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# *Hyperventilation in the Treatment of Metabolic Acidosis Does Not Adversely Affect Pulmonary Gas Exchange*

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***Background:*** **Hyperventilation has been recommended to increase blood *p*H during metabolic acidosis. However, hypocapnia may adversely affect arterial blood oxygenation, especially in the presence of lung disease. We therefore studied the effects of metabolic acidosis, with and without normalization of *p*H by hyperventilation, on pulmonary gas exchange in dogs with permeability pulmonary edema.**

***Methods:*** **Six pentobarbital-anesthetized dogs were administered 0.06 ml/kg of oleic acid at least 150 min before study. Ventilation was set with an inspired $O_2$ fraction of 0.90 and a tidal volume of 18 ml/kg, and the respiratory rate was adjusted to alter the arterial $CO_2$ tension ($Pa_{CO_2}$) per the experimental protocol. The protocol in random order was (1) normal *p*H (7.36 ± 0.01)/normal $Pa_{CO_2}$ (39 ± 1 mmHg); (2) low *p*H (7.20 ± 0.01)/normal $Pa_{CO_2}$ (40 ± 1 mmHg); (3) low *p*H (7.18 ± 0.01)/hyperventilation with inspired $CO_2$ ($Pa_{CO_2}$ = 40 ± 1 mmHg); and (4) normal *p*H (7.35 ± 0.01)/hyperventilation with low $Pa_{CO_2}$ (24 ± 1 mmHg). In phases 2–4, the *p*H was slowly reduced by intravenous infusion of 2 N hydrochloric acid. The *p*H was normalized in phase 1 where necessary by infusion of sodium bicarbonate. The *p*H in phase 4 was normalized by reducing the $Pa_{CO_2}$ by increasing the respiratory rate. Gas exchange was assessed by the multiple inert-gas elimination technique.**

***Results:*** **The hemodynamic measurements remained constant throughout the protocol. Arterial $O_2$ tension increased from 244 ± 55 to 293 ± 49 mmHg in the presence of metabolic acidosis ($P < 0.05$). Hyperventilation to normalize the *p*H during metabolic acidosis (phase 4), increased arterial $O_2$ tension (313 ± 44 mmHg, $P < 0.05$), and reduced shunt (from 20 ± 5% to 12 ± 3%, $P < 0.05$) compared with normal acid–base conditions (phase 1). No change in shunt was observed with hyperventilation compared with metabolic acidosis alone (phase 2). The decrease in pulmonary shunt was not attributable to the direct effects of hyperventilation, because shunt was increased (20 ± 5%) when $Pa_{CO_2}$ was normalized during hyperventilation by inspiration of $CO_2$ (phase 3).**

***Conclusions:*** **Hyperventilation to normalize blood *p*H during hydrochloric acid–induced metabolic acidosis did not adversely affect pulmonary gas exchange in dogs with permeability pulmonary edema. (Key words: Acidosis: metabolic. Lung(s): gas exchange; hyperventilation; hypocapnia; oleic acid injury; pulmonary edema. Measurement techniques: multiple inert-gas elimination.)**

THE metabolic acidosis that develops during cardiopulmonary resuscitation, severe hypoxemia, and shock may further impair myocardial functioning[1] and diminish the hemodynamic responses to catecholamines.[2] In addition to treating the primary disorder, sodium bicarbonate has traditionally been administered to normalize the arterial blood *p*H, in an attempt to attenuate the adverse hemodynamic effects of an acidosis. Recently, however, use of bicarbonate to treat lactic acidosis has become controversial.[3–8] Sodium bicarbonate may be ineffective in normalizing *p*H,[3,6] it may promote formation of additional lactic acid,[3,6] it increases $CO_2$ formation,[3,6,7] and it may adversely affect coronary perfusion pressure.[7]

Alternatively, hyperventilation to reduce the arterial $CO_2$ tension ($Pa_{CO_2}$), has been advocated as a more effective and safer method to normalize arterial blood *p*H during metabolic acidosis.[4,8] However, hyperventilation has several potential side effects such as decreasing venous return and cardiac output,[9] it may adversely affect arterial blood oxygenation,[10,11] and it may increase the likelihood of lung barotrauma.[12,13] We recently found that hypocapnia decreased arterial $O_2$ tension ($Pa_{O_2}$) by increasing ventilation–perfusion ($\dot{V}_A/\dot{Q}$) mismatch in dogs with oleic acid–induced pulmonary edema.[11] The adverse effects of hypocapnia on pulmonary gas exchange may thereby exacerbate hypoxemia in patients with shock who have concurrent

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aspiration pneumonia, atelectasis, pulmonary contusion, or pulmonary edema. We therefore studied the effects of metabolic acidosis, with and without normalization of *p*H by hyperventilation on pulmonary gas exchange using a similar canine model of oleic acid–induced pulmonary edema.[11] Oleic acid–induced lung injury has been used as an animal model of adult respiratory distress syndrome because it increases pulmonary vascular permeability and results in hemorrhagic pulmonary edema.[14] The multiple inert-gas elimination technique was used to assess pulmonary gas exchange, as it can provide information about the pattern of $\dot{V}_A/\dot{Q}$ relationships in the lung, as well as specifically determine intrapulmonary shunt and dead space.[15,16] It therefore provides greater information regarding gas exchange than the classical methods of inefficiency of $O_2$ exchange (*e.g.*, intrapulmonary shunt or venous admixture) and inefficiency of $CO_2$ exchange (*e.g.*, physiologic and anatomic dead space) independent of the respiratory gas partial pressures.

## Materials and Methods

The study was approved by the Animal Care Committee of the authors' institution.

*Instrumentation*

Six mongrel dogs of both sexes (21–25 kg) were anesthetized with pentobarbital sodium (30 mg/kg intravenously, supplemented with 30–90 mg/h). After tracheal intubation, their lungs were ventilated with an inspired $O_2$ fraction ($F_{I_{O_2}}$) of 0.50, at a tidal volume of 18 ml/kg and respiratory rate adjusted to maintain normocapnia. Diaphragmatic paralysis was assured with succinylcholine (100 mg intramuscularly, supplemented with 20–40 mg/h intravenously). Carotid and pulmonary arterial catheters were placed *via* peripheral cut-down. Oleic acid (0.06 ml/kg) was administered into the right atrium by infusion pump over 10 min. A 5-mm adjustable arteriovenous fistula was constructed between a femoral artery and vein in order to alter cardiac output as necessary to maintain a stable cardiac output. Heparin (7,500 U is followed by 500 U intravenously, hourly) was administered. The lungs were hyperinflated hourly to a peak airway pressure of 40 $cmH_2O$. One to 1.5 l 0.9% sodium chloride and 500 ml 6% hetastarch in 0.9% sodium chloride (Hespan, DuPont Pharmaceuticals, Wilmington, DE) were administered during the 10–12-h study to maintain a cardiac output of approximately 2.5 l/min.

*Inert Gas Measurements*

The multiple inert-gas elimination technique was used to assess gas exchange.[15–17] 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 (Pa) and in mixed expired gas. 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.*[18] 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,[14,19] we waited to begin experimental manipulations for at least 120 min after 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. The $F_{I_{O_2}}$ was increased to 0.90 to allow comparison with a previous study.[11] The protocol (table 1) was: 1. normal *p*H (7.36 ± 0.01)/normal $Pa_{CO_2}$ (39 ± 1 mmHg); 2. low *p*H (7.20 ± 0.01)/normal $Pa_{CO_2}$ (40 ± 1 mmHg); 3. low *p*H (7.18 ± 0.01)/hyperventilation with inspired $Pa_{CO_2}$ (40 ± 1 mmHg); and 4. normal *p*H (7.35 ± 0.01)/hyperventilation with low $Pa_{CO_2}$ (24 ± 1 mmHg). In phases 2–4, the *p*H was slowly reduced by intravenous infusion of 2 N hydrochloric acid. The *p*H was normalized in phase 1, where necessary, by infusion of sodium bicarbonate. The *p*H in phase 4 was normalized by reducing the $Pa_{CO_2}$ by increasing the respiratory rate to 35 breaths/min. Phase 1 (normal *p*H/normal $Pa_{CO_2}$) was studied first in half of the animals and last in half of the animals. Ventilation and $P_{CO_2}$ changes during the metabolic acidosis phases were performed in completely randomized order. The grouping of study phases (table 1) allowed us to compare normal to metabolic acidosis (phases 1 and 2) and metabolic acidosis to metabolic acidosis with normalization of *p*H by hyperventilation (phases 2 and 4). In order to control for

**Table 1. Experimental Protocol**

| Phase | Name | Metabolic Acidosis | Ventilation | *p*H | $Pa_{CO_2}$ |
|---|---|---|---|---|---|
| 1 | Normal *p*H/normal $P_{CO_2}$ | No | Normal $\dot{V}_E$ | Normal | Normal |
| 2 | Low *p*H/normal $P_{CO_2}$ | Yes | Normal $\dot{V}_E$ | Low | Normal |
| 3 | Low *p*H/inspired $CO_2$ | Yes | Hyperventilation (with inspired $CO_2$) | Low | Normal |
| 4 | Normal *p*H/low $P_{CO_2}$ | Yes | Hyperventilation (no inspired $CO_2$) | Normal | Low |

the mechanical and hemodynamic effects of the increased respiratory rate (used in phase 4), the $Pa_{CO_2}$ was normalized by adding $CO_2$ to the inspired gas mixture during metabolic acidosis in phase 3. All changes in blood *p*H due to metabolic components were accomplished extremely slowly (over a 2–3-h period), as more rapid changes resulted in marked instability of the animal's hemodynamics and degree of lung injury. Severe pulmonary hypertension, unrelated to blood *p*H, may occur after rapid administration of hydrochloric acid.[20] A relatively constant cardiac output was maintained with the slow changes of *p*H and by the intravenous infusion of 500 ml of Hespan and 1–1.5 l sodium chloride in the animals. In two of the animals the arteriovenous fistula was also variably opened in order to maintain a steady cardiac output and $P\bar{v}_{O_2}$ during the final phase of the study. In one animal, it was opened during phase 4 (metabolic acidosis with low $Pa_{CO_2}$) and in another animal, it was opened during phase 1 (normal *p*H/normal $P_{CO_2}$).

*Measurements*

After 20 min of stable *p*H and $Pa_{CO_2}$ in each phase, hemodynamic, blood gas, and inert gas measurements were made. These included systemic arterial, pulmonary arterial (Ppa), pulmonary artery occlusion, and peak airway pressures; heart rate; and cardiac output by thermodilution in triplicate at end-expiration 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 ($P_{O_2}$, $P_{O_2}$ and *p*H; Instrumentation Laboratory 813, Lexington, MA) and hemoglobin concentration and oxyhemoglobin saturation (Instrumentation Laboratory 282 co-oximeter) were measured. Temperature corrections were small because of maintenance of constant temperature close to 37°C (37.2 ± 0.1°C). Solubilities and concentrations of inert gases were measured in arterial and mixed venous blood and in mixed expired gases. After completion of the experiment, the dogs were killed by an overdose of sodium thiopental and potassium chloride.

*Data Analysis*

Gas exchange was assessed by changes in the perfusion and ventilation distributions predicted by the 50-compartment model of Evans and Wagner[15,16] and by the arterial–alveolar difference [(a-A)D] area derived from retention and excretion data of the tracer inert gases.[17] Inert-gas shunt ($\dot{Q}s/\dot{Q}T$); dead space; 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 $\dot{V}$); logarithmic standard deviations of the perfusion and ventilation 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. Changes in mean $\dot{V}A/\dot{Q}$ and percentage of perfusion and ventilation to high $\dot{V}A/\dot{Q}$ units primarily provided descriptive data.

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.[17] The (a-A)D area can be subdivided into a retention 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 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 retention (a-A)D area increases more in the presence of low $\dot{V}A/\dot{Q}$ regions (as in pulmonary edema), and the excretion (a-A)D area increases more in the presence of high $\dot{V}A/\dot{Q}$ regions (as with pulmonary embolism).[21] 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 pro-

vides an assessment of the inert gas data that is independent of the 50-compartment model.

*Statistical Analysis*

The most important gas exchange variables for our study were shunt and the (a-A)D area and its components, as changes in these variables are most likely to affect $Pa_{O_2}$. The data were analyzed by a within-factor analysis of variance and further differences were compared by Duncan's *post hoc* test. A multiple regression analysis of the relationship of Ppa, mixed venous oxygen saturation ($S\bar{v}_{O_2}$), and cardiac output to inert-gas shunt and $Pa_{O_2}$ was performed. $P < 0.05$ was deemed significant. Results are presented as means ± SE.

## Results

The general experimental conditions, including systemic arterial pressure, peak airway pressure, Ppa, pulmonary artery occlusion pressure, $S\bar{v}_{O_2}$, and cardiac output, remained constant throughout the study (table 2). Heart rate decreased slightly during the normal *p*H/hyperventilation with low $P_{CO_2}$ phase (phase 4). $P\bar{v}_{O_2}$ was increased ($P < 0.05$) during the low *p*H phases, however, the differences in $P\bar{v}_{O_2}$, were within the range expected by the Bohr effect.[22]

$Pa_{O_2}$ was significantly increased ($P < 0.05$) during all metabolic acidosis phases (phases 2–4) compared to normal (phase 1, table 2). $Pa_{O_2}$ was increased by 50 mmHg in the presence of metabolic acidosis (low *p*H/normal $P_{CO_2}$ [phase 2]). Hyperventilation did not further increase $Pa_{O_2}$ (table 2).

The gas exchange data derived from the multiple inert-gas elimination technique are shown in table 3. Increasing the respiratory rate during low *p*H/inspired $P_{CO_2}$ (phase 3) and normal *p*H/low $P_{CO_2}$ (phase 4), increased ($P < 0.05$) the mean $\dot{V}A/\dot{Q}$ of the ventilation and perfusion distributions, the percentages of ventilation and perfusion to high $\dot{V}A/\dot{Q}$ units, and dead space (table 3). Compared to normal acid–base conditions (phase 1), shunt was significantly decreased ($P < 0.05$) when *p*H during metabolic acidosis was normalized by hyperventilation (normal *p*H/low $P_{CO_2}$ phase [phase 4], table 3). Shunt was decreased ($P < 0.05$) during phase 4 (normal *p*H/low $P_{CO_2}$) when compared to phase 3 (low *p*H/hyperventilation with inspired $CO_2$) and it was unchanged from that during an isolated metabolic acidosis (phase 2, low *p*H/normal $P_{CO_2}$). Perfusion of low $\dot{V}A/\dot{Q}$ units and $\dot{V}A/\dot{Q}$ mismatch, indicated by the (a-A)D area were not affected by the study manipulations.

Multiple regression analysis did not reveal a significant relationship between Ppa, $S\bar{v}_{O_2}$, cardiac output and inert-gas shunt or $Pa_{O_2}$.

## Discussion

We studied the effects of metabolic acidosis, with and without normalization of *p*H by hyperventilation, on pulmonary gas exchange in dogs with permeability pulmonary edema. We found that hyperventilation to normalize blood *p*H during metabolic acidosis did not adversely affect pulmonary gas exchange. Compared to normal acid–base conditions (phase 1), $Pa_{O_2}$ was increased and intrapulmonary shunt was decreased.

*Metabolic Acidosis*

$Pa_{O_2}$ was significantly increased by 50 mmHg (from 244 to 293 mmHg) in the presence of the isolated metabolic acidosis, whereas pulmonary shunt was not changed. Perfusion of low $\dot{V}A/\dot{Q}$ units, the ventilation distribution, and $\dot{V}A/\dot{Q}$ mismatch, indicated by the tracer inert-gas (a-A)D area, were not affected by metabolic acidosis. The Bohr effect and changes in $S\bar{v}_{O_2}$ were insufficient to account for the change in $Pa_{O_2}$. An increase in $Pa_{O_2}$ may have occurred in the presence of statistically insignificant differences in shunt because small changes in arterial blood content may cause large changes in $Pa_{O_2}$ during 100% $O_2$ ventilation.

Our results are consistent with several studies in normal lungs in which metabolic acidosis did not affect gas exchange.[23,24] Other studies in animals with preexisting $\dot{V}A/\dot{Q}$ mismatch have demonstrated an improvement in $\dot{V}A/\dot{Q}$ matching with metabolic acidosis.[25,26] Haas and Bergofsky[25] found that metabolic acidosis increased $Pa_{O_2}$ (from 75 to 87 mmHg) and decreased venous admixture (from 18% to 11%) in dogs. Using a model similar to ours (dogs with oleic acid–induced pulmonary edema), Brimioulle *et al.*[26] found that reducing *p*H to 7.20 by infusion of hydrochloric acid significantly increased $Pa_{O_2}$ (from 55 to 83 mmHg) and reduced pulmonary shunt (from 44% to 33%). Our results may be different from those of Brimioulle *et al.*[26] because of differences in experimental conditions, including $FI_{O_2}$, severity of injury, length of stabilization period, and inert gas used to measure shunt. Brimioulle *et al.*[26] used a lower $FI_{O_2}$

**Table 2. Cardiopulmonary Variables**

| | Normal *p*H/ Normal $P_{CO_2}$ | Low *p*H/ Normal $P_{CO_2}$ | Low *p*H/ Inspired $P_{CO_2}$ | Normal *p*H/Low $P_{CO_2}$ |
|---|---|---|---|---|
| RR (breaths/min) | 14 ± 1 | 14 ± 1 | 35 ± 1 | 35 ± 1 |
| $V_T$ (ml) | 414 ± 11 | 414 ± 11 | 414 ± 11 | 414 ± 11 |
| Paw ($cmH_2O$) | 21 ± 2 | 19 ± 3 | 22 ± 4 | 20 ± 3 |
| Psa (mmHg) | 124 ± 6 | 112 ± 8 | 108 ± 33 | 124 ± 10 |
| HR (beats/min) | 135 ± 7 | 130 ± 4 | 125 ± 4 | 117 ± 6*‡ |
| Ppa ($cmH_2O$) | 28 ± 2 | 29 ± 2 | 31 ± 1 | 28 ± 1 |
| Ppaop ($cmH_2O$) | 11 ± 2 | 8 ± 1 | 9 ± 2 | 10 ± 2 |
| $\dot{Q}_T$ (l/min) | 2.8 ± 0.3 | 2.9 ± 0.3 | 3.3 ± 0.4 | 2.7 ± 0.4 |
| $Pa_{O_2}$ (mmHg) | 244 ± 55*† | 293 ± 49‡ | 302 ± 55‡ | 313 ± 44‡ |
| $Pa_{O_2}$ (mmHg) | 39 ± 1 | 40 ± 1 | 40 ± 1 | 24 ± 1*†‡ |
| *p*H | 7.36 ± 0.01*† | 7.20 ± 0.00‡ | 7.18 ± 0.01‡ | 7.35 ± 0.01*† |
| $P\bar{v}_{O_2}$ (mmHg) | 47 ± 3*† | 54 ± 4‡ | 59 ± 5‡ | 46 ± 5*† |
| $S\bar{v}_{O_2}$ (mmHg) | 70 ± 5 | 72 ± 5 | 72 ± 5 | 67 ± 6 |
| Hb (g/dl) | 10.6 ± 0.6 | 9.8 ± 0.9 | 9.0 ± 0.6‡ | 9.6 ± 0.6 |

Values are mean ± SE.

RR = respiratory rate; $V_T$ = tidal volume; Paw = peak airway pressure; Psa = mean systemic arterial pressure; Ppa = mean pulmonary artery pressure; Ppaop = pulmonary artery occlusion pressure; $\dot{Q}_T$ = cardiac output; $Pa_{O_2}$ = arterial $O_2$ tension; $Pa_{CO_2}$ = arterial carbon dioxide tension; *p*H = arterial blood *p*H; $P\bar{v}_{O_2}$ = mixed venous oxygen tension; $S\bar{v}_{O_2}$ = mixed venous oxygen saturation; Hb = arterial hemoglobin.

RR and VT were not tested statistically.

* $P < 0.05$ *versus* Low *p*H/Normal $P_{CO_2}$.

† $P < 0.05$ *versus* Low *p*H/Inspired $CO_2$.

‡ $P < 0.05$ *versus* Normal *p*H/Normal $P_{CO_2}$.

**Table 3. Gas Exchange**

| | Normal *p*H/ Normal $P_{CO_2}$ | Low *p*H/ Normal $P_{CO_2}$ | Low *p*H/ Inspired $P_{CO_2}$ | Normal *p*H/Low $P_{CO_2}$ |
|---|---|---|---|---|
| Mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$ | 0.8 ± 0.2* | 0.9 ± 0.1* | 2.1 ± 0.3†‡ | 2.4 ± 0.5†‡ |
| Mean $\dot{V}_A/\dot{Q}$ of $\dot{V}$ | 2.3 ± 0.6* | 2.9 ± 0.4 | 5.4 ± 0.7†‡ | 6.0 ± 0.7†‡ |
| Log $SD_{\dot{Q}}$ | 1.06 ± 0.20 | 1.35 ± 0.10 | 1.37 ± 0.08 | 1.34 ± 0.20 |
| Log $SD_{\dot{V}}$ | 1.00 ± 0.12 | 0.85 ± 0.04 | 0.84 ± 0.07 | 0.93 ± 0.19 |
| Dead space (%) | 45 ± 2* | 47 ± 1 | 50 ± 2† | 53 ± 2†‡ |
| $\dot{V}$ high $\dot{V}_A/\dot{Q}$ (%) | 5 ± 2* | 4 ± 1* | 11 ± 3†‡ | 12 ± 2†‡ |
| $\dot{Q}$ high $\dot{V}_A/\dot{Q}$ (%) | 0.9 ± 0.3* | 0.8 ± 0.4* | 4 ± 1†‡ | 5 ± 2†‡ |
| Shunt (%) | 19.8 ± 5.0 | 15.6 ± 4.2 | 19.7 ± 5.1 | 12.5 ± 2.8*† |
| $\dot{Q}$ low $\dot{V}_A/\dot{Q}$ (%) | 3.7 ± 0.8 | 5.5 ± 0.1 | 3.9 ± 0.8 | 4.9 ± 1.7 |
| (a-A)D area | 0.43 ± 0.04 | 0.46 ± 0.05 | 0.39 ± 0.04 | 0.42 ± 0.09 |
| R(a-A)D area | 0.24 ± 0.02 | 0.27 ± 0.03 | 0.22 ± 0.02 | 0.23 ± 0.05 |
| E(a-A)D area | 0.19 ± 0.02 | 0.19 ± 0.01 | 0.17 ± 0.02 | 0.19 ± 0.05 |

Values are mean ± 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; log $SD_{\dot{Q}}$ = log standard deviation of the perfusion distribution; log $SD_{\dot{V}}$ = log standard deviation of the ventilation distribution; dead space = dead space determined by inert gases; $\dot{V}$ high $\dot{V}_A/\dot{Q}$ = ventilation of high $\dot{V}_A/\dot{Q}$ units; $\dot{Q}$ high $\dot{V}_A/\dot{Q}$ = perfusion of high $\dot{V}_A/\dot{Q}$ units; shunt = intrapulmonary shunt determined by inert gases; $\dot{Q}$ low $\dot{V}_A/\dot{Q}$ = perfusion of low $\dot{V}_A/\dot{Q}$ units; (a-A)D area = tracer inert gas arterial-alveolar difference area; R(a-A)D area = retention component of (a-A)D area; E(a-A)D area = excretion component of (a-A)D area.

* $P < 0.05$ *versus* Low *p*H/Inspired $CO_2$.

† $P < 0.05$ *versus* Normal *p*H/Normal $PCO_2$.

‡ $P < 0.05$ *versus* Low *p*H/Normal $CO_2$.

(0.21), a more severe lung injury, a shorter stabilization period after administration of oleic acid (60 min), and the retention of $SF_6$ alone was used to estimate shunt. Estimation of shunt from the retention of $SF_6$ alone would overestimate the true shunt because the Ostwald blood-gas partition coefficient for $SF_6$ is high enough to be influenced by low and even normal $\dot{V}_A/\dot{Q}$ units.[17] Thus the decrease in inert-gas shunt with metabolic acidosis in Brimioulle *et al.*'s[26] study may be smaller in magnitude if the measurement was based on the retentions of all six inert gases. Of greater importance is the use of a high $F_{I_{O_2}}$ in the present study, which was chosen to allow comparison with a respiratory acidosis in our previous work.[11] In diseased lungs, hypoxic pulmonary vasoconstriction (HPV)–induced diversion of blood flow away from atelectatic or flooded alveoli, is an important means of preserving oxygenation. Whereas in dogs metabolic acidosis potentiates HPV,[27,28] use of the high $F_{I_{O_2}}$ may have prevented the observed reduction in shunt with metabolic acidosis by promoting absorption atelectasis or releasing HPV.[29,30] In addition, the lack of significant change in shunt fraction during this phase (low *p*H/normal $P_{CO_2}$) may be a type II error, due to the small sample size. Calculation of power for our experiment revealed a power of 0.75, suggesting that the likelihood of occurrence of a type II error was 0.25 in our experiment.

### *Normalization of Arterial Blood* p*H during Metabolic Acidosis Using Hyperventilation*

Some clinicians have advocated that increasing the minute ventilation to reduce the $Pa_{CO_2}$ is safer and more effective in the treatment of metabolic acidosis than is the administration of sodium bicarbonate. However, hyperventilation may acutely decrease venous return and cardiac output[9] and a respiratory alkalosis may adversely affect arterial blood oxygenation[10,11] by increasing $\dot{V}_A/\dot{Q}$ mismatch in the lung.[11,31] We were concerned that a respiratory alkalosis might also exacerbate hypoxemia in human patients with lung disease, such as atelectasis, pneumonia, pulmonary contusion, or pulmonary edema, when it is used to correct the blood *p*H during metabolic acidosis. We therefore designed a study which investigated the gas exchange effects of hyperventilation during hydrochloric acid–induced metabolic acidosis in dogs with permeability pulmonary edema.

Our study found that pulmonary gas exchange in diseased lungs was not impaired by the use of hyperventilation during metabolic acidosis. Hyperventilation increased the mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$ and $\dot{V}$ distributions, the dead space, and ventilation and perfusion of high $\dot{V}_A/\dot{Q}$ units, as would be expected from the increased respiratory rate. $Pa_{O_2}$ and intrapulmonary shunt were not affected by a respiratory alkalosis, when used to correct the blood *p*H to normal during hydrochloric acid–induced acidosis. Our results are consistent with the finding that overall *p*H is more important than a direct $CO_2$ effect in affecting pulmonary gas exchange in dogs.[24] $\dot{V}_A/\dot{Q}$ matching in the lung is preserved by both airway (*e.g.*, hypocapnic bronchoconstriction and collateral ventilation) and vascular (*e.g.*, HPV) mechanisms. Of interest, both pulmonary vascular contraction[32] and bronchial contraction[33] are *p*H-dependent.

Compared to normal acid–base conditions (phase 1), hyperventilation during metabolic acidosis (phase 4) increased $Pa_{O_2}$ by 69 mmHg and reduced pulmonary shunt by 7.3%. These effects were not attributable to the mechanical effects of the increased respiratory rate, as the shunt was increased (to 20%) when $Pa_{CO_2}$ was normalized by inspiration of $CO_2$ during hyperventilation.

The etiology for the significant decrease in intrapulmonary shunt with hyperventilation to normalize the arterial blood *p*H compared to normal acid–base conditions is unclear. It is possible that small variations in Ppa, $S\bar{v}_{O_2}$, and cardiac output may contribute to larger decreases in pulmonary shunting. However, multiple regression analysis did not find a significant relationship between these variables and pulmonary shunt. A change in intracellular and extracellular *p*H in the airways or the pulmonary vasculature may account for the difference compared to normal acid–base conditions. As cell membranes are freely permeable to $CO_2$[34] but not bicarbonate,[35] intracellular and extracellular *p*H during the mixed acid–base disorder may be different from those during normal acid–base status, despite a similar *p*H. Unfortunately, we did not measure intracellular *p*H and we cannot state the relative intracellular and extracellular *p*H in our preparation during the different study phases.

### *Relationship with Clinical Setting*

The metabolic acidosis that develops during cardiopulmonary resuscitation, shock, and severe hypoxemia has several detrimental hemodynamic effects, including impairment of myocardial functioning[1] and attenuation of the hemodynamic response to catecholamines.[2] Although sodium bicarbonate has traditionally been used

to treat metabolic acidosis, its use has become controversial.[3–8] Sodium bicarbonate may not only be ineffective in normalizing *p*H,[3,6] but it may also promote formation of additional lactic acid,[3,6] it increases $CO_2$ formation,[3,6,7] and its hypertonic load may reduce coronary perfusion pressure.[7] In contrast, hyperventilation to reduce $Pa_{CO_2}$ has been recommended as the preferred method to normalize arterial blood *p*H during metabolic acidosis.[4,8] The present study adds to its reported safety by suggesting that an adverse effect on arterial blood oxygenation would not occur. Therefore, we predict that hyperventilation to normalize arterial blood *p*H would probably not adversely affect oxygenation in acidotic patients with pulmonary edema, provided cardiac output is maintained.

However, there are a number of important differences between our experimental model and the clinical situation which would affect generalization of our results to human patients. These differences include use of oleic acid lung injury, pentobarbital anesthesia, a high $FI_{O_2}$, induction of metabolic acidosis by infusion of hydrochloric acid, maintenance of constant cardiac output, use of sodium bicarbonate to restore normal acid–base conditions, and lack of study of the long term consequences of hyperventilation on barotrauma and lung injury. Oleic acid is a noxious fatty substance that increases pulmonary vascular permeability, resulting in a hemorrhagic form of noncardiogenic pulmonary edema.[14] Although it has been used as an animal model of human adult respiratory distress syndrome, it is pathophysiologically different from that syndrome, which is a multisystem organ injury arising from a systemic intravascular inflammatory process.[14,36] We studied animals whose severity of lung injury had stabilized before experimental manipulations, in contrast to patients, in whom the lung disease may not have stabilized. As the animals were anesthetized with sodium pentobarbital, which may have a small but significant inhibitory effect on HPV,[37] the effects of the acid–base changes may have been smaller than in the nonanesthetized patient. The $FI_{O_2}$ of 0.90 was greater than would be used in human patients where $FI_{O_2}$ is chosen to maintain $Pa_{O_2}$ in the range of 60–100 mmHg instead of 200–300 mmHg. Promotion of absorption atelectasis and/or release of HPV by a high $FI_{O_2}$[29,30] may have attenuated the effects of acid–base status on gas exchange in the present study.

Another significant difference with the clinical setting is that metabolic acidosis was created by the infusion of hydrochloric acid, in contrast to the formation of lactic acid, which is the end result of widespread metabolic derangements. Hydrochloric acid has been reported to possess respiratory and pulmonary vascular effects independent of a decrease in arterial blood *p*H,[20,38] perhaps related to stimulation of thromboxane synthesis and release from platelets.[39] These effects are probably related to the infusion rate of hydrochloric acid, as higher infusion rates than we infused typically cause larger Ppa changes for similar blood *p*H variations. As our pilot data also demonstrated marked degrees of pulmonary hypertension and resultant instability of the degree of lung injury with rapid infusion rates, hydrochloric acid was infused very slowly in the present study. Using similar rates, concentrations, animal species, and infusion sites, Lejeune *et al.*[28] only observed *p*H-related effects of hydrochloric acid. Therefore, we believe our results are most likely attributable to the induced *p*H changes rather than to the specific use of hydrochloric acid.

In three of the dogs, the acid–base status was returned to normal (phase 1) after first studying metabolic acidosis phases. This was accomplished by discontinuing the hydrochloric acid infusion, waiting for *p*H to recover over a 2–3-h period and then administering sodium bicarbonate slowly and in small quantities (to 20–30 mEq). Gas exchange and hemodynamics in these animals were not different than in the animals which did not receive any sodium bicarbonate.

We attempted to maintain a constant cardiac output in this study, to avoid the complicating effects of changes in $S\bar{v}_{O_2}$ and cardiac output on pulmonary gas exchange. This was accomplished primarily by the slow induction and correction of metabolic acidosis and changes in blood *p*H due to hyperventilation. Intravenous fluids were administered judiciously, in order to maintain a constant pulmonary artery occlusion pressure of around 10 $cmH_2O$, without causing fluid overload and potential exacerbation of the lung injury. An arteriovenous fistula was opened in one dog during a metabolic acidosis phase (phase 4) and in another animal during normal acid–base conditions (phase 1). In contrast, in human patients, cardiac output is usually dramatically reduced (part of the cause for the metabolic acidosis) and mechanical hyperventilation may additionally depress venous return and cardiac output. Although pulmonary shunt may be reduced by decreases in cardiac output in generalized lung disease, $Pa_{O_2}$ may fall due to a decrease in $P\bar{v}_{O_2}$.[40] Hence, our results suggest that oxygenation will not be impaired during hyperventilation if cardiac output is maintained.

Our ability to translate our findings to clinical application is also hindered by the fact that we did not study the long-term consequences of hyperventilation on barotrauma and lung injury. It is possible that the potential barotrauma in the diseased lung, increased dead space, and administration of fluid to maintain cardiac output, might increase edema formation and lung injury with time. Although barotrauma has traditionally been thought to occur with high airway pressures[41,42] due to high lung volumes,[42] tidal ventilation at very low lung volumes has recently been shown to worsen lung injury.[12,13] Increases in respiratory rate at normal tidal volumes may enhance lung damage due to repeated closure and opening of small airways with each respiratory cycle. Of interest, Stewart *et al.*[43] demonstrated in a 6-month follow-up of patients with adult respiratory distress syndrome by using high-resolution computerized tomographic scans that areas that previously had been atelectatic were later normal and that areas that were "recruited" were later damaged. Consequently, increasing the number of barotrauma producing inspirations per minute by hyperventilation may have an adverse effect on pulmonary gas exchange and lung function over time. Although hyperventilation is often only briefly used in the management of the patient with acidotic trauma, the long term consequences of its use are unclear.

In summary, hyperventilation to normalize arterial blood *p*H during hydrochloric acid–induced metabolic acidosis did not adversely affect pulmonary gas exchange in dogs with permeability pulmonary edema. $Pa_{O_2}$ was increased and intrapulmonary shunt was decreased compared to normal acid–base conditions. We conclude that hyperventilation to normalize *p*H should not adversely affect $Pa_{O_2}$ in acidotic patients with increased permeability pulmonary edema, provided cardiac output is maintained. However, we suggest caution be used in the translation of these findings to clinical application in patients as the long-term consequences of hyperventilation on barotrauma and lung injury are as yet unknown.

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