Use of Neonatal Chest Ultrasound to Predict Noninvasive Ventilation Failure

AUTHORS: Francesco Raimondi, MD, PhD,a Fiorella Migliaro, MD,a,1 Angela Sodano, MD,a Teresa Ferrara, MD,a Silvia Lama, MD,a Gianfranco Vallone, MD,b and Letizia Capasso, MD2
1Division of Neonatology, Section of Pediatrics, Department of Translational Medical Sciences, and 2Division of Pediatric Diagnostics, Department of Biomorphological and Functional Sciences, Università “Federico II,” Naples, Italy

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abstract

BACKGROUND: Noninvasive ventilation is the treatment of choice for neonatal moderate respiratory distress (RD). Predictors of nasal ventilation failure are helpful in preventing clinical deterioration. Work on neonatal lung ultrasound has shown that the persistence of a hyper-echogenic, “white lung” image correlates with severe distress in the preterm infant. We investigate the persistent white lung ultrasound image as a marker of noninvasive ventilation failure.

METHODS: Newborns admitted to the NICU with moderate RD and stabilized on nasal continuous positive airway pressure for 120 minutes were enrolled. Lung ultrasound was performed and blindly classified as type 1 (white lung), type 2 (prevalence of B-lines), or type 3 (prevalence of A-lines). Chest radiograph also was examined and graded by an experienced radiologist blind to the infant’s clinical condition. Outcome of the study was the accuracy of bilateral type 1 to predict intubation within 24 hours from scanning. Secondary outcome was the performance of the highest radiographic grade within the same time interval.

RESULTS: We enrolled 54 infants (gestational age 32.5 ± 2.6 weeks; birth weight 1703 ± 583 g). Type 1 lung profile showed sensitivity 88.9%, specificity 100%, positive predictive value 100%, and negative predictive value 94.7%. Chest radiograph had sensitivity 38.9%, specificity 77.8%, positive predictive value 46.7%, and negative predictive value 71.8%.

CONCLUSIONS: After a 2-hour nasal ventilation trial, neonatal lung ultrasound is a useful predictor of the need for intubation, largely outperforming conventional radiology. Future studies should address whether including ultrasonography in the management of neonatal moderate RD confers clinical advantages. Pediatrics 2014;134:e1089–e1094

WHAT’S KNOWN ON THIS SUBJECT: Lung ultrasound outperforms conventional radiology in the emergency diagnosis of pneumothorax and pleural effusions. In the pediatric age, lung ultrasound has been also successfully applied to the fluid-to-air transition after birth and to rapid pneumonia diagnosis.

WHAT THIS STUDY ADDS: Nasal ventilation has dramatically decreased the need for invasive mechanical respiratory support. This study demonstrates that, after a short trial on nasal continuous positive airway pressure, lung ultrasonography reliably predicts the failure of noninvasive ventilation unlike the conventional chest radiogram.
Chest ultrasound has recently been applied with success in different settings of adult medicine, ranging from cardiopulmonary emergencies and trauma surgery to the care of pre-eclamptic women or patients with renal failure.\(^1\)–\(^4\)

A systematic ultrasound semiology has been validated across a wide span of ages using both chest anatomic structures (ie, the ribs or the pleural line) and artifactual images, such as the B-lines, that are discrete, laserlike vertical hyperechoic reverberations arising from the pleural line. Multiple diffuse bilateral B-lines are suggestive of interstitial syndrome (eg, pulmonary edema, interstitial pneumonia, diffuse parenchymal lung disease)\(^5\) (Fig 1A). In the neonate, one can accurately differentiate the aerated dry lung, appearing as uniform hypoechogenic pattern, sliding with respiration and often showing horizontal reverberations of the pleural image (the A-lines) (Fig 1B) from the hyperechogenic “white” pattern of the markedly “wet” or inflamed organ (Fig 1C)\(^6\)–\(^8\).

Noninvasive ventilation (NIV) is widely used for the treatment of moderate respiratory disease of the newborn to stabilize spontaneous breathing while avoiding the complications of invasive ventilation.\(^9\),\(^10\) NIV-assisted infants are more easily accessed by parents and health care givers, allowing an optimization also of nonventilatory strategies. However, clinical monitoring of these infants is needed, as some will progressively show increased respiratory effort and/or deterioration of blood gas exchange requiring endotracheal intubation, surfactant administration, and mechanical ventilation. At present, there is a need for reliable predictors of NIV failure that would spare the infant becoming exhausted from ineffective breathing. As clinics and chest radiographs are often discordant in grading the severity of neonatal respiratory distress syndrome, conventional radiology is often of little help. On the other hand, the persistence of a “white-lung” ultrasound image has been shown to correlate with clinical respiratory distress (RD) in preterm infants.\(^11\) In the present study, we hypothesized that this marker may predict the failure of nasal continuous positive airway pressure (nCPAP) in aerating the premature lung, heralding the need for a more invasive approach.

**METHODS**

The study was conducted from December 2012 to July 2013 in a level 3 hospital with 2400 total births per year. The investigation received permission from the local institutional review board and formal consent was obtained from the parents. Newborns were enrolled if admitted to the NICU for moderate RD and treated with nCPAP. These criteria included infants of any degree of prematurity who had mild symptoms (tachypnea, shallow breathing, grunting, nasal flaring, sub- and intercostal retractions) before stabilization on nCPAP (+4–5 cm H\(_2\)O and FiO\(_2\) <0.4 to keep oxygen saturation in the 92%–96% range, with a respiratory rate <60/min and pH >7.28, PaO\(_2\) >50 mm Hg, PaCO\(_2\) <60 mm Hg).\(^12\) Infants with major congenital malformations and those intubated in the delivery room or within 20 minutes after admission to the NICU were excluded from the study.

Failure of NIV was defined as endotracheal intubation and surfactant administration (Curosurf, Parma, Italy; 200 mg/kg) without attempting further NIV strategies. This procedure was eventually performed by the attending neonatologist, who was blind to the study, in case chest dynamics were deteriorating (evidence of severe upper/lower chest or xyphoid retractions, marked nares dilatation, or expiratory grunting) and/or if the infant failed to maintain adequate blood gas values as reported previously.

At admission, infants were placed on nCPAP in an incubator and vascular access was established. After 120 minutes from nCPAP application, lung ultrasound images were acquired scanning each lung in the anterior and lateral projections with the infant in the...
supine position. This time point was chosen because it is the conventional time limit for early versus late surfactant rescue\(^\text{13}\) and because of experimental animal evidence that lung fluid clearance is accomplished in 2 hours.\(^\text{14}\)

A broadband linear transducer (mod L12–5; Philips, Eindhoven, Netherlands) that encompasses the superior and inferior lung fields in the same image was used. Images were classified as type 1 (white lung), type 2 (prevalence of B-lines), and type 3 (prevalence of A-lines), as previously described.\(^\text{15}\)

Chest radiographs were acquired in the same time frame with a portable device (Practix 33 plus; Philips, Eindhoven, Netherlands) at the infant’s incubator. Images were classified as grade 1 (fine homogeneous ground glass shadowing), grade 2 (addition of widespread air bronchograms), grade 3 (development of confluent alveolar shadowing), and grade 4 (complete white-out of the lung fields with obscuring of the cardiac border in the most severe cases).\(^\text{16}\)

To ensure proper blinding, lung ultrasound scans and chest radiographs were coded when acquired in the NICU and classified as previously described by an experienced pediatric radiologist who was blind to the infants’ clinical condition. Blind evaluation of coded lung scans was also performed by an experienced neonatologist to assess interobserver variability. The main outcome of the study was the accuracy of the sonographic profile with maximal echodensity (type 1 or white lung) to predict intubation within 24 hours from scanning. The secondary outcome was the accuracy of the highest radiographic grade to predict intubation within the same time interval.

**Statistics**

In a nursery setting,\(^\text{15}\) a type 1 lung ultrasound profile had a 77.7% sensitivity in predicting the need of ventilatory support shortly after birth. We calculated that a population of 54 preterm neonates was required to estimate the 99% confidence intervals (CIs) for a sensitivity of type 1 lung ultrasound profile of 85.0% ± 12.5%. We defined true-positive (TP) as type 1 and intubated; true-negative (TN) as type 2 or 3 and not intubated; false-positive (FP) as type 1 and not intubated; false-negative (FN) as type 2 or 3 and intubated. The specificity of the test was defined as TN/(TN+FP); sensitivity was TP/(TP+FN); positive predictive value (PPV) was TP/(TP+FP); negative predictive value (NPV) was TN/(TN+FN). Ninety-five percent CIs around measures of test characteristics were calculated by using the normal distribution mode, according to the following formula:

\[
\text{sample value} \pm 1.96 \times \text{standard error.}
\]

The \(\kappa\) coefficient was also provided to assess the interobserver variability. Our cohort was divided by gestational age (>29 weeks vs <29 weeks); \(P\) values to show differences between these groups were calculated by using Student \(t\) test for continuous variables and exact \(\chi^2\) test for categorical variables. A level of \(P < .05\) was chosen as statistically significant.

**RESULTS**

A total of 72 neonates presented with RD and were initially treated with nCPAP; 18 were excluded because of endotracheal intubation before entering the NICU (15 infants) or within 20 minutes from admission. Fifty-four infants were then enrolled in the study; their demographic characteristics are shown in Table 1. There was no significant difference between infants who succeeded or failed nCPAP (data not shown). Based on lung ultrasound scan after 120 minutes on nCPAP, 24 neonates were assigned to type 3, 12 to type 2, and 16 to type 1. The remaining 2 neonates showed a type 1 on one side and type 2 on the other. All newborns with either unilateral or bilateral type 1 were intubated after an average interval of 6 hours. No infant with type 2 or type 3 profile was intubated. In predicting failure of NIV, bilateral type 1 had the following accuracy: sensitivity 88.9% (CI 67.2–96.8), specificity 100% (CI 94.9–100), PPV 100% (CI 80.6–100), NPV 94.7% (CI 82.7–98.5).

On the basis of the chest radiograph, no infant was assigned to grade 4 or 3, whereas 15 neonates were assigned to grade 2 and 39 to grade 1. The accuracy of grade 2 to predict intubation was as follows: sensitivity 38.9% (CI 20–61.1), specificity 77.8% (CI 61.7–88.5), PPV 46.7% (CI 24.8–69.9), NPV 71.8% (CI 56.2–83.4). Concordance of ultrasound and radiographic results is shown in Table 2. There was full interobserver agreement in the images’ interpretation (\(\kappa = 1\)). The average duration of a complete ultrasound scan was 2.5 minutes and the examination was well tolerated by enrolled patients. All scans showed a normal pleural line and sliding sign; no air-leak syndromes were documented throughout the study.

<table>
<thead>
<tr>
<th>TABLE 1 Demographic Characteristics of the Study Cohort</th>
</tr>
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<tbody>
<tr>
<td>Characteristics GA &lt;29 wk n = 10 vs GA &gt;29 wk n = 44 P</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Mean birth weight, g (SD)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
</tr>
<tr>
<td>Apgar &lt;7 @ 1 min</td>
</tr>
<tr>
<td>Apgar &lt;7 @ 5 min</td>
</tr>
<tr>
<td>ROM &gt;12 h</td>
</tr>
<tr>
<td>Prenatal steroids, 2 doses</td>
</tr>
<tr>
<td>Failed nCPAP</td>
</tr>
<tr>
<td>(\text{PaO}_2) at intubation (SD)</td>
</tr>
<tr>
<td>(\text{PaCO}_2) at intubation (SD)</td>
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| GA, gestational age; N/A, not applicable; ROM, rupture of membranes. |
DISCUSSION

Our data show that, unlike the conventional radiograph, lung ultrasound can accurately predict those newborns with RD who will fail NIV (Fig 2). In the NICU setting, our work marks a novel approach to both neonatal respiratory management and lung ultrasonography. Previous authors had described ultrasound signs for hyaline membrane disease,11 transient tachypnea of the newborn,17 pneumonia,18 pneumothorax,19 and pleural effusion.20 We provide evidence to a functional application of lung ultrasound. This information is rapidly obtained at the bedside without any radiation exposure and can be acquired with a fairly steep learning curve.5 In the study by Shah et al,21 only 60 minutes of training was needed to accurately diagnose pneumonia in children, outperforming conventional chest radiographs. Using lung ultrasonography as an NIV failure predictor can be particularly useful for level 1 and 2 nurseries where limited respiratory support may be occasionally available but transferring a neonate to a level 3 NICU has to be carefully planned in advance.

There is a paucity of data on techniques or parameters that monitor RD reliably enough to predict intubation. A clinical-radiologic correlation was attempted by Kero and Mäkinen22 in 55 preterm infants (mean gestational age: 33 weeks) with mild, moderate, and severe RDS. It is not clear whether the investigation was properly masked, but they report a 38% general disagreement between clinical and radiologic criteria and only a 50% agreement rate on moderate RDS. The same radiologic criteria were used in association with clinical intubation predictors in a large retrospective cohort by Ammari et al.23 None of the 3 variables associated with CPAP failure (positive pressure ventilation at birth, an alveolar-arterial oxygen tension

TABLE 2 Concordance of Ultrasound and Radiographic Results

<table>
<thead>
<tr>
<th>Ultrasound Result</th>
<th>Radiographic Result</th>
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<tbody>
<tr>
<td></td>
<td>Grade 4</td>
</tr>
<tr>
<td>Type 1</td>
<td>0</td>
</tr>
<tr>
<td>Type 2</td>
<td>0</td>
</tr>
<tr>
<td>Type 3</td>
<td>0</td>
</tr>
<tr>
<td>Type 1/2</td>
<td>0</td>
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</tbody>
</table>

FIGURE 2

Compared chest ultrasound and radiograph of 31-week twins on CPAP because of moderate RD after birth. Twin 1 was intubated and received a surfactant dose; twin 2 transitioned to room air. Lung ultrasound showed uniform hyperechogenicity for twin 1 (B) and A-lines for twin 2 (D). Both radiographs showed ground glass opacity and bronchograms (A–C).
gradient >180 mm Hg and severe RDS on the initial chest radiograph) had a positive predictive value >55%. A different clinical predictor, such as the maximal oxygen requirement in the first 72 hours of life, was studied by Morosini and Davies in a retrospective cohort of 592 infants with a gestational age >32 weeks and any cause of RD. They found that a maximal FiO2 ≥0.5 gave a PPV of 60% and NPV of 100% (sensitivity = 0.93, specificity = 0.91) for need for intubation and intermittent positive pressure ventilation. From their data, however, it is unclear exactly when this maximal oxygen requirement was reached before intubation. The lack of this piece of information and of prospective validation are important limits to the practical application of this interesting article. Boo et al prospectively investigated 97 consecutive preterm infants (<37 weeks) with an unspecified level of nCPAP: pneumothorax and sepsis during treatment were significant CPAP failure predictors. In the adult, lung ultrasonography also has been proven a useful predictor of extubation failure but data in the pediatric or neonatal settings are currently lacking.

We acknowledge that our protocol has some limitations that restrict the immediate generalization of our results. First, by applying a narrow interval of CPAP (4–5 cm H2O), we might have included in the NIV failure group some infants who would have achieved a better lung recruitment with higher pressures. However, multiple CPAP adjustments would have required repeated ultrasound scans, which, in turn, represent a conspicuous intrusion into the routine clinical care and a threat to the study masking. We believe that investigating lung ultrasound changes in response to CPAP optimization is a clinically relevant topic for a separate study, as already attempted in the adult. In addition, a fixed CPAP level was used in some of the largest international, multicenter trials on continuous distending pressure. Although the Neocosur trial used 5 cm H2O, the COIN trial with 8 cm H2O documented a significant higher rate of air-leak syndromes, restricting the window of clinically useful pressures. Second, our series encompasses a wide range of birth weights. We feel, however, that the CPAP failure rate in our series (33%) is in keeping with current practices. Recent data from the Vermont Oxford Network regarding 200 very low birth weight infants report an early CPAP failure rate of 34.3%, with an upper quartile set at 46.2%.

**CONCLUSIONS**

Although NIV is an effective and gentle way of respiratory support in the preterm infant, it is not without limits or risks. At the bedside, lung ultrasonography is an accurate method for predicting the failure of NIV and it is advantageous over chest radiography.

**ACKNOWLEDGMENTS**

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