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Ventilatory control and supplemental oxygen in premature infants with apparent chronic lung disease

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Abstract

Objectives—Our goal was to evaluate changes in respiratory pattern among premature infants born at less than 29 weeks gestation who underwent a physiologic challenge at 36 weeks post-menstrual age with systematic reductions in supplemental oxygen and inspired airflow.

Study Design—Subjects were all infants enrolled in the Prematurity and Respiratory Outcomes Program at St. Louis Children's Hospital and eligible for a physiologic challenge protocol because they were receiving supplemental oxygen or augmented airflow alone as part of their routine care. Continuous recording of rib cage and abdominal excursion and hemoglobin oxygen saturation (SpO₂%) were made in the newborn intensive care unit.

Results—Thirty seven of 49 infants (75.5%) failed the challenge, with severe or sustained falls in SpO₂%. And 16 of 37 infants (43.2%) who failed had marked increases in the amount of periodic breathing at the time of challenge failure.

Conclusions—An unstable respiratory pattern is unmasked with a decrease in inspired oxygen or airflow support in many premature infants. Although infants with significant chronic lung disease may also be predisposed to more periodic breathing, these data suggest that the classification of chronic lung disease of prematurity based solely on clinical requirements for supplemental oxygen or airflow do not account for multiple mechanisms that are likely contributing to the need for respiratory support.

Keywords

bronchopulmonary dysplasia; chronic lung disease; prematurity; hypoxemia; periodic breathing

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INTRODUCTION

Clinical manifestations of chronic lung disease of prematurity (CLD), also known as bronchopulmonary dysplasia, have changed over the last 45 years.^{1,2} CLD has been defined by persistence of a supplemental oxygen requirement at 36 weeks post-menstrual age (PMA) among infants born before 32-weeks gestation who usually have persistent respiratory symptoms and chest radiograph changes. Historically, chronic lung disease of prematurity has been considered a consequence of lung immaturity and lung injury caused by immature surfactant production, incomplete alveolarization, oxygen toxicity, barotrauma, and infection.³ Despite important advances in treatment, many infants still require supplemental oxygen at 36 weeks PMA.

Infants with CLD have long-term respiratory morbidity with higher rates of re-hospitalization and are more likely to require respiratory medications during the first year of life. The cost for treatment of CLD in the United States in 2005 exceeded \$2 billion.^{4,5}

Although supplemental oxygen use has come to be synonymous with CLD,⁶ this conventional definition has limitations. While a persistent supplemental oxygen requirement may indicate that a newborn has only airway or alveolar disease, unstable ventilatory control can lead to hypoxemia that will also respond to supplemental oxygen support.⁷⁻¹¹ In some studies, lengthy periods of spontaneous periodic breathing were recorded in more than half of premature subjects.^{12,13}

This paper describes a single-center study within the Prematurity and Respiratory Outcomes Project (PROP), a multicenter study intended to identify genetic modifiers and biomarkers that will lead to targeted therapies for CLD. We examined breathing patterns during a systematic reduction in supplemental oxygen and flow in 49 consecutive preterm infants prescribed supplemental oxygen or airflow support for hypoxemia, and who met current clinical criteria for CLD. We assessed the prevalence of unstable ventilatory control to determine how often it might contribute to the child's hypoxemia. These findings suggest a more complete phenotypic description of CLD is needed when gas exchange is altered, a step that is critical to identifying mechanistic factors and understanding the degree of involvement of alveolar and airway disease, or immature ventilatory control.

EXPERIMENTAL METHODS

PATIENTS

From August 12, 2011 to July 30, 2013, one hundred twenty-four (124) consecutive neonates born between 24 and 28-weeks gestation were enrolled prospectively at Saint Louis Children's Hospital, one of the 7 centers participating in the National Institutes of Health-supported PROP. At 36 weeks PMA, the age at which the diagnosis of CLD is typically assigned, infants receiving supplemental oxygen or airflow support via nasal cannula were eligible to undergo a physiologic challenge, to confirm that without supplemental oxygen or augmented airflow their SpO₂% would be unacceptably low and consistent with a diagnosis of CLD. Infants requiring mechanical ventilation or those

deemed unstable by the clinical care team were excluded. The type and degree of support were chosen by the clinical care team without predetermined criteria. (Figure 1)

Informed consent was obtained from the parents of each participant. The study was approved by the Washington University Human Research Protection Office and the PROP Observational Study Monitoring Board.

RESPIRATORY OUTCOME MEASURES

At 36 weeks PMA, infants receiving supplemental oxygen or airflow support via nasal cannula at fraction of inhaled oxygen (FiO_2) of 0.21 underwent a physiologic challenge protocol according to the PROP Manual of Procedures.¹⁴

Infants were studied in the supine position, and the study was initiated with infants in behaviorally defined quiet sleep.^{15,16} During a 5-minute run-in period, the infant received the FiO_2 and airflow rate prescribed by the clinicians supervising care. $SpO_2\%$ was recorded continuously using a NONIN^R pulse oximeter (NONIN Medical, Inc., Minneapolis, MN). In response to a change in arterial oxyhemoglobin saturation ($SaO_2\%$), the oximeter has an effective averaging time in newborns of 1.5 to 3.0 sec, depending on the pulse rate.

Respiratory inductance plethysmography (RIP) was recorded (Biocapture, Cleveland Medical Devices, Cleveland, OH), by placing elastic bands around the infant at the nipple line and the umbilicus,^{17,18} during the run-in period, when the infant received prescribe FiO_2 and flow, and during the challenge period. Data describing $SpO_2\%$, percent of quiet sleep time in periodic breathing (%PB), and minute ventilation during quiet sleep from QDC-calibrated RIP,¹⁸ were compared before and during the challenge.

RIP was also used to provide an index of the severity of respiratory system disease. The degree of Rib Cage vs. Abdomen Dyssynchrony over 60 breaths for each infant was described by a phase angle (ϕ) calculated from the plot of Rib cage vs. Abdominal excursion.^{17,19} Healthy term infants have ϕ near 12 degrees during quiet sleep.²⁰

After the 5-minute run-in, FiO_2 was reduced to 0.21 in steps by 0.20 or less, followed by wean of airflow provided by nasal cannula. Each step down in FiO_2 was observed for 5 minutes, each step down in flow for 10 minutes. Failure at any step in the weaning protocol resulted in termination of the challenge with resumption of the prescribed support. If the infants tolerated all decrements of support during the weaning period, an observation period of up to 60 minutes ensued with the infant breathing only ambient room air. **Physiologic challenge failure was defined** as $SpO_2 < 90\%$ for five consecutive minutes within any step in the challenge, or $SpO_2 < 80\%$ for 15 consecutive seconds. If the infant did not worsen to meet criteria for failure during the 60-minute observation, he or she was deemed to have passed the room air challenge (RAC). In most instances we refer to the challenge as a “physiologic” challenge, rather than RAC, because many infants failed before breathing room air alone.

MEASUREMENTS DURING PHYSIOLOGIC CHALLENGE

Relative changes in minute ventilation were calculated from QDC-calibrated RIP.¹⁸ Periodic breathing (PB) was defined as at least 3 central apneas lasting at least 3 seconds separated by fewer than 20 seconds of regular breathing.²¹

Minute ventilation and percentage of time with PB for the entire run-in period were compared to the final minutes of the challenge. For minute ventilation, the 5-minute run in period was compared to the last minute of the challenge (failure, or completion). For PB, the percent of time in PB for the 5-minute run in was compared to the percent during the last 3 minutes before failure or completion of challenge. Some infants were still receiving caffeine as prescribed by the clinical team, and its potential impact on PB and challenge failure was also analyzed. Caffeine levels were not routinely measured in these infants or in our NICU, in general.

STATISTICAL MEASUREMENT AND COMPARISONS

Kruskal-Wallis test was used for comparison of caffeine effect among each of 3 groups. Categorical comparisons based on passing or failing the challenge were done by Chi square. Statistical significance was defined as $p < 0.05$.

RESULTS

One hundred twenty-four infants were enrolled (Figure 1). Three infants failed during the run-in period when continuous recordings showed that the prescribed support did not maintain SpO₂% in the passing range. Forty-nine infants underwent the challenge (Table 1). Twelve infants (24.5%) maintained oxygen saturations for 60 minutes of observation breathing room air alone and passed the RAC. Five infants had PB during the run-in period while on prescribed support before the challenge (range 5.1 to 102.0 seconds of PB, 1.7% – 34.0% of 5 minute period). Two of these did not maintain adequate SpO₂% during the run-in period and were not tested further. Seventeen infants displayed more PB during the physiologic challenge, and 16 of these infants failed. (Figure 2) These 16 represented 43.2% of infants failing the challenge. The increase in percent of time with periodic breathing during the challenge, for those showing an increase, was $48.6 \pm 21.6\%$ (range 15.0% to 100.0%) That is, a hypothetical infant with 1 minute of PB during the 5 minute run in period (20% of recording time) and 2 minutes of PB during the last 3 minutes of the challenge (67% of the time) would have had an increase by 47 in the percent of recording time with PB.

Because caffeine treatment may limit periodic breathing, we assessed the impact on PB of caffeine use, retrospectively. Six infants were treated with caffeine at the time of the challenge (12.2% of subjects); 4 of 6 passed the RAC without any PB; the 2 failing while on caffeine had 33% and 41% increases in the % of time with PB, but the caffeine concentrations were not measured. Thus, while only 12.2% of subjects were receiving caffeine at the time of the challenge, they accounted for 33.0% of those passing (4 of 12).

The number of days since caffeine had been discontinued was not different among infants failing without periodic breathing, passing the RAC, or failing with increased periodic

breathing (Kruskal-Wallis, $p = 0.73$, medians, 11.2 days, 11.6 days, and 10.7 days without caffeine at the time of challenge).

Seven of 37 infants failing the challenge had an increase in QDC-calibrated minute ventilation during challenge, with 3 of 12 infants passing the challenge also showing increased minute ventilation. (Table 2, figure 3)

Analysis of the impact of birth weight, gestational age, PMA, gender, and level of support on rates of passing and failing the challenge is best left to evaluation of the much larger sample from the multi-center PROP cohort. The size of our single center sample did not permit sufficient statistical power for subgroup comparisons. In our sample of only 49 subjects, however, those passing did not differ statistically from those failing by birth weight ($p=0.09$), gestational age ($p=0.51$), the diagnosis of intraventricular hemorrhage using ultrasonography (Chi square with Fisher exact test, $p = 0.32$), PMA ($p = 0.60$), gender (Chi square, $p = 0.62$) or FiO_2 ($p = 0.30$). Those failing had higher flow rates prescribed before the challenge started (0.4 vs. 1.1 lpm, $p = 0.01$). Sixteen infants failed with increased periodic breathing; the subgroup failing at 36 weeks PMA with more PB had slightly lower mean gestational age than those 12 infants who passed the RAC, but this did not reach statistical significance ($p = 0.10$, 95% confidence limits of difference, -1.8 weeks to 0.2 weeks). To the extent that PB leads to clinically recognized apnea, these findings are consistent with a later resolution of apnea among infants born earlier.²²

Although none of the infants was intubated or receiving mechanical ventilatory support at 36 weeks PMA, they are likely at considerable risk for CLD (Table 1). The median duration for mechanical ventilation was 12.0 days. Many also had marked RC-ABD dyssynchrony with a mean ϕ in the range described for preterms with BPD.²⁰

DISCUSSION

In this study, we show that a large proportion of premature infants who meet clinical criteria for CLD, defined by supplemental oxygen or augmented airflow use at 36 weeks PMA, had unstable control of breathing that was unmasked during the physiologic challenge. Unstable ventilatory control may contribute to the inability of the clinical teams to further decrease the flow or FiO_2 . Specifically, we show that 32.7% of the infants studied treated with supplemental oxygen and airflow support at 36 weeks PMA need nasal cannula support at least in part due to periodic breathing and periodic apnea, and only 16.0% of infants who failed the challenge demonstrated a potentially beneficial response to hypoxemia by increasing minute ventilation. Furthermore, we show that 24.5% of infants receiving supplemental oxygen and airflow via nasal cannula at the time of the challenge were able to tolerate room air in the short term, using PROP criteria.^{14,23}

These results have important implications for study design and subject selection for future investigations that attempt to define the pathophysiological bases of CLD phenotypes. Within PROP, which is designed to identify clinical risk factors and candidate biomarkers for CLD among infants born between 24 and 28-weeks PMA, we suspect that the current clinical definition of CLD will complicate our studies, because the need for supplemental

oxygen support at 36 weeks PMA may be multifactorial and reflect an interaction between parenchymal dysfunction due to lung disease and immature respiratory control. Infants with significant CLD may also be particularly susceptible to developing PB when they become hypoxic with even brief central apneas.^{24,25} Some of the infants studied had marked chest wall dyssynchrony (Table 1) in addition to requiring supplemental O₂ suggesting that significant respiratory system compromise contributed to their propensity for desaturation during PB. Some infants meeting clinical criteria for CLD did in fact tolerate room air when evaluated using a formal protocol, while others showed an immature respiratory pattern such as PB that worsened during hypoxemia but that can be corrected with supplemental oxygen. A more physiologic definition of CLD is needed to ensure that mechanistic biomarkers being evaluated are actually linked to parenchymal lung disease, and to distinguish these infants from those that are otherwise well, or have hypoxemia for different reasons.²

Correction of respiratory pattern with supplemental O₂ may be particularly applicable to infants born at the earliest gestational ages who otherwise would be expected to have higher rates of CLD.

Based on published reports,²³ we expected that some subjects would pass RAC and thus not have CLD as currently defined, which was the case (24.5% passed RAC). However, the high frequency of challenge failures in infants who developed periodic apnea with characteristic oscillations in oxyhemoglobin saturations was not anticipated, even though supplemental oxygen therapy has been shown to stabilize breathing patterns in preterm infants who have PB.^{26,27} Thus, although the association of PB and hypoxemia is established, the frequency with which PB might contribute to the need for supplemental O₂ among a group of infants at risk for CLD has not previously been quantified.

In this regard, it is likely (Figure 2 with oscillations) that observations made at the crib side, even by experienced nurses and clinicians, do not reliably identify infants that have altered breathing pattern causing hypoxemia, leading to under recognition of this phenomenon in the intensive care nursery. The frequent occurrence of intermittent hypoxemia during PB, but before physiologic challenge criteria for sustained hypoxemia were met, is demonstrated in the first minutes of the tracing in Figure 2. RIP scalar tracing allowed us to continuously capture respiratory patterns clearly over many minutes, and provided a record of respiratory pattern that can quickly be reviewed.

Five of our 52 subjects potentially eligible for the challenge study displayed PB while on their prescribed support, and 2 of these 5 infants failed to maintain passing SpO₂% during the run-in period. A limitation of this study is that we did not record respiratory pattern for longer periods before reducing supplemental oxygen support, and it is possible that other infants in our cohort may have substantial PB on prescribed support that was not captured before the challenge.

We speculate that our findings may be relevant to the thus far unexplained observation from a large study showing that prior therapy with caffeine reduced the rate of BPD among treated premature infants.^{28,29} A plausible mechanism for the reduced need for supplemental oxygen in the group randomized to caffeine therapy before 36 weeks PMA would be that

caffeine reduced rates of periodic breathing and apnea in these subjects, perhaps by accelerating the development of stable respiratory control.^{30–33}

Other sites within the PROP collaborative did not routinely record respiratory pattern using RIP during the challenge, but it would be surprising if our findings were not generalizable and applicable to the larger cohort, given the clear propensity of premature infants to develop PB^{10–13,21,22}

In conclusion, we want to emphasize that unstable control of breathing is common in premature infants who met clinical criteria for CLD. Unstable respiratory patterns may occur alone or in conjunction with airways and airspace diseases in many infants born between 24 and 28-weeks gestation, and contribute to the supplemental oxygen requirement at 36 weeks PMA. The role of PB and immature breathing patterns must be considered if we are to better understand the real contribution of lung disease to hypoxemia in premature infants.

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Glossary

List of Abbreviations	CLD, chronic lung disease
NICU	Neonatal intensive care unit
FiO₂	fraction of inhaled oxygen
lpm	liters per minute air flow rate
PB	periodic breathing
PMA	post-menstrual age
PROP	Prematurity and Respiratory Outcomes Project
RAC	room air challenge
RIP	respiratory inductance plethysmography

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What is known about this topic

Infants born prematurely are said to have chronic lung disease if they require supplemental oxygen at 36 weeks post-menstrual age. These infants also sometimes have unstable respiratory patterns that can cause hypoxemia and that can be made more stable by treating them with oxygen.

What this study adds

This study quantifies the prevalence, in a small cohort, of the potential contribution of an unstable respiratory pattern to the need for supplemental oxygen. It shows that a substantial minority of infants with presumed chronic lung disease who cannot be weaned to room air during a physiologic challenge fail the challenge after developing periodic breathing.

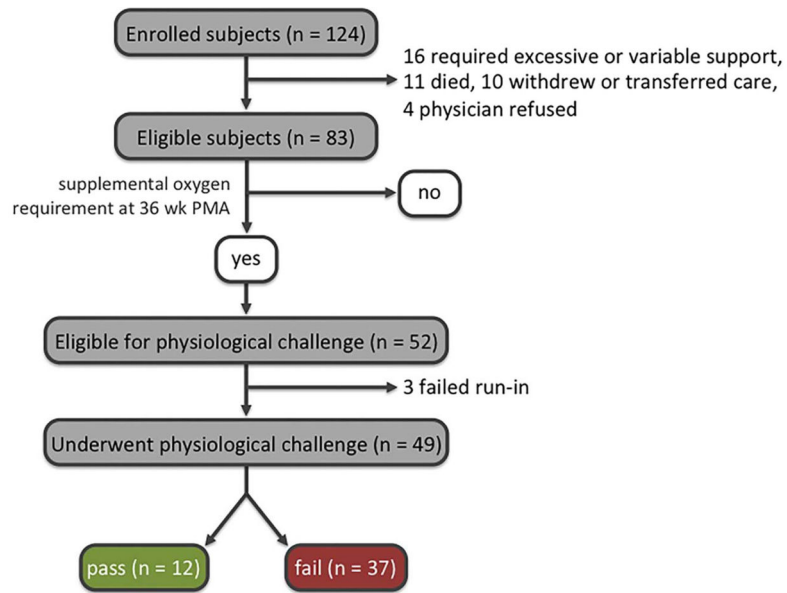


Figure 1. Subject enrollment and outcomes.

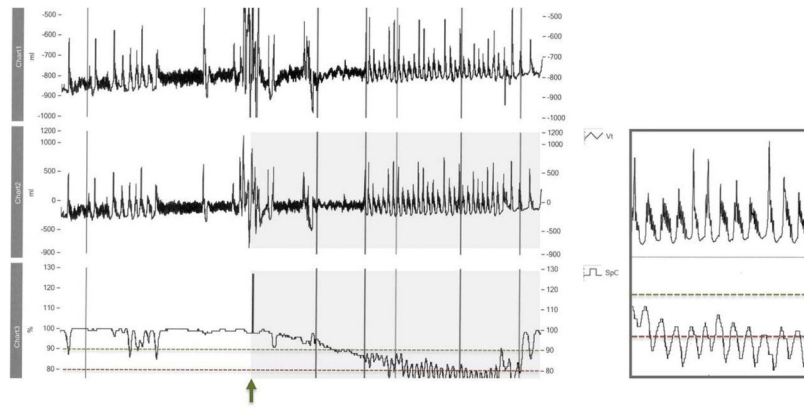


Figure 2.

Diagram showing a 5-minute recording from a patient who failed the challenge. The upper 2 tracings show respiratory excursions. The lowest tracing is SpO₂% averaged every 3 to 5 sec. Note the stable SpO₂% > 90% when respirations are regular. Note the intermittent hypoxemia and characteristic oscillations in SpO₂% seen with the brief run of periodic breathing early in the tracings, and the continuous oscillations when PB is established. This pattern occurred in 43.2% of challenge failures. For this subject, continuous periodic pattern was associated with failure-range falls in SpO₂% to < 80%.

First vertical mark: challenge begun, followed by brief run of periodic breathing. 2nd vertical mark: quiet sleep. 6th vertical mark: RAC failure was declared. The smaller box is an enlarged 30 sec excerpt from between vertical marks 5 and 6.

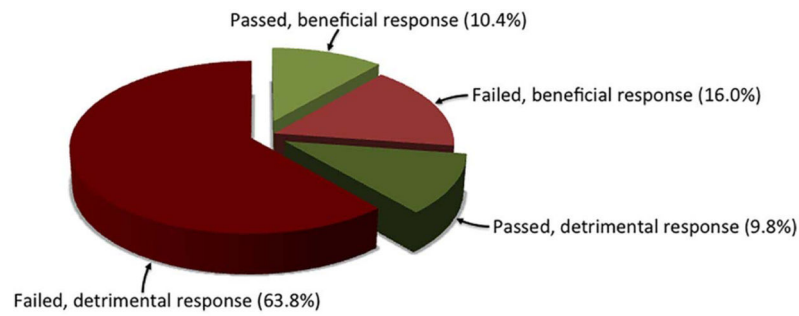


Figure 3. Prevalence of changes in minute ventilation and respiratory pattern among infants receiving the physiologic challenge. The majority of infants (73.6%), whether they passed or failed, either developed PB or did not increase their minute ventilation, or both, in response to the challenge. Potentially beneficial response defined as increase in minute ventilation and no periodic breathing. Potentially detrimental, or dysfunctional, response is no change or reduction in minute ventilation, much periodic breathing, or combination of failure to increase minute ventilation while having periodic breathing.

TABLE 1

Descriptive statistics for infants undergoing physiologic challenge: birth weight, gestational age, post-menstrual age, gender, FiO₂, Flow rate for air and O₂ delivered by nasal cannula, days receiving mechanical ventilation, and phase angle (φ) as a measure for rib cage-abdominal dyssynchrony. The use of 100% O₂ via nasal cannula at flow < 1 liter per minute among infants at 36 weeks PMA is a common practice in St. Louis Children's Hospital NICU

Birth weight	837 ± 168 grams (range, 400 to 1160]
Gestational age	26 2/7 ± 12/7 weeks
Post-menstrual age	36 2/7 ± 4/7 weeks
Females	31 (63.3%)
FiO₂	0.7 ± 0.4
Supplemental O₂ flow rate	1.0 ± 1.1 lpm (median 1.0 lpm, range 0.06 to 5.0 lpm)
Days on Mechanical Ventilation	Median 12.0 days, range 0 to 62 days
Phase Angle φ	78.3 ± 42.1, range 12.2 to 157.8 degrees

TABLE 2

Comparison of changes in minute ventilation and changes in percent of sleep time with periodic breathing between those passing and those failing the physiologic challenge

	Pass (n=12)	Fail (n=37)
Minute volume increased	3	7
Periodic breathing		
During run-in	0	3
Increased during Challenge	1	16
None or reduced during Challenge	11	21

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