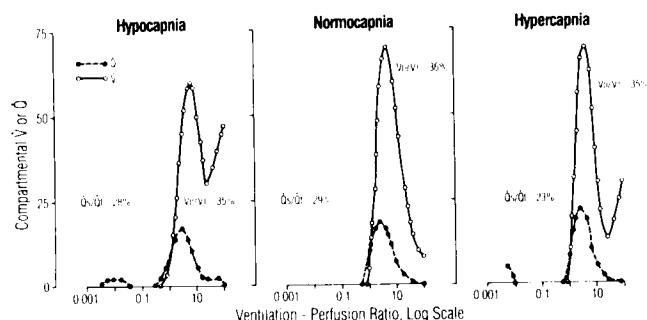


Fig. 2. Effect of inspired CO_2 on ventilation to perfusion (\dot{V}_A/\dot{Q}) distributions relative to \dot{V}_A/\dot{Q} ratio in oleic acid-induced pulmonary edema in a single representative dog. *Left:* hypocapnia; *middle:* normocapnia; *right:* hypercapnia. True shunt was increased in all conditions and was not affected by inspired CO_2 . The ventilation (open circles) and perfusion (closed circles) distributions in pulmonary edema were broad during normocapnia. Both distributions became even broader during hypocapnia and hypercapnia. \dot{Q}_s/\dot{Q}_T = inert gas shunt; V_d/V_T = inert gas dead space. Inert gas values not shown on figure: hypocapnia: $\log SD_{\dot{Q}} = 1.37$, $\log SD_{\dot{V}} = 0.95$, \dot{Q} of low $\dot{V}_A/\dot{Q} = 9\%$, \dot{Q} of high $\dot{V}_A/\dot{Q} = 10\%$, \dot{V} of high $\dot{V}_A/\dot{Q} = 30\%$; normocapnia: $\log SD_{\dot{Q}} = 0.56$, $\log SD_{\dot{V}} = 0.76$, \dot{Q} of low $\dot{V}_A/\dot{Q} = 0\%$, \dot{Q} of high $\dot{V}_A/\dot{Q} = 3\%$, \dot{V} of high $\dot{V}_A/\dot{Q} = 12\%$; and hypercapnia: $\log SD_{\dot{Q}} = 1.72$, $\log SD_{\dot{V}} = 1.14$, \dot{Q} of low $\dot{V}_A/\dot{Q} = 7\%$, \dot{Q} of high $\dot{V}_A/\dot{Q} = 4\%$, \dot{V} of high $\dot{V}_A/\dot{Q} = 20\%$.

hypocapnia by analysis of variance. Additionally, when excluding this animal, the multiple regression analysis revealed a significant relationship ($P < .05$) of perfusion of shunt and low \dot{V}_A/\dot{Q} units, \dot{Q}_T , P_{pa} , and $S\bar{V}O_2$ with P_{aCO_2} .

The presence of marked pulmonary edema was evident on *post mortem* lung gravimetric analysis. The wet-weight to dry-weight ratio of the lungs was 12.3 ± 0.5 , compared to laboratory control value of 4.8 ± 0.1 .

Discussion

Effect of P_{aCO_2} on Gas Exchange

Normocapnia. During normocapnia, gas exchange in oleic acid-induced pulmonary edema was characterized by a marked increase in inert gas shunt ($22 \pm 3\%$) and broadening of the perfusion distribution. These abnormalities in gas exchange were consistent with those previously reported with oleic acid injury, in which increased pulmonary shunt and perfusion of low \dot{V}_A/\dot{Q} areas were observed.^{14,16} The mean \dot{V}_A/\dot{Q} s of both the perfusion and the ventilation distributions (table 2) were higher than would be expected under normal minute ventilations. The increases probably are related to ventilation with higher tidal volume

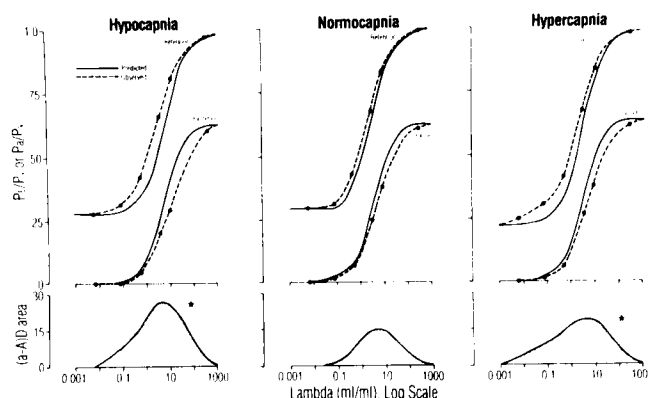


Fig. 3. Effect of inspired CO_2 in oleic acid-induced pulmonary edema on retention-excretion curves (*top*) and tracer inert gas arterial-alveolar difference ($[a-A]D$) area (*bottom*) plotted against inert gas solubility in same dog as in figure 1. *Left:* hypocapnia; *middle:* normocapnia; *right:* hypercapnia. Solid lines at the top of the figure represent values predicted for a homogeneous lung with identical shunt and dead space. Dashed lines represent observed values. The best fit retention and excretion curves are derived from six different tracer inert gases over a wide range of solubility. During both hypocapnia and hypercapnia, the difference areas between the measured retention curve and homogeneous retention curve ($R[a-A]D$ area) and between the measured excretion curve and the homogeneous excretion curve ($E[a-A]D$ area) were increased compared to normocapnia. Added together, these form the $[a-A]D$ area shown in the lower portion of the figure. The $[a-A]D$ areas were significantly increased during hypocapnia and hypercapnia. $*P < .05$ compared to normocapnia. Inert gas values not shown on figure: hypocapnia: $R[a-A]D$ area = 0.26, $E[a-A]D$ area = 0.21; normocapnia: $R[a-A]D$ area = 0.08, $E[a-A]D$ area = 0.10; and hypercapnia: $R[a-A]D$ area = 0.30, $E[a-A]D$ area = 0.24).

Table 2. Gas Exchange Data

	Hypocapnia	Normocapnia	Hypercapnia
Mean \dot{V}_A/\dot{Q} of \dot{Q}	2.2 ± 0.3	2.4 ± 0.3	2.1 ± 0.3
Mean \dot{V}_A/\dot{Q} of \dot{V}	$9.7 \pm 1.0^*$	7.9 ± 1.0	8.9 ± 1.1
\dot{Q} of high \dot{V}_A/\dot{Q} (%)	8 ± 2	7 ± 2	7 ± 2
\dot{V} of high \dot{V}_A/\dot{Q} (%)	29 ± 4	24 ± 5	28 ± 4
\dot{Q} of low \dot{V}_A/\dot{Q} (%)	6 ± 1	4 ± 2	6 ± 2
Inert gas shunt (%)	23 ± 3	22 ± 3	21 ± 3
V_d/V_T (%)	37 ± 4	38 ± 4	35 ± 4
$\log SD_{\dot{Q}}$	$1.60 \pm 0.15^*$	1.35 ± 0.19	1.61 ± 0.16
$\log SD_{\dot{V}}$	1.12 ± 0.12	0.97 ± 0.12	$1.13 \pm 0.10^*$
(a-A)D area	$0.63 \pm 0.09^*$	0.50 ± 0.09	$0.63 \pm 0.11^*$

Values are mean \pm SE. Mean \dot{V}_A/\dot{Q} of \dot{Q} = mean ventilation-perfusion (\dot{V}_A/\dot{Q}) ratio of the perfusion distribution; mean \dot{V}_A/\dot{Q} of \dot{V} = mean \dot{V}_A/\dot{Q} ratio of the ventilation distribution; \dot{Q} of high \dot{V}_A/\dot{Q} = perfusion of high \dot{V}_A/\dot{Q} units (\dot{V}_A ratio of 10–100); \dot{V} of high \dot{V}_A/\dot{Q} = ventilation of high \dot{V}_A/\dot{Q} units; \dot{Q} of low \dot{V}_A/\dot{Q} = perfusion of low \dot{V}_A/\dot{Q} units (\dot{V}_A/\dot{Q} ratio of 0.001–0.1); V_d/V_T = inert gas dead space; $\log SD_{\dot{Q}}$ = log standard deviation of the perfusion distribution; $\log SD_{\dot{V}}$ = log standard deviation of the ventilation distribution; (a-A)D area = tracer inert gas arterial-alveolar difference area.

* $P < .05$ versus normocapnia.

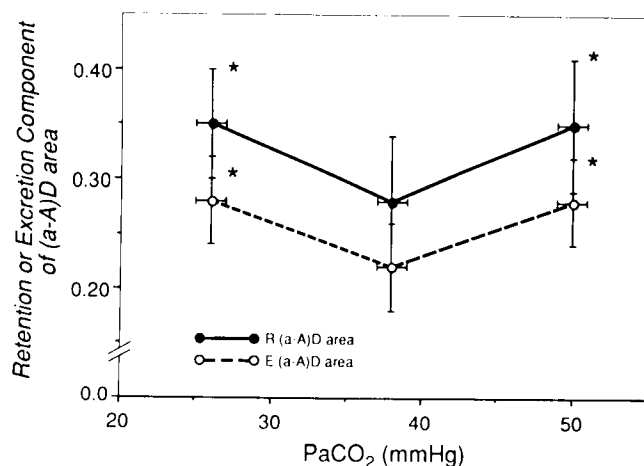


Fig. 4. Effect of inspired CO₂ on the retention (R) and excretion (E) components of the [a-A]D area measure of \dot{V}_A/\dot{Q} heterogeneity. Hypocapnia and hypercapnia increased both the R[a-A]D area and the E[a-A]D areas. * $P < .05$ compared to normocapnia.

and higher respiratory rates than under normal circumstances, with inspiration of CO₂ to achieve normocapnia.

Hypercapnia. P[A-a]_{O₂} and Pa_{O₂} were not significantly affected by hypercapnia. This finding is in contrast to animal studies in dogs with normal lungs²⁴ and sheep with gram-negative pneumonia²¹ that showed a decrease in P[A-a]_{O₂} and an improvement in arterial blood oxygenation with hypercapnia. The different result in the present study may be due to differences in the type of lung injury, the use of a high Fi_{O₂}, rapid respiratory rate, larger than normal tidal volume, amount of inspired CO₂, and the lack of concurrent increases in \dot{Q}_T in the present study.

The multiple inert gas elimination technique data revealed that \dot{V}_A/\dot{Q} heterogeneity was increased during hypercapnia, indicated by significant increases in the log SD \dot{V} and [a-A]D area indexes (fig. 3, table 2). As the retention and excretion components of the [a-A]D area increased equally (25% and 27%, respectively; fig. 4), the increase in \dot{V}_A/\dot{Q} heterogeneity occurred in both low and high \dot{V}_A/\dot{Q} regions within the range of finite \dot{V}_A/\dot{Q} ratios. The increase in \dot{V}_A/\dot{Q} mismatch did not adversely affect arterial blood oxygenation because a small, insignificant decrease in inert gas shunt accompanied the increase in low \dot{V}_A/\dot{Q} . Shunt has a greater impact on Pa_{O₂} than \dot{V}_A/\dot{Q} heterogeneity at high Fi_{O₂}. The net result was that the blood flow to shunt and low \dot{V}_A/\dot{Q} areas was not different from that observed during normocapnia. Increases in \dot{V}_A/\dot{Q} heterogeneity due to

high \dot{V}_A/\dot{Q} units also were accompanied by a small, insignificant decrease in \dot{V}_D/\dot{V}_T . These findings differed from those observed in dogs with normal lungs.¹³ In the latter study, hypercapnia did not affect \dot{V}_A/\dot{Q} heterogeneity and the trends in decreasing inert gas shunt and dead space were not observed. The differences in results may reflect difficulties with the inert gas technique to distinguish between low \dot{V}_A/\dot{Q} areas and shunt and between high \dot{V}_A/\dot{Q} areas and dead space with hypercapnia in the oleic acid injury model. A reduction in collateral or bronchiolar resistance with hypercapnia¹¹ also may contribute to the conversion of some shunt areas to low \dot{V}_A/\dot{Q} . The increase in Ppa with hypercapnia in oleic acid injury may aid in converting some dead space to high \dot{V}_A/\dot{Q} . Changes in HPV are unlikely to be important, because a respiratory acidosis does not affect HPV.¹⁰ As we did not measure collateral or bronchial resistance and pulmonary vascular zone states, the etiology remains speculative. However, the results of the current study have the same physiologic consequences as in normal lungs, namely that hypercapnia does not have any major influence on Pa_{O₂} or \dot{V}_A/\dot{Q} matching when evaluated across the range of \dot{V}_A/\dot{Q} .

Hypocapnia. Compared to normocapnia, Pa_{O₂} was reduced by 18% and the P[A-a]_{O₂} was increased by 8% during hypocapnia (fig. 1). As the minute ventilation and hemodynamics did not change and the reduction in P \bar{V} O₂ with hypocapnia can be entirely accounted for by the Bohr effect,²² the decrease in Pa_{O₂} with hypocapnia cannot be attributed to changes in these variables.

Our finding of increased P[A-a]_{O₂} with low Pa_{CO₂} in canine oleic acid-induced pulmonary edema is consistent with prior work. Hypocapnia increased the P[A-a]_{O₂}^{2,3,11} in anesthetized patients. While the increased P[A-a]_{O₂} in patients may be due to reductions in cardiac output with hypocapnia, pulmonary shunt (which takes S \bar{V} O₂ into account) also increased if cardiac output was unchanged.² Increases in venous admixture with hypocapnia were greater in anesthetized obese patients, who may have increased atelectasis during general anesthesia.¹¹

The multiple inert gas data indicate that the decrease in Pa_{O₂} was due to an increase in \dot{V}_A/\dot{Q} mismatch with hypocapnia. The log SD \dot{Q} and [a-A]D area indexes of \dot{V}_A/\dot{Q} heterogeneity were increased by 18% and 26%, respectively (fig. 3, table 2). The changes in \dot{V}_A/\dot{Q} heterogeneity with hypocapnia in this animal model are consistent with those observed in dogs with normal

lungs.¹³ In normal dogs, hypocapnia increased the dispersion parameters such as the [a-A]D area with hyperventilation using similar tidal volumes and respiratory rates as in this study.

The changes in \dot{V}_A/\dot{Q} matching occurred within the range of finite \dot{V}_A/\dot{Q} ratios, as inert gas shunt and dead space were not significantly different from those during normocapnia. As the retention and excretion components of the [a-A]D area increased equally (25% and 27%, respectively; fig. 4), the increase in \dot{V}_A/\dot{Q} heterogeneity with hypocapnia occurred in both the low and the high \dot{V}_A/\dot{Q} ranges.

Increases in blood flow to low \dot{V}_A/\dot{Q} and shunt units contribute most to arterial hypoxemia. With hypocapnia, there was a small but insignificant increase in blood flow to shunt and low \dot{V}_A/\dot{Q} (29% compared to 26% with normocapnia). Multiple regression analysis revealed a significant influence of blood flow to shunt and low \dot{V}_A/\dot{Q} units on Pa_{O_2} , with no further influence of cardiac output, $\text{S}\bar{\text{v}}_{\text{O}_2}$, or Ppa. Therefore, the modest decrease in Pa_{O_2} observed with hypocapnia may be due to increased perfusion of shunt and low \dot{V}_A/\dot{Q} units. A statistically significant decrease in Pa_{O_2} in the presence of a statistically insignificant increase in shunt and low \dot{V}_A/\dot{Q} may have occurred in our study because, during oxygen-ventilation, small changes in arterial blood content may cause larger changes in Pa_{O_2} .

If the dog with severe pulmonary edema, in which we were unable to lower Pa_{CO_2} below 30 mmHg, is excluded from the analysis, a statistically significant increase in blood flow to shunt and low \dot{V}_A/\dot{Q} units was observed with hypocapnia. Multiple regression analysis excluding this animal revealed that changes in Pa_{O_2} in less severe pulmonary edema may have been due to the interaction of modest changes in shunt and perfusion of low \dot{V}_A/\dot{Q} units with cardiac output, $\text{S}\bar{\text{v}}_{\text{O}_2}$, and Ppa. We believe that it is appropriate to exclude this dog from the supplemental analysis, in that it did not meet our experimental parameters. However, we did not exclude it from the analysis of the study proper, as the statistical assumptions were based on randomization with intention to have Pa_{CO_2} of 26 mmHg. The net effect of including this dog is to attenuate the differences among the groups.

The increase in \dot{V}_A/\dot{Q} heterogeneity in both the low and the high \dot{V}_A/\dot{Q} regions may reflect changes in HPV or bronchoconstriction due to hypocapnia. The HPV response in dogs with global alveolar hypoxia¹⁰ and regional hypoxia⁸ and in isolated dog lobes⁷ and rat lungs⁹ is attenuated by respiratory alkalosis. As HPV is

important in diverting blood flow away from damaged, nonaerated alveoli, the increase in \dot{V}_A/\dot{Q} heterogeneity in low \dot{V}_A/\dot{Q} areas with hypocapnia may be reflective of a modest reduction in HPV. Hypocapnia also causes bronchoconstriction of airways of all sites and reduces collateral ventilation.^{11,12} Severinghaus *et al.*²⁵ found that occlusion of a single pulmonary artery in dogs reduced alveolar CO_2 of the lung and caused bronchoconstriction and a shift of ventilation toward the contralateral lung. This was reversed with 5% CO_2 . The increase in \dot{V}_A/\dot{Q} heterogeneity in high \dot{V}_A/\dot{Q} regions may reflect the influence of hypocapnic bronchoconstriction. The slight but insignificant increase in peak Paw is suggestive of the presence of hypocapnic bronchoconstriction in this model. However, as we did not measure HPV, collateral, or bronchial resistance, the mechanism(s) behind the increase in \dot{V}_A/\dot{Q} heterogeneity with hypocapnia remains speculative.

Relationship of Our Experimental Model to the Clinical Setting

There are a number of important differences between our experimental model and the clinical setting. We employed a canine model of noncardiogenic pulmonary edema, induced by the intravenous administration of oleic acid. Oleic acid is a noxious fatty substance that increases pulmonary vascular permeability, resulting in a hemorrhagic form of pulmonary edema.¹⁴ The oleic acid injury is patchy, in which areas of normal lung are separated by areas of alveolar collapse, microvascular obstruction, hemorrhage, cell necrosis, and inflammatory exudate.¹⁴

Although oleic acid injury induces a form of permeability pulmonary edema and it has been used as animal model of human ARDS, it is pathophysiologically different from ARDS.²⁶ In humans, ARDS results from a systemic intravascular inflammatory process involving the activation of a variety of mediators which leads to lung and multisystem organ injury. Although the I:E ratio was 1:1 and the respiratory rate was rapid, there was no evidence of auto-positive end-expiratory pressure or increased lung volume in our model. Thus, the oleic acid injury also does not resemble human asthma or chronic obstructive pulmonary disease.

Secondly, the animals were anesthetized with sodium pentobarbital. Compared to the awake state, barbiturates may have a small but significant inhibitory effect on HPV.²⁷ With a reduction in preexisting vascular tone, further inhibition of HPV by hypocapnia may have

a smaller influence on \dot{V}_A/\dot{Q} mismatch than in the unanesthetized subject.

Another difference between the current study and the clinical setting is the $F_{I_{O_2}}$ chosen. In clinical respiratory failure, $F_{I_{O_2}}$ is chosen to maintain $P_{a_{O_2}}$ in the desired range, e.g., 60–100 mmHg. In the present study, $F_{I_{O_2}}$ was 0.90 and $P_{a_{O_2}}$ averaged approximately 200 mmHg. The high $F_{I_{O_2}}$ was chosen to prevent systemic hypoxemia, which was a problem in several pilot dogs and in one experimental animal that had severe pulmonary edema. Rather than drop the animal from the study or change our experimental conditions in midstream, we used the same $F_{I_{O_2}}$ for all of the animals, even though $P_{a_{O_2}}$ was substantially higher than would be desired in the clinical setting. However, our use of a $F_{I_{O_2}}$ of 0.90 may have attenuated the adverse effect of hypocapnia. High $F_{I_{O_2}}$ may cause absorption atelectasis (with larger inert gas shunt and smaller low \dot{V}_A/\dot{Q} areas) or it may release HPV. In fact, $F_{I_{O_2}}$ had a significant effect on the influence of a known inhibitor of HPV, sodium nitroprusside, on gas exchange in canine oleic acid injury.²⁸ Sodium nitroprusside did not affect gas exchange, measured by the multiple inert gas elimination technique, when $F_{I_{O_2}}$ was 1.0. In contrast, inert gas shunt, log SD \dot{Q} , and [a-A]D area were severely impaired by sodium nitroprusside when the $F_{I_{O_2}}$ was lower (room air). These findings suggest that inhalation of O_2 increased P_{O_2} in poorly ventilated alveoli to above the threshold for HPV so that an inhibitor of HPV would have a smaller adverse effect. On the basis of the data with sodium nitroprusside,²⁸ we believe that the high $F_{I_{O_2}}$ used in the current study may have attenuated the adverse effect of hypocapnia on gas exchange. Therefore, greater increases in \dot{V}_A/\dot{Q} heterogeneity and shunt may be observed if a lower $F_{I_{O_2}}$ is used.

Another difference with the clinical setting is the manner in which $P_{a_{CO_2}}$ was modified. In clinical care, $P_{a_{CO_2}}$ is altered by varying minute ventilation. In the present study, $P_{a_{CO_2}}$ was altered by varying inspired CO_2 . We chose to hold minute ventilation constant and vary inspired CO_2 because of concern that changes in cardiac output^{29,40} and minute ventilation²¹ may effect gas exchange, independent in any manipulation of $P_{a_{CO_2}}$. Increasing respiratory rate and tidal volume to achieve hypocapnia may depress \dot{Q}_T and thereby alter gas exchange by changing $\bar{S}\bar{V}_{O_2}$, Ppa, and pulmonary vascular zone states. Increases in minute ventilation may affect gas exchange by altering the amount of dead space, lung volume, respiratory time constants, and collateral resistance. Due to the variation in the effect

of hypocapnia with differences in tidal volume in normal lungs,¹³ it is likely that the net result of hypocapnia and hypercapnia in a given situation depends upon the respiratory rate and tidal volume. The tidal volume used in the present study (20 ml/kg) was considerably greater than would be used clinically in humans. As even larger tidal volumes (30 ml/kg) abolish the adverse effect of hypocapnia on gas exchange in normal dogs,¹³ it is likely that differences in tidal volumes may influence the effect of hypocapnia on gas exchange in humans. In patients, hypocapnia also may further reduce $P_{a_{O_2}}$ if \dot{Q}_T is reduced as the minute ventilation is increased. Additionally, hypercapnia may actually improve $P_{a_{O_2}}$ at lower tidal volumes and airway pressures, when changes in collateral resistance may be more significant. Carbon dioxide-induced changes in gas exchange will need to be studied in humans using clinically relevant methods of altering P_{CO_2} before any firm recommendations for clinical care can be made.

Finally, the present study varied $P_{a_{CO_2}}$ and thereby altered pH. In clinical practice, $P_{a_{CO_2}}$ and pH may be varied independently, as in the use of hyperventilation to treat a metabolic acidosis, or hypoventilation plus bicarbonate administration for severe ARDS. At least in normal dogs, the overall pH appears to be more important than the direct CO_2 effect in affecting gas exchange.³¹

In conclusion, hypocapnia increased \dot{V}_A/\dot{Q} mismatch and was associated with a modest decrease in $P_{a_{O_2}}$ in canine oleic acid pulmonary edema. These results suggest that hyperventilation to reduce $P_{a_{CO_2}}$ may worsen arterial hypoxemia in some patients with lung disease.

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