

Radiographic Lung Disease and Response of Persistent Pulmonary Hypertension to Mean Airway Pressure and Alkalosis

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Summary. Persistent pulmonary hypertension of the newborn (PPHN) is associated with multiple cardiopulmonary diseases. Therapy often includes hyperventilation/alkalosis despite little evidence as to its efficacy in diverse conditions. To determine (1) if part of the improvement of arterial oxygen tension (P_{aO_2}) attributed to alkalosis is actually related to increased mean airway pressure (P_{aw}) and (2) if the presence of radiographic pulmonary disease predicts the response to alkalosis or mean airway pressure, we reviewed records of 19 newborns with well-documented PPHN. Arterial blood gases and corresponding ventilator settings were recorded during the first day of life. To adjust for lower F_{iO_2} , corrected P_{aO_2} (cP_{aO_2}) was calculated when the $F_{iO_2} < 1.0$, such that $cP_{aO_2} = \text{calculated arterial/alveolar oxygen ratio} \times (713 - P_{aCO_2}/0.8)$. Regression equations were obtained and mean slopes of these were compared for P_{aw} vs. cP_{aO_2} , and pH vs. cP_{aO_2} by one group t-tests (with assumed population slope of zero). There was no correlation between P_{aw} and cP_{aO_2} (mean slope \pm SD = -8.4 ± 30.8 , $P = 0.25$), but there was a moderate correlation between pH and cP_{aO_2} (mean slope = 333.1 ± 480.5 , $P = 0.007$). Patients were then classified by chest radiographs as having severe or minimal/no lung disease. Relationships of P_{aw} and pH to cP_{aO_2} were then re-examined. No correlation was present between P_{aw} and cP_{aO_2} in 11 patients with PPHN and severe radiographic disease (mean slope = -7.4 ± 26.9 , $P = 0.38$) or in eight patients with PPHN and minimal/no lung disease (mean slope = -9.8 ± 37.5 , $P = 0.48$). There was no correlation between pH and cP_{aO_2} in patients with severe radiographic lung disease and PPHN (mean slope = 92.1 ± 399.5 , $P \cong 0.46$), but patients with PPHN and minimal/no lung disease showed a strong correlation (mean slope = 664.5 ± 385.8 , $P = 0.002$). We conclude that P_{aw} (≤ 18 cm H₂O) with conventional mechanical ventilation has no apparent effect on oxygenation in patients with PPHN regardless of lung disease; however, severe radiographic lung disease may be a predominant variable predicting a poor response to alkalosis. We speculate that different diseases cause pulmonary hypertension by different mechanisms. *Pediatr Pulmonol.* 1994; 17:239–245.

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INTRODUCTION

Despite advances in treatment, persistent pulmonary hypertension of the newborn (PPHN) remains a poorly understood entity and a vexing management problem. Initially Gersony et al.¹ described two patients with clear lung fields and elevated pulmonary artery pressures; however, since that time multiple conditions have been described as causing or being associated with PPHN, including cardiac dysfunction, aspiration syndromes, shock, sepsis, and respiratory distress syndrome.^{2–6}

Concomitant with the delineation of the associated conditions, Peckham et al.⁷ and Drummond et al.⁸ documented the use of hyperventilation for lowering pulmonary artery pressure. In demonstrating the association between increased arterial P_{aO_2} and decreased P_{aCO_2} or alkalosis, these studies did not consider other variables,

such as changes in mean airway pressure possibly occurring during hyperventilation or different underlying lung disease. Despite the uncontrolled nature of these studies and the small number of patients, hyperventilation became a common method of treating PPHN. Only recently has the need for hyperventilation been questioned,⁹ and this strategy remains controversial.

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In view of the diversity of underlying pulmonary disorders, it seems unwise to consider PPHN as a single entity. The wide variety of conditions associated with PPHN suggests that the mechanisms causing elevated pulmonary vascular resistance may be different and thus the response to treatment may differ. It is plausible that the treatment of PPHN should be based on the underlying diagnosis rather than the presence of PPHN.

We reviewed a population of babies diagnosed as having PPHN in an attempt to answer two questions: (1) Is part of the increased $P_{a_{O_2}}$ that is attributed to increasing pH actually due to increases in mean airway pressure occurring during the management of PPHN? (2) Does the presence or absence of radiographic lung disease affect the relationship of pH (or mean airway pressure) to $P_{a_{O_2}}$?

MATERIALS AND METHODS

Records of babies admitted to the University of Michigan Holden Neonatal Intensive Care Unit from 1/1/88 until 7/1/92 with the discharge diagnosis of PPHN were considered. In order to eliminate inconsistencies in the diagnosis of PPHN and to avoid the uncertain effects of pulmonary injury induced by oxygen or barotrauma,⁹ only infants who were inborn or transferred from level one or two nurseries in the first day of life were included. In addition, babies who had major congenital anomalies, who did not have an indwelling post-ductal arterial catheter or who were not mechanically ventilated in the first 24 hours of life were excluded from further review.

The diagnosis of PPHN was confirmed based on the following criteria:

1. Gestational age ≥ 34 weeks.
2. Hypoxemia ($P_{a_{O_2}} \leq 70$) on at least three arterial blood gases (ABG) during adequate mechanical ventilation with $F_{i_{O_2}} \geq 0.90$.
3. Normal intracardiac anatomy (VSD, ASD, or PDA are acceptable) with:
 - a. pre/post-ductal $P_{a_{O_2}}$ difference ≥ 20 torr by ABG or transcutaneous $P_{a_{O_2}}$ monitor, or $\geq 10\%$ difference in oximetry; or
 - b. echocardiographic doppler documentation of right to left or bidirectional atrial or ductal shunt, or decreased right ventricular function with tricuspid regurgitation; or
 - c. estimated measurement of right ventricular systolic pressure by regurgitant tricuspid jet velocity to be $\geq 90\%$ of systemic.

Infants were ventilated with either Sechrist IV-100B or Bird V.I.P. ventilators. The respiratory records of those babies meeting the diagnostic criteria for PPHN were then examined. Blood gas values and ventilator settings of the first 24 hours of life were recorded. If an infant

required extracorporeal life support (ECMO) or high frequency oscillatory ventilation (HFOV) before 24 hours of age, no blood gas values after commencing these rescue therapies were recorded or analyzed.

In order to standardize the $P_{a_{O_2}}$ in the event an infant was receiving $F_{i_{O_2}} < 1.0$, the $cP_{a_{O_2}}$ was calculated. This value was used to estimate what the $P_{a_{O_2}}$ would be if the patient were receiving $F_{i_{O_2}} 1.0$, by assuming the arterial/alveolar oxygen tension (a/A) ratio to be similar in either instance. The $cP_{a_{O_2}}$ was determined by first calculating the a/A ratio for each arterial blood gas:

$$P_{A_{O_2}} = (713 \times F_{i_{O_2}}) - P_{a_{CO_2}}/0.8$$

where $P_{A_{O_2}}$ is alveolar oxygen. The a/A ratio was then multiplied by what the alveolar oxygen level would be if the $F_{i_{O_2}}$ were 1.0, to yield $cP_{a_{O_2}}$:

$$cP_{a_{O_2}} = a/A \text{ ratio} \times (713 - P_{a_{CO_2}}/0.8).$$

The relationships between mean airway pressure and $cP_{a_{O_2}}$, and between pH and $cP_{a_{O_2}}$ were examined in babies meeting diagnostic criteria for PPHN. Regression equations and correlation coefficients (r values) were determined for pH vs. $cP_{a_{O_2}}$, and P_{aw} vs. $cP_{a_{O_2}}$ in each patient. For each of the two different correlations, the regression equations of the individual patients were used to determine the mean slope (\pm SD) for all patients. The mean slope was compared by one group t-test to an assumed population mean slope of zero (no correlation). Correlations after radiographic stratification (see below) were compared in the same fashion. A P -value ≤ 0.008 , after Bonferroni correction for multiple comparisons, was accepted as indicating a significant difference. The mean of individual r values of each group is reported, but was not used in the statistical analysis.

The chest radiographs of all PPHN infants were initially reviewed separately by a neonatologist (KSD) and a pediatric radiologist (AES). The patients were separated based on the chest radiographic findings from the first day of life into two groups: those with minimal or no apparent lung disease and those with severe lung abnormalities. Lung conditions diagnosed radiographically included respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), pneumonia, retained lung fluid, and nonspecific abnormalities (e.g., haziness, mild granularity). Differences between the two reviewers were resolved by consensus after joint review of radiographs. Both viewers were unaware of the clinical course of the patients being re-reviewed until after consensus was reached.

Similar correlations of P_{aw} vs. $cP_{a_{O_2}}$ and pH vs. $cP_{a_{O_2}}$ were assessed for patients based on their radiographic group assignments, PPHN with minimal/no lung disease, or PPHN with severe lung disease. Mean slopes (\pm SD)

TABLE 1—PPHN Patients—Descriptive Data^a

	All patients (n = 19)	Minimal/no lung disease (n = 8)	Severe lung disease (n = 11)
Weight (kg ± SD)	3.40 ± 0.80	3.59 ± 0.93	3.27 ± 0.64
Gest. age (wks)	38.6 ± 2.1	38.2 ± 1.2	3.87 ± 2.6
Sex (M/F)	10/9	5/3	5/6
P _{aO₂} (Torr ± SD) ^b		83 ± 87	88 ± 55
P _{aw} (cm H ₂ O ± SD) ^b		12.5 ± 2.5	11.3 ± 1.8
FiO ₂ * (±SD)		0.96 ± 0.15	0.92 ± 0.17
pH ^c		7.49	7.37
Other diagnoses			
MAS	3		3
RDS	2		2
Asphyxia	4	4	
Presumed sepsis	2	2	
Pneumonia (?)	6	2	4
Shock lung (?)	2		2

MAS, meconium aspiration syndrome; RDS, respiratory distress syndrome.

^aDescriptive information on 19 patients fulfilling criteria for the diagnosis of PPHN. Diagnoses in question were thought to be the most likely clinical diagnoses by the attending physician. No patients had positive blood or CSF cultures.

^bMean values during the first 6 hours of life.

^cMedian values during the first 6 hours of life.

for each group were again determined and tested against an assumed population value of zero, as above.

RESULTS

Between 1/1/88 and 7/1/92, 177 patients were admitted with a discharge diagnosis of PPHN. Of these, 33 patients were identified who had no significant congenital anomalies, and were either inborn or transferred from level one or two nurseries in the first 24 hours of life. Seven of these were eliminated because they had no post-ductal arterial line (n = 5) or had not undergone mechanical ventilation in the first day of life (n = 2). The remaining 26 patients were reviewed in detail.

Of the remaining 26 patients, 7 did not meet the diagnostic criteria for PPHN, 4 had echocardiograms which did not meet criteria for PPHN, and 3 patients had fewer than three P_{aO₂} ≤ 70 torr during mechanical ventilation with FiO₂ ≥ 0.90. Nineteen patients met the criteria for the diagnosis of PPHN. Descriptive information for the 19 patients with PPHN is shown in Table 1. During the time period encompassed by these patients, hyperventilation with adjunctive alkali therapy (sodium bicarbonate) was generally the treatment for PPHN in this unit. Supportive therapy usually also included antibiotic coverage, intravascular volume expansion, pressors, sedation, and pancuronium. Only one infant received exogenous surfactant.

Sixty-six of the 233 (28.3%) P_{aO₂} values were obtained when the FiO₂ < 1.0 (FiO₂ range, 0.60–1.0), and P_{aO₂} was calculated to correct for the lower FiO₂ in these instances. In general, the correction was very modest, because the

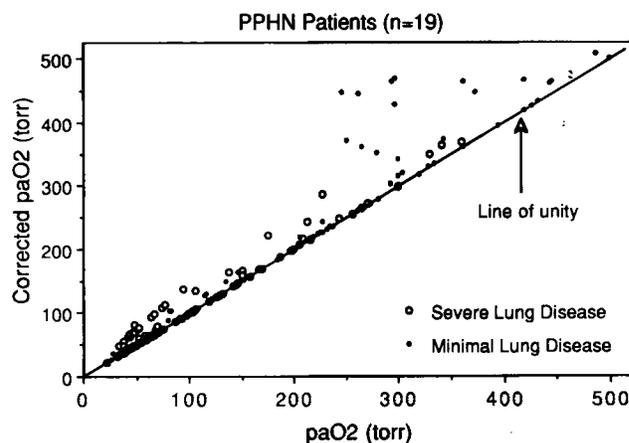


Fig. 1. Comparison of P_{aO₂} to corrected cP_{aO₂}. Magnitude of correction is vertical distance from any given point to line of unity. Large corrections result when P_{aO₂} is already high or when FiO₂ is well below 1.0.

FiO₂ was usually near 1.0 and/or the a/A ratio was quite low. Large corrections occurred only in the few instances when the P_{aO₂} was already high and the FiO₂ relatively low (Fig. 1).

In the 19 patients with PPHN, no correlation was found between mean airway pressure and cP_{aO₂} (mean slope ± SD = -8.42 ± 3082; P = 0.25; mean r = 0.01). A modest, but significant, correlation was found between pH and cP_{aO₂} (mean slope = 333.1 ± 480.5, P = 0.007, mean r = 0.38) in PPHN patients (Fig. 2).

After PPHN patients were categorized by the severity of radiographic lung disease the severe and minimal lung disease groups did not differ statistically during the first 6

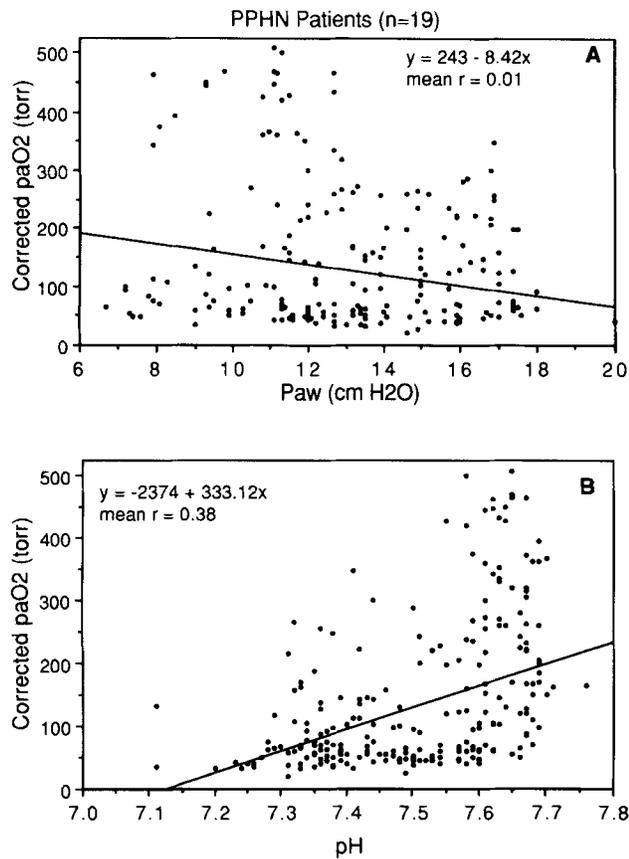


Fig. 2. Relationships between P_{aw} and cP_{aO_2} (A), and pH and cP_{aO_2} (B), in all patients fulfilling diagnostic criteria for PPHN. Regression equations, lines, and r values are the mean values obtained from individual correlations. There is a significant correlation based on mean slope between pH and cP_{aO_2} ($P = 0.007$) in PPHN patients as a group.

hours of life with respect to mean (\pm SD) P_{aO_2} (88 ± 55 vs. 83 ± 87), P_{aw} (11.35 ± 1.84 vs. 12.52 ± 2.53), or F_{iO_2} (0.92 ± 0.17 vs. 0.96 ± 0.15), respectively. However, the median pH was slightly lower when in the presence of severe lung disease was (7.37 vs. 7.49).

After radiographic stratification, no correlation was found between P_{aw} and cP_{aO_2} in patients with severe lung disease (mean slope = -7.40 ± 26.9 ; $P = 0.38$; mean, $r = -0.03$) or patients with minimal lung disease (mean slope = -9.83 ± 37.5 ; $P = 0.48$; mean $r = 0.05$) (Fig. 3). Conversely, in patients with severe lung disease and PPHN, there was no correlation between pH and cP_{aO_2} (mean slope = 92.10 ± 399.5 ; $P = 0.46$; mean $r = 0.20$), but if only minimal lung disease was present the correlation was strong (mean slope = 664.5 ± 385.8 ; $P = 0.002$, mean $r = 0.64$) (Fig. 4).

Of the 11 patients with PPHN and severe lung disease 7 eventually required ECMO, compared to only 2 of 8 in the PPHN/minimal lung disease group. Two patients with severe lung disease were treated with HFOV at 14.5 and

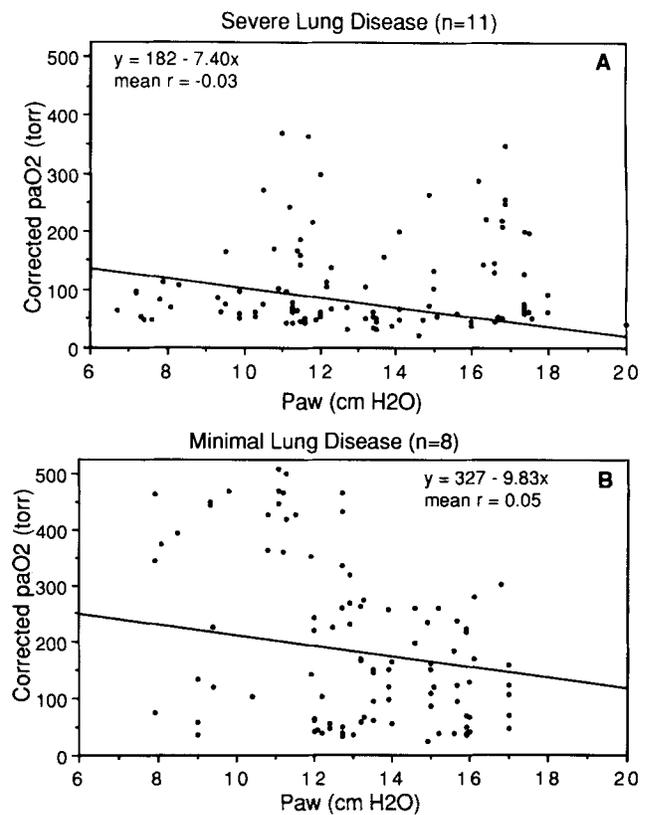


Fig. 3. Relationship between P_{aw} and cP_{aO_2} in patients with severe lung disease (A) and minimal lung disease (B) by chest radiography. Regression equations, lines, and r values are means obtained from individual correlations.

19 hours of life, and both were subsequently treated with ECMO within 3.5 hours. Blood gas data during ECMO or HFOV were not included in data analysis.

DISCUSSION

Drummond et al.⁸ convincingly showed a correlation between increased arterial pH induced by vigorous ventilation and increased P_{aO_2} in babies with pulmonary hypertension. Increased minute ventilation may be accomplished with increased, decreased, or unchanged P_{aw} . However, it seems likely that substantially increased P_{aw} will occur as respiratory support is increased while the diagnosis is confirmed and during early management of patients with PPHN. Then, depending on the approach of the clinician, further increases in P_{aw} might also occur during the hyperventilation process. Thus, some or all of the increase in P_{aO_2} attributed to alkalosis might actually be due to improved lung inflation and alveolar recruitment because of increased P_{aw} . This concurrent change was not considered for its possible effect on P_{aO_2} by Drummond. We attempted to examine the relationship of P_{aw} to P_{aO_2} in patients with PPHN.

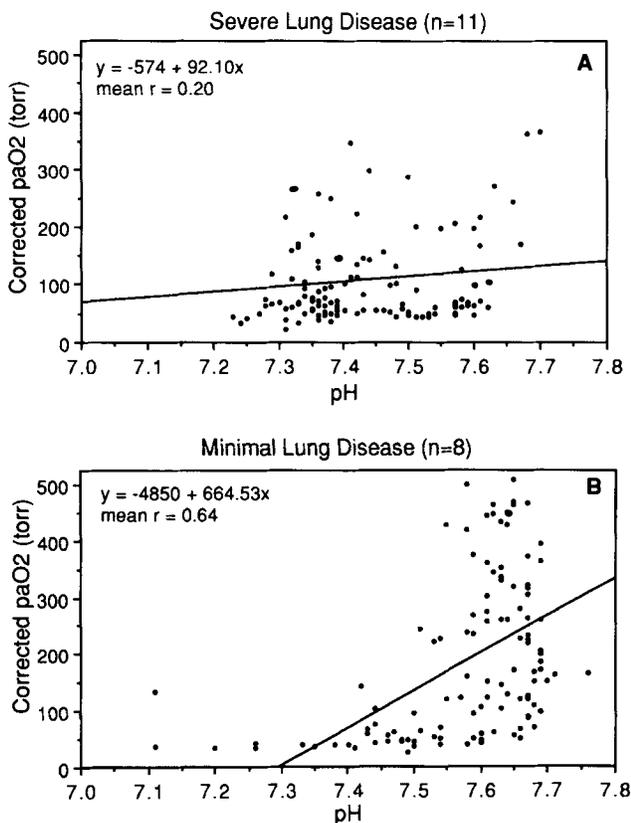


Fig. 4. Relationship between pH and $cP_{a_{O_2}}$ in patients with severe lung disease (A) and minimal lung disease (B) by chest radiography. Regression equations, lines, and r values are means obtained from individual correlations. There is a significant correlation in patients with minimal lung disease ($P = 0.002$).

Although previous studies have documented the effects of P_{aw} on $P_{a_{O_2}}$ in newborns with RDS,^{10,11} our data do not support the contention that increases of mean airway pressure during the management of patients with PPHN have a significant effect on $P_{a_{O_2}}$. The mean slope of regression lines did not differ significantly from zero. In addition, correlation coefficients from only 2 of 19 patients were greater than 0.50 (range, -0.78 – 0.56), and many (8 of 19) had negative r values.

Several explanations may account for the poor correlation between P_{aw} and $P_{a_{O_2}}$. Mean airway pressure can be changed in multiple ways, many of which may be ineffective at increasing $P_{a_{O_2}}$ depending on underlying lung disease, cardiac function, and other patient-specific factors. Thus, the benefit of one method of increasing P_{aw} might be obscured by other maneuvers which, although they increase P_{aw} , do not improve oxygenation. In addition, the mean airway pressures used in our patients rarely exceeded 18 cm H_2O , probably reflecting the general clinical management in this neonatal unit. This level may have been insufficient for adequate lung inflation

and alveolar recruitment, especially in the face of severe lung disease. Alternatively, the presence of extrapulmonary right to left shunting may be the predominant factor. Mean airway pressure effects on oxygenation would certainly require adequate pulmonary blood flow. If the increased P_{aw} did not improve pulmonary flow or ventilation-perfusion (\dot{V}/\dot{Q}) matching, oxygenation would not improve. Furthermore, the dynamic, variable nature of shunting during PPHN would make any correlation of P_{aw} and $P_{a_{O_2}}$ even more difficult to demonstrate.

This lack of correlation between P_{aw} and $P_{a_{O_2}}$ persisted when patients were divided based on the presence or absence of severe lung disease. A more specific categorization of patients by specific pulmonary diagnoses might be informative; however, the number of patients available for review was inadequate to allow this.

Persistent pulmonary hypertension has been associated with a wide spectrum of clinical conditions, yet there is a common tendency to lump PPHN patients together, with PPHN considered the principal clinical problem. The diversity of the associated cardiopulmonary conditions suggests that PPHN is not a single entity, but should be considered in the context of the concomitant conditions. Animal research supports the concept that the mechanisms of pulmonary hypertension are multiple.^{12–15} We attempted to ascertain the response to alkalosis of babies with PPHN who had either severe or minimal radiographic lung disease. This division was chosen based on the hypothesis that the mechanism of pulmonary hypertension in infants with severe lung disease is often alveolar hypoxia. These babies would, therefore, be expected to be less responsive to alkalosis because of a persistent hypoxic stimulus.

Patients with PPHN as a group showed a modest, statistically significant correlation between pH and $cP_{a_{O_2}}$. However, there was considerable individual variability in this relationship. After stratification based on severity of lung disease apparent on chest radiograph, the correlation between pH and $cP_{a_{O_2}}$ was much more pronounced in patients having minimal or no apparent lung disease (mean $r = 0.64$) than in patients with severe lung disease (mean $r = 0.20$) (Fig. 4). Patients with severe pulmonary parenchymal abnormalities were more resistant to the vasodilatory effects of hyperventilation/alkalosis therapy, suggesting different mechanisms of increased pulmonary vascular resistance.

It might be argued that the lack of response in the infants with severe abnormalities on radiographs is because these babies were more ill, in effect saying, "sicker babies do worse." We do not believe this explanation is representative of the pathophysiology of these two groups of infants. Based on the values of $P_{a_{O_2}}$, $F_{i_{O_2}}$, and P_{aw} during the first 6 hours of life, the two groups were comparable. In addition, although it was difficult to achieve a pH of 7.55 or greater in babies with severe

radiographic lung abnormalities, only 48% (11/23) of $cP_{a_{O_2}}$ values were greater than 100 torr when this pH level was achieved, as opposed to 83% (64/77) of $cP_{a_{O_2}}$ values in the minimal lung disease group ($P < 0.002$, chi square).

This lack of response to alkalosis in patients with severe lung disease is consistent with the hypothesis that different mechanisms are responsible for pulmonary hypertension in the two groups of patients. There are several obvious hypothetical categories into which patients with PPHN can be placed, in terms of mechanisms of pulmonary hypertension. Patients with mild radiographic parenchymal lung disease would likely be comprised of those with cardiac dysfunction, retained fetal lung fluid, so-called primary PPHN, and possibly sepsis without pneumonia. Although the mechanisms of pulmonary hypertension in these conditions probably differ, none of them would be likely to result in widespread alveolar hypoxia, especially in the face of vigorous ventilation. Without the potent pulmonary vasoconstrictive stimulus of alveolar hypoxia, the pulmonary vasodilatory effects of alkalosis would be more likely to be effective.

Patients with severe parenchymal lung disease would include infants with meconium aspiration syndrome, RDS, shock lung, or pneumonia. Despite vigorous mechanical ventilation, the most severe cases would have continued alveolar hypoxia due to diffuse microatelectasis, alveolar injury and edema, and/or airway obstruction. Atelectasis and alveolar hypoxia in experimental models¹⁶ increase pulmonary vascular resistance and pulmonary artery pressure. This response is crucial in matching ventilation and perfusion to maintain oxygenation, but when diffuse severe alveolar disease is present, elevated pulmonary vascular resistance, \dot{V}/\dot{Q} mismatch, and right-to-left shunting are common. Alkalosis will attenuate but not abolish pulmonary vasoconstriction if alveolar hypoxia is still present¹⁷; thus the clinical response to alkalosis would be poor.

In the group of patients with severe lung disease, it can be argued that pulmonary hypertension is the pathologic exaggeration of a "normal" response to the condition of the lungs. Indeed, in the initial description of "PFC Syndrome," Gersony et al.¹ stated that the condition "represents a diagnosis of exclusion and is to be distinguished from right-to-left shunting in association with pulmonary disease." Early studies on premature infants with RDS documented that nearly half of these infants exhibited right-to-left ductal shunting, which resulted in a pre/post-ductal $P_{a_{O_2}}$ difference of 20 torr or greater.^{18,19} By today's standards, this is generally adequate to make a diagnosis of PPHN. This high proportion of infants having clear evidence of PPHN documents that pulmonary hypertension is very common in the presence of RDS. In addition, these findings suggest that some degree of pul-

monary hypertension is the rule rather than the exception with RDS, and it is merely the severity of the pulmonary hypertension in any given case that determines whether a baby is considered to have straightforward RDS or RDS with PPHN. Furthermore, if pulmonary hypertension is indeed a usual accompaniment of severe pulmonary disease, the question arises of whether or not one should attempt to specifically treat this secondary phenomenon. The development of more effective methods of managing severe lung disease in newborns may be the most important factor in treating PPHN; as the lung disease improves, the resolution of the concomitant pulmonary hypertension will follow.

Other forms of severe lung disease may have different or even multiple mechanisms of pulmonary hypertension at work. Pulmonary hypertension in infants with pneumonia and sepsis may be the result of both alveolar hypoxia and vasoactive substances affecting pulmonary vascular tone^{12,13} and cardiac function. Infants with congenital diaphragmatic hernia or pulmonary hypoplasia, not represented in our patients, likely have pulmonary hypertension due pulmonary vascular remodeling.

The marked difference in the response to alkalosis in our two groups of patients is consistent with these clinical categories. This difference in responsiveness may also have implications for therapy. Low likelihood of response to increased pH during conventional mechanical ventilation, difficulty in hyperventilation, and the possibility that pulmonary hypertension is a "naturally" occurring and reversible part of severe lung injury provide substantive arguments against the use of hyperventilation unless adequate oxygenation cannot be maintained with conventional ventilatory techniques.

In conclusion, no demonstrable effect of mean airway pressure (up to P_{aw} of 18 cm H₂O) on oxygenation was noted during conventional mechanical ventilation in patients with PPHN, regardless of the degree of radiographic lung disease present. The response of these patients to alkalosis, however, differed based on underlying radiographic lung disease. Thus, the management of patients with PPHN should take into account the concomitant cardiopulmonary diseases, likely pathophysiologic mechanisms of PPHN, and the likelihood of positive response to any therapy, particularly hyperventilation.

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