Increased Arterial pH, Not Decreased PaCO₂, Attenuates Hypoxia-Induced Pulmonary Vasoconstriction in Newborn Lambs

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ABSTRACT. Mechanically induced hyperventilation is used in the treatment of newborn infants with persistent pulmonary hypertension syndrome to induce respiratory alkalosis, which may attenuate their pulmonary vasoconstriction. Whether this treatment is effective because of the increase in arterial pH or the decrease in PaCO₂ was investigated in nine sedated, mechanically ventilated newborn lambs with hypoxia-induced pulmonary vasoconstriction. We found that respiratory alkalosis and metabolic alkalosis were equally effective in attenuating hypoxia-induced pulmonary vasoconstriction, but that hypocapnia (low PaCO₂ with a normal arterial pH) was ineffective. These results indicate that increased arterial pH, not decreased PaCO₂, attenuates hypoxia-induced pulmonary vasoconstriction in newborn lambs and possibly the pulmonary vasoconstriction in newborn infants with persistent pulmonary hypertension syndrome. (*Pediatr Res* 20: 113–117, 1986)

Respiratory alkalosis, produced by mechanically induced hyperventilation, is the mainstay of treatment for newborn infants with persistent pulmonary hypertension syndrome. Respiratory alkalosis improves oxygenation and reverses pulmonary vasoconstriction by decreasing the mean pulmonary arterial pressure when the arterial pH is greater than 7.55 and the PaCO₂ is less than 22 mm Hg (1, 2). Whether these beneficial effects are caused by the increase in arterial pH or the decrease in PaCO₂, or by the alteration in mechanical lung factors necessary to produce respiratory alkalosis, is not known.

The majority of previous studies investigating the effects of acid-base status on pulmonary vasoconstriction have studied the effects of acidosis (3–5) rather than alkalosis. The few studies that have investigated the effect of respiratory alkalosis on pulmonary vasoconstriction induced by hypoxia have suggested that the increase in pH, not the decrease in PaCO₂, decreases pulmonary vascular resistance (6–9). The results of these studies are somewhat confusing because of differences between studies in animal ages, species, or experimental methods. Many physicians who care for newborn infants with persistent pulmonary hypertension syndrome still believe it is the decrease in PaCO₂ (10),

not the increase in pH, that improves these patients during respiratory alkalosis produced by mechanically induced hyperventilation.

The purpose of the present study was to determine how mechanically induced hyperventilation reverses hypoxia-induced pulmonary vasoconstriction. For this purpose we compared the effects of three treatments—respiratory alkalosis, metabolic alkalosis, and hypocapnia—on hypoxia-induced pulmonary vasoconstriction in newborn lambs with mechanical lung factors held constant. The strategy behind this approach was that if respiratory alkalosis reverses pulmonary vasoconstriction because of the increase in pH, then metabolic alkalosis (increased pH and a normal PaCO₂) should have a similar effect. Conversely, if respiratory alkalosis reverses pulmonary vasoconstriction because of the decrease in PaCO₂, then hypocapnia (normal pH and a decreased PaCO₂) should have a similar effect.

METHODS

Nine mixed breed newborn lambs (5.5 ± 2.3 days; 4.4 ± 1.0 kg) (mean ± SD) were operated on under local anesthesia with 1% lidocaine hydrochloride. Polyvinyl catheters were placed in both hind leg arteries and veins and advanced to the descending aorta and inferior vena cava, respectively. A polyvinyl catheter was also placed in a fore leg artery and passed retrograde to the ascending aorta and positioned above the aortic valve to obtain arterial blood samples and measure systemic arterial pressure. A no. 5 French end-hole, balloon-tip, flow-directed thermodilution catheter, with the proximal injection port 15 cm from the tip, was introduced into the internal jugular vein and advanced into the pulmonary artery to measure pulmonary arterial pressure and pulmonary arterial wedge pressure. The lambs were then placed under a radiant warmer to maintain body temperature, and an intravenous infusion of dextrose (4–6 mg/kg/min) in isotonic saline (3 ml/kg/h) was started. Two hours was allowed for recovery.

Next, the lambs were sedated with a continuous infusion of ketamine hydrochloride (1–2 mg/kg/h). Muscle relaxation was maintained with pancuronium bromide (1–2 mg/kg). The lambs were intubated with a cuffed endotracheal tube (ID 5.0 mm), and ventilated with a Baby Bird pressure-limited time-cycled infant ventilator (Bird Corp., Palm Springs, CA). A catheter was placed in the trachea alongside the endotracheal tube to measure proximal airway pressure.

In order to differentiate the effects of increased pH from decreased PaCO₂ on hypoxia-induced pulmonary vasoconstriction, we compared lambs during four (one control and three treatments) different conditions: 1) hypoxic control (normal arterial pH, normal PaCO₂, and low PaO₂), 2) hypoxic respiratory alkalosis (high arterial pH, low PaCO₂, low PaO₂), 3) hypoxic metabolic alkalosis (high arterial pH, normal PaCO₂, and low

PaO$_2$), and 4) hypoxic hypocapnia (normal arterial pH, low PacO$_2$, and low PaO$_2$). To change conditions, pH and PacO$_2$ were independently varied between these four conditions by the intravenous infusion of acid or alkali and the addition or deletion of 5% CO$_2$ from the inspired gas mixture.

Because some experimentation was necessary to produce the desired degree of respiratory alkalosis in individual lambs, changes in the ventilator variables were made during normoxia. Once the ventilatory rate, peak inspiratory and end-expiratory pressures, and inspiratory time that produced the desired degree of respiratory alkalosis (normoxic respiratory alkalosis) were found, they were not changed throughout the study. Five percent CO$_2$ was then added to the gas mixture to normalize arterial pH and PacO$_2$ (normoxic control). Nitrogen was then added to the inspired gas mixture (Fio$_2$ 0.08–0.11) to produce hypoxemia (hypoxic control) and induce stable pulmonary vasoconstriction. The inspired oxygen concentration during the hypoxic conditions was not changed throughout the remainder of the study.

All lambs received both acid and alkali infusions. Because the order of intervention, *i.e.* whether the lambs received acid or alkali first, may have affected the results, we randomized the order of intervention (Fig. 1). In group 1, the 5% CO$_2$ was then removed from the gas mixture to produce hypoxic respiratory alkalosis. Then, 0.5 N hydrochloric acid (4.5 ± 0.7 ml/kg) was slowly infused intravenously (17.5 ± 6.5 min) during hypoxic respiratory alkalosis to produce hypoxic hypocapnia. When the

hemodynamic variables were unchanged for 10 min, 0.9 M sodium bicarbonate (1 mEq/ml) (9.5 ± 0.2 mEq/kg) was infused slowly intravenously (47.5 ± 17.6 min) and 5% CO$_2$ was added to the inspired gas mixture to produce hypoxic metabolic alkalosis. In group 2, the order of acid and alkali infusions was reversed. First, during hypoxic control, 0.9 M sodium bicarbonate (8.5 ± 2.1 mEq/kg) was slowly infused intravenously (26.0 ± 10.8 min) to produce hypoxic metabolic alkalosis. When the hemodynamic variables were unchanged for 10 min, 5% CO$_2$ was removed from the inspired gas mixture and 0.5 N hydrochloric acid (7.5 ± 1.9 ml/kg) was slowly infused intravenously (70.0 ± 30.8 min) to produce hypoxic hypocapnia. Throughout the study, each condition—hypoxic control, hypoxic respiratory alkalosis, hypoxic metabolic alkalosis, and hypoxic hypocapnia— was produced one to three times (Fig. 1). To further prevent bias from both the length of study and the order of intervention, all hemodynamic variables and arterial pH and blood gas values produced for each condition were averaged.

The absence of left-to-right ductus arteriosus shunting during the experiment was shown by injecting 3 ml of iced saline into the ascending aorta and finding no temperature change in the pulmonary artery. At the end of the experiment, the lambs were given a lethal dose of pentobarbitol. At autopsy in each lamb, catheter positions were confirmed, the ductus arteriosus was found to be closed, and the atrial septum was found to be intact.

Right atrial pressure was measured through the proximal port of the thermodilution catheter. Cardiac output was determined by the thermodilution method and calculated by computer (Electro-Catheter Model 5000, Electro-catheter Corp., Rahway, NJ). For each measurement, 3 ml of iced saline was injected into the proximal port. The cardiac output value was taken as the average of three consecutive injections. Pulmonary and systemic arterial, right atrial, and proximal airway pressures were measured with Statham P23Db pressure transducers and recorded continuously on a Beckman multichannel direct writing recorder. Mean pressures were obtained by electrical integration. In three lambs, a balloon-tip silastic catheter with known pressure-volume characteristics was placed in the mouth and advanced to the mid-esophagus to measure esophageal pressure. Their transpulmonary pressure (proximal airway pressure minus esophageal pressure) was measured using a Validyne DP-45 (± 1 cm H$_2$O) differential pressure transducer and amplified with a Validyne CD-15 carrier demodulator. In two of these lambs, tidal volume was also measured by the integrated flow signal obtained with a Fleisch 00 pneumotachograph attached to a Celesco differential pressure transducer (range of q 2.5 cm H$_2$O, frequency response flat to 30 Hz). Arterial pH and blood gases, obtained immediately before measurement of hemodynamic variables, were measured by a Corning 175 automated pH/blood gas analyzer.

Cardiac output and pulmonary arterial wedge pressure were measured during all normoxic and hypoxic conditions. Response values were taken when all hemodynamic variables were unchanged for at least 10 min. Pulmonary vascular resistance was calculated from mean pulmonary arterial pressure minus mean pulmonary arterial wedge pressure divided by cardiac output per kg of body weight. Systemic vascular resistance was calculated from mean systemic arterial pressure minus mean right atrial pressure divided by cardiac output per kg of body weight.

The means ± SD were computed for the vascular pressures and resistances, cardiac output, arterial pH and blood gases, proximal airway, ventilator peak inspiratory and end-expiratory pressures, inspiratory time, and ventilator rate during the normoxic and during the hypoxic conditions for groups 1 and 2. The data from groups 1 and 2 were compared by unpaired Student t tests (11), found to be similar, and pooled. During normoxia, the differences in these variables between control and respiratory alkalosis were analyzed by a paired Student's t test with the Bonferroni correction. The normoxic control was also compared to the hypoxia control of a paired Student's t test with the Bonferroni correction. During hypoxia, the differences be-
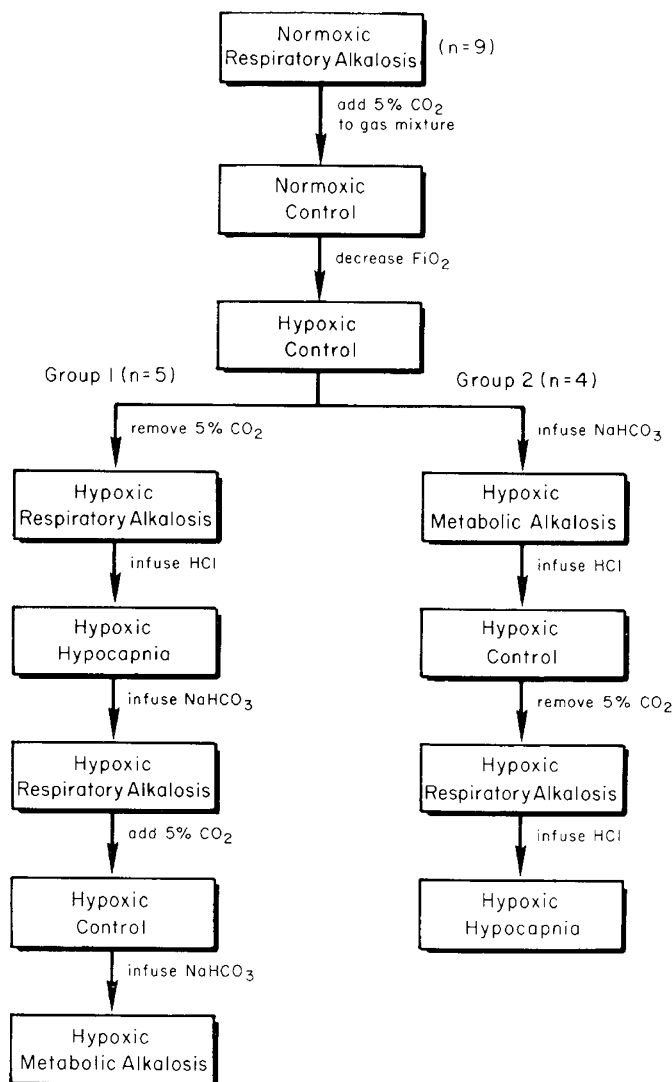

Fig. 1. Schematic representation of the experimental protocol.

tween the four experimental conditions (hypoxic control, hypoxic respiratory alkalosis, hypoxic metabolic alkalosis, and hypoxic hypocapnia) were analyzed by two-way analysis of variance and the Newman-Keuls test for multiple comparisons (11). A $p < 0.05$ was considered statistically significant.

RESULTS

As expected, hypoxia induced pulmonary vasoconstriction. During hypoxic ventilation with 5% CO_2 added (hypoxic control) (Table 1), mean pulmonary arterial pressure increased by 80% ($p < 0.05$) and pulmonary vascular resistance increased by 112% ($p < 0.05$) from normoxic control values (Table 2). Although heart rate increased by 17% ($p < 0.05$), cardiac output did not change significantly. Mean systemic arterial pressure increased by 11% ($p < 0.05$) but systemic vascular resistance was not significantly changed from the normoxic control value.

Respiratory alkalosis attenuated the hypoxia-induced pulmonary vasoconstriction. During hypoxic respiratory alkalosis (Table 1), mean pulmonary arterial pressure was 33% lower ($p <$

0.05) and pulmonary vascular resistance was 31% lower ($p < 0.05$) than during the hypoxic control. Mean systemic arterial pressure was 13% lower ($p < 0.05$) than during the hypoxic control (Table 2). There was no statistically significant change in cardiac output or systemic vascular resistance. Respiratory alkalosis during normoxic ventilation (Table 1) had a similar effect on the pulmonary circulation but to a much lesser degree than during hypoxic ventilation (Table 2).

Metabolic alkalosis caused changes very similar to those caused by respiratory alkalosis. During hypoxic metabolic alkalosis (Table 1), both mean pulmonary arterial pressure and pulmonary vascular resistance were 33% lower ($p < 0.05$) than during the hypoxic control (Table 2). Mean systemic arterial pressure was 14% lower ($p < 0.05$) than during the hypoxic control, but cardiac output and systemic vascular resistance were unchanged.

Hypocapnia, however, did not attenuate hypoxia-induced pulmonary vasoconstriction and, in fact, increased it. During hypoxic hypocapnia (Table 1), mean pulmonary arterial pressure was 9% higher ($p < 0.05$) and pulmonary vascular resistance was 54% higher ($p < 0.05$) than hypoxic control (Table 2). Cardiac output was 27% lower ($p < 0.05$) and systemic vascular resistance was 58% higher ($p < 0.05$) than during the hypoxic control but systemic arterial pressure was not changed.

Pulmonary arterial wedge pressure and heart rate did not change significantly with changes in arterial pH, PacO₂, or PaO₂ (Table 2). Right atrial pressure during hypoxic hypocapnia was slightly (by 1.2 mm Hg), but significantly, lower than during the other hypoxic conditions (p < 0.05).

The peak inspiratory pressure was 15.8 ± 2.5 mm Hg with a positive end-expiratory pressure of 3.3 ± 2.1 mm Hg. The mean ventilatory rate was 74.3 ± 3.7 breaths/min with a mean inspiratory time of 0.31 ± 0.08 s. These ventilatory parameters resulted in a mean proximal airway pressure of 8.3 ± 1.5 mm Hg. These values did not change throughout each study. Esophageal pressure was 3–8 mm Hg in the three lambs in which it was measured. In two of these, transpulmonary pressure and tidal volume were measured. These variables did not change when the arterial pH was increased or the PacO₂ was decreased.

There was no significant difference in PaO₂ between any of the hypoxic conditions (Table 1). PacO₂ values were similar during hypoxia-induced control and hypoxic metabolic alkalosis, and during hypoxic respiratory alkalosis and hypoxic hypocapnia. Arterial pH was similar during hypoxic control and hypoxic hypocapnia, and during hypoxic respiratory and metabolic alkalosis.

Table 1. *Arterial pH and blood gases during normoxic and hypoxic ventilation*

	pH	PacO₂ (mm Hg)	PaO₂ (mm Hg)
Normoxic			
Control	7.34 ± 0.01 (7.32–7.38)	41.9 ± 3.5 (39–46)	98.8 ± 8.8 (83–100)
Respiratory alkalosis	7.61 ± 0.01* (7.57–7.67)	22.1 ± 1.7* (20–25)	92.3 ± 14.1 (72–100)
Hypoxic			
Control	7.36 ± 0.06 (7.33–7.41)	40.7 ± 3.5 (36–44)	32.5 ± 4.7 (29–45)
Respiratory alkalosis	7.62 ± 0.04† (7.61–7.67)	19.6 ± 2.3† (15–23)	32.0 ± 4.1 (25–38)
Metabolic alkalosis	7.60 ± 0.04† (7.55–7.66)	38.1 ± 3.7 (17–22)	33.8 ± 4.1 (28–36)
Hypocapnia	7.40 ± 0.05 (7.32–7.44)	20.7 ± 2.1† (17–22)	33.6 ± 4.1 (28–36)

* $p < 0.05$ vs normoxic control, $n = 8$.
† $p < 0.05$ vs hypoxic control, $n = 9$.

Table 2. *Hemodynamic variables during normoxic and hypoxic ventilation (mean ± SD)*

	Mean pulmonary arterial pressure (mm Hg)	Pulmonary vascular resistance (mm Hg/liter/min/kg)	Mean systemic arterial pressure (mm Hg)	Systemic vascular resistance (mm Hg/liter/min/kg)	Right atrial pressure (mm Hg)	Pulmonary arterial wedge pressure (mm Hg)	Heart rate (beats/min)	Cardiac output (liter/min/kg)
Normoxic control	22.3 ±4.4	52.7 ±14.4	74.1 ±11.2	214.8 ±58.6	1.4 ±2.1	2.9 ±3.7	206.3 ±43.9	0.38 ±0.08
Normoxic respiratory alkalosis	18.6* ±4.2	48.1 ±13.2	75.0 ±13.6	223.1 ±6.1	1.3 ±1.8	2.4 ±4.0	217.0 ±44.0	0.34 ±0.06
Hypoxic control	40.1 ±7.6	111.7 ±86.6	87.8 ±13.3	267.2 ±156.9	1.7 ±2.4	5.1 ±2.8	241.1 ±45.7	0.39 ±0.12
Hypoxic respiratory alkalosis	26.7† ±5.9	76.9† ±51.1	76.7† ±8.5	257.8 ±133.2	1.5 ±2.1	4.5 ±3.6	260.2 ±39.1	0.33 ±0.10
Hypoxic metabolic alkalosis	26.8† ±4.7	74.8† ±39.1	75.3† ±12.8	234.6 ±109.6	1.5 ±1.9	3.6 ±3.4	245.0 ±50.8	0.37 ±0.14
Hypoxic hypocapnia	43.7† ±7.1	172.1† ±78.3	87.1 ±7.0	422.2† ±161.9	0.5† ±1.9	6.2 ±5.0	239.4 ±31.7	0.24† ±0.08

* $p < 0.05$ vs normoxic control, $n = 8$.
† $p < 0.05$ vs hypoxic control, $n = 9$.

DISCUSSION

This study in newborn lambs demonstrates that respiratory alkalosis produced by mechanical hyperventilation attenuates hypoxia-induced pulmonary vasoconstriction because of the increase in arterial pH not because of the decrease in $PaCO_2$. Respiratory and metabolic alkalosis had almost identical circulatory effects: both decreased pulmonary arterial pressure and pulmonary vascular resistance. In contrast, hypocapnia—low $PaCO_2$, with a normal arterial pH—increased pulmonary arterial pressure and pulmonary vascular resistance. During normoxia, similar, but less substantial, effects of alkalosis on the pulmonary vasculature were seen.

Previous studies investigating the effects of alkalosis on hypoxia-induced pulmonary vasoconstriction have yielded discrepant results. Results similar to ours were found in adult dog lungs perfused with a constant pulmonary blood flow (7). Respiratory alkalosis reversed the hypoxia-induced increase in pulmonary vascular resistance. Pulmonary vasoconstriction was restored by normalizing the arterial pH with an infusion of acid. These findings suggested that increased arterial pH plays a role in the changes seen with respiratory alkalosis. The effects of metabolic alkalosis were not studied. Hypoxia-induced pulmonary vasoconstriction was not, however, attenuated by alkalosis in *in situ* perfused neonatal calf lungs (6).

Studies by Malik and Kidd (9) provided further support for alkalosis attenuating hypoxia-induced pulmonary vasoconstriction. The development of respiratory alkalosis in their spontaneously breathing adult dogs was also associated with an attenuation of hypoxia-induced pulmonary vasoconstriction. Pulmonary vasoconstriction persisted when either 5% CO_2 was added to the inspired gas mixture or fixed mechanical ventilation prevented the fall in $PaCO_2$ and the development of respiratory alkalosis. However, the alkalosis-induced decrease in pulmonary vascular resistance in that study was due predominantly to an increase in cardiac output, not to a decrease in pulmonary arterial pressure. These results are in contrast to our study and to a study in adult cats (8), in which the alkalosis-induced fall in pulmonary arterial pressure caused the decrease in pulmonary vascular resistance. Finally, Rudolph and Yuan (5) found that hypoxia-induced pulmonary vasoconstriction in the intact neonatal calf was attenuated by normalizing pH to 7.35. This finding implied that acidosis was necessary for hypoxia to cause pulmonary vasoconstriction. However, the effect of alkalosis was not investigated. These differences in the response of the pulmonary vasculature to alkalosis may reflect differences in ages, species, or experimental methods.

A pressure-limited time-cycled ventilator, similar to those used in the management of infants with persistent pulmonary hypertension syndrome, was used in this study. Peak inspiratory, end expiratory, and mean airway pressures, ventilator rate, and inspiratory time were held constant. There were no changes in tidal volume or transpulmonary pressure, in the two lambs studied, during changes in arterial pH, $PaCO_2$, or PaO_2. Because ventilation remained constant throughout each study and measurements of lung mechanics did not change, the cardiovascular effects could not have resulted from changes in mechanical lung factors.

The reported effect of acute hypoxia on cardiac output is quite variable: increasing (9, 12), decreasing (5), or neither (13–15). In our study, hypoxia caused no significant change in cardiac output. However, cardiac output did change in one of the four hypoxic experimental conditions: there was a marked decrease in cardiac output during hypocapnia. This decrease may reflect a combination of factors. First, low $PaCO_2$ may decrease cardiac output (16, 17). Second, an infusion of acid either may cause direct myocardial depression or may damage platelets or endothelial cells releasing vasoactive substances that alter myocardial function. Either effect would result in a decrease in cardiac output. In our study, although each lamb received both acid and

alkali, lambs were randomly assigned as to which they would receive first. There were no differences detected between the two groups and, thus no prolonged ill effects of acid infusion. Therefore, regardless of what caused the decrease in cardiac output, the effect was both transient and reversible.

Alkalosis during both normoxia and hypoxia had similar effects on the systemic circulation to those seen on the pulmonary circulation. In agreement with our findings, systemic arterial pressure has been previously reported to decrease during alkalosis in both humans (18) and animals (17, 19). However, Rudolph and Yuan (5) found these changes to be inconsistent in newborn calves. Alkali infusion either slightly decreases or has no apparent effect, as seen in our study, on systemic vascular resistance (19, 20).

The mechanism through which an increase in pH attenuates hypoxia-induced pulmonary vasoconstriction remains unknown. Several possibilities exist. One mechanism may be a change in the ratio of ionized to bound calcium. This ratio is pH dependent, with alkalosis decreasing the ionized calcium. Because calcium is very important in smooth muscle contraction, decreasing the available ionized calcium, through alkalosis, may relax vascular smooth muscle and reverse pulmonary vasoconstriction (21). Further evidence for the importance of calcium is that nifedipine, a calcium-channel blocker, infused into isolated perfused pig lungs reduced hypoxia-induced pulmonary vasoconstriction (22). Nifedipine also decreases pulmonary and systemic arterial pressures and cardiac output in newborn lambs (23). These effects of nifedipine are similar to those seen during alkalosis in our study, implying a possible role for calcium flux. A second possible mechanism may involve potassium flux because alkalosis also decreases intracellular potassium (24). This decrease may alter nerve and muscle cell membrane polarization and lead to the observed circulatory changes—a decrease in pulmonary and systemic arterial blood pressures (24). Electrophysiological changes seen during both metabolic and respiratory alkalosis support this hypothesis (25).

Although multiple drug therapies have been used to treat newborn infants with persistent pulmonary hypertension syndrome, mechanically induced hyperventilation remains the most effective form of therapy (10, 26). Aggressive mechanical hyperventilation, however, may be associated with an increased incidence of complications, including pneumothorax, pneumomediastinum, barotrauma, and chronic lung disease (26). In addition, in some infants with persistent pulmonary hypertension syndrome, the degree of respiratory alkalosis necessary to attenuate pulmonary vasoconstriction cannot be reached because of severe lung disease or the development of metabolic acidosis. Our study indicates that mechanical hyperventilation resulting in respiratory alkalosis attenuates pulmonary vasoconstriction because of an increase in arterial pH, not because $PaCO_2$ is decreased as previously reported (10), or because of mechanical lung changes. Thus, alkali infusions used judiciously together with mechanically induced hyperventilation may help to achieve the desired degree of alkalosis and also decrease the incidence of pulmonary complications.

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