Ultrasonografía pulmonar para diagnosticar hemorragia pulmonar del recién nacido.
Xiao-Ling Ren, Wei Fu, Jing Liu, Ying Liu & Rong-Ming Xia.
Bayi Children’s Hospital, the Army General Hospital of the Chinese PLA, Beijing, China

OBJETIVOS: El objetivo de este estudio fue investigar la aplicación de la ecografía pulmonar para el diagnóstico de hemorragia pulmonar del recién nacido (HPN).

MÉTODOS: De julio de 2013 a junio de 2016, 157 neonatos fueron incluidos en el estudio. Se dividieron en dos grupos: un grupo de estudio de 57 recién nacidos, a quienes se les diagnosticó hemorragia pulmonar neonatal (HPN) de acuerdo con su historia clínica, manifestaciones clínicas y radiografías de tórax, y un grupo control de 100 neonatos sin enfermedad pulmonar. Todos los sujetos se sometieron a ultrasonido de pulmón en estado de reposo, posición supina, lateral o prona, realizado por un único médico experto. Los hallazgos ecográficos se compararon entre los dos grupos.

RESULTADOS: Los hallazgos principales de la ecografía pulmonar asociados a la HPN incluyeron consolidación pulmonar con broncograbado aéreo con una incidencia de 82,5%, signo de desgarramiento con incidencia de 91,2%, derrame pleural con incidencia de 84,2% (pleurocentesis confirmó que el líquido sangraba), atelectasia con incidencia de 33,3%, anomalías de la línea pleural, así como líneas A desaparecidas con una incidencia del 100%, y 11,9% de estos pacientes presentaron las principales manifestaciones del síndrome alveolar intersticial (AIS). El signo de destello mostró una sensibilidad del 91,2% y una especificidad del 100% en el diagnóstico de HPN.

CONCLUSIONES: La ecografía pulmonar es útil y confiable para el diagnóstico de HPH, que es adecuada para la aplicación de rutina en la unidad de cuidados intensivos neonatales.
Lung ultrasonography to diagnose pulmonary hemorrhage of the newborn

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To cite this article: Xiao-Ling Ren, Wei Fu, Jing Liu, Ying Liu & Rong-Ming Xia (2017) Lung ultrasonography to diagnose pulmonary hemorrhage of the newborn, The Journal of Maternal-Fetal & Neonatal Medicine, 30:21, 2601-2606, DOI: 10.1080/14767058.2016.1256997

To link to this article: http://dx.doi.org/10.1080/14767058.2016.1256997

Accepted author version posted online: 03 Nov 2016.
Published online: 22 Nov 2016.

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Lung ultrasonography to diagnose pulmonary hemorrhage of the newborn

Xiao-Ling Ren1,2*, Wei Fu2*, Jing Liu1,2*, Ying Liu1*, and Rong-Ming Xia1*

1Department of Neonatology and NICU, Beijing Chaoyang District Maternal and Child Health Care Hospital, Beijing, China and 2Department of Neonatology and NICU of Bayi Children’s Hospital, the Army General Hospital of the Chinese PLA, Beijing, China

Abstract
Objectives: This study was aimed to investigate the application of lung ultrasound for the diagnosis of pulmonary hemorrhage of the newborn (PHN).

Methods: From July 2013 to June 2016, 157 neonates were enrolled in the study. They were divided into two groups: a study group of 57 neonates, who were diagnosed with PHN according to their medical history, clinical manifestations and chest X-ray findings, and a control group of 100 neonates with no lung disease. All subjects underwent bedside lung ultrasound in a quiet state in a supine, lateral or prone position, performed by a single expert physician. The ultrasound findings were compared between the two groups.

Results: The lung ultrasound main findings associated with PHN included lung consolidation with air bronchograms with an incidence of 82.5%, a shred sign with an incidence of 91.2%, pleural effusion with an incidence of 84.2% (pleurocentesis confirmed the fluid was really bleeding), atelectasis with an incidence of 33.3%, pleural line abnormalities, as well as disappearing A-lines with an incidence of 100%, and 11.9% of these patients had the main manifestations of alveolar-interstitial syndrome (AIS). The shred sign exhibited a sensitivity of 91.2% and a specificity of 100% in diagnosing PHN.

Conclusions: Lung ultrasonography is useful and reliable for diagnosing PHN, which is suitable for routine application in the neonatal intensive care unit.

Keywords
Lung ultrasound, pulmonary hemorrhage, infants, newborn

Introduction
Pulmonary hemorrhage of the newborn (PHN) is a common severe and critical disease in newborn infants, and it has complicated etiologies, rapid progression and a high mortality rate [1,2]. Recently, great progress has been made in the treatment of PHN, but the mortality rate remains high. Rapid and accurate diagnosis is of great significance in guiding treatment and improving the prognosis of PHN patients. Until now, a diagnosis of PHN has been mainly based on the case history, typical clinical manifestations, arterial blood gas analysis and chest X-rays findings, while lung ultrasound has not been applied in the diagnostic protocol. Recently, ultrasounds have been used extensively and successfully in the diagnosis of many types of neonatal lung diseases, such as respiratory distress syndrome (RDS), pneumonia, atelectasis, meconium aspiration syndrome (MAS), transient tachypnea of the newborn (TTN) and pneumothorax, among others [3–9]. However, no studies have addressed PHN. Therefore, this study aimed to investigate the diagnostic value of lung ultrasonography for PHN.

Patients and methods

Patients
The institutional review board of the Army General Hospital of the Chinese PLA approved the study (protocol number 2011-LC-Ped-01). There was no consent needed from the patients because the ultrasound procedure is harmless to patients. From July 2013 to June 2016, 57 newborn infants with PHN and 100 neonates with no lung disease were enrolled in this study. All the enrolled patients were admitted to the Department of Neonatology and NICU of Bayi Children’s Hospital, which is affiliated to the Army General Hospital of the Chinese PLA (Beijing, China).

Instruments and examination method
A high-frequency linear 10–14 MHz probe (GE Voluson i or Logiq e; GE Medical Systems, Kretz, Austria) was used for ultrasound examinations. While in a quiet state, infants were positioned in a supine, lateral or prone position. The probe was perpendicular (the most frequently used) or parallel to the ribs, and each side of the lung was divided into three regions...
(anterior, lateral and posterior) by the anterior and posterior axillary lines. Each region of both sides of the lung was scanned, and the ultrasonic findings were recorded. All of the lung ultrasonography examinations were performed by one doctor. The clinical data were collected by different doctors, and the ultrasound operator was blinded to the clinical condition of the neonates.

Observation indices

The observation indices included pleural lines, A-lines, B-lines, interstitial syndrome, white lung, lung consolidation with an air bronchogram or fluid bronchogram, double lung point, and pleural effusion, which were defined as the following [10–18]: (1) Pleural line: the regular echogenic line under the superficial layers of the thorax moving continuously during respiration, while abnormal pleural lines were pleural lines that disappeared or had a thickened, irregular or coarse and indistinct appearance; (2) A-line: a series of echogenic, horizontal, parallel lines equidistant from one another below the pleural line; (3) B-lines: also known as ultrasound lung comets, are hyperechoic narrow-based artifacts spreading like laser rays from the pleural line to the edge of the screen; (4) Alveolar-interstitial syndrome (AIS): defined as the presence of more than three B-lines in every examined area; (5) White lung: defined as the presence of compact B-lines in the six areas without horizontal reverberation; (6) Lung consolidation: defined as areas of hepatization with the presence of air bronchograms and/or fluid bronchograms; an air or fluid bronchogram is caused by reflection of ultrasound beams in the air-filled or fluid-filled bronchi surrounded by consolidated tissue; (7) Shred sign: a shred sign appears when the border of an aerated lung and consolidated lung is not sharp; (8) Double point: Due to a difference in severity or the nature of pathological changes in different areas of the lung, a longitudinal scan shows a clear difference between the upper and lower lung fields; this sharp cut-off point between the upper and lower lung field is known as a double point; and (9) Pleural effusion: defined as anechoic-dependent collections limited by the diaphragm and the pleura.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 19.0 software (Wuxi, China) was used to statistically analyze the data. Fisher’s exact test was used to compare the positive rates of the ultrasound test results of the newborns of each group, and the specificity and sensitivity of the main test results for the diagnosis of PHN were calculated. A value of \( p < 0.05 \) indicated statistically significant differences. The information reported was evaluated by an expert.

Results

General information for the two groups

The perinatal clinical characteristics of the two groups are shown in Table 1.

The etiology and onset time of PHN

According to the case history, clinical manifestations and laboratory findings, it was hypothesized that the possible reasons for PHN were the following: severe intrauterine infection (pneumonias and/or sepsis) 19 cases (33.3%); severe fetal distress and/or birth asphyxia, 12 cases (21.1%); RDS, 12 cases (21.1%); MAS, 8 cases (14.0%); and postnatal sepsis and or disseminated intravascular coagulation (DIC), 6 cases (10.5%). The onset time was within 6 h after birth in 46 patients (80.7%), within 24 h after birth in 48 patients (84.2%), within 1 week after birth in 52 cases (91.2%), while only less than 10% of the cases (5 cases, 8.8%) occurred after 1 week of birth.

Normal lung ultrasound appearance

The ultrasound appearance of a normal lung is black. The pleural line appears as a smooth echogenic line that exhibits respirophasic movement. A-lines are present as a series of echogenic parallel lines, equidistant from one another below the pleural line. B lines, which can be seen in healthy term newborns, are echogenic vertically orientated lines that start at the pleural line and reach the lower edge of the image; however, there is no pleural effusion and lung consolidation (Figure 1).

Table 1. General clinical information in two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Male/Female</th>
<th>GA (Weeks)</th>
<th>Birth weight (g)</th>
<th>Premature/Term</th>
<th>VD/CD/FD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>100</td>
<td>56/44</td>
<td>31–4/C24</td>
<td>1650–4120</td>
<td>18/8</td>
<td>54/37/9</td>
</tr>
</tbody>
</table>

PHN: pulmonary hemorrhage of the newborn; GA: gestational age; VD: vaginal delivery; CD: cesarean delivery; FD: forceps delivery.

Figure 1. Normal neonatal lung ultrasound. The lung field is hypoechoic (black). The pleural and A-lines are smooth, clear, parallel, echogenic lines. They are arranged in parallel with each other. The A-line echo gradually weakened and finally disappeared from the surface to the depth of the lung field.
The ultrasound manifestations of PHN

The main ultrasound manifestations of PHN were the following: (1) Shred sign: every baby who had lung consolidation had a shred sign at the edge of the consolidation area and the shred sign was the major ultrasound findings in the other five infants; the total incidence rate of this sign was 91.2% (Figures 2–6). (2) Lung consolidation with an air bronchogram or fluid bronchogram: 47 babies had lung consolidation with an air bronchogram (82.5%) and eight of these babies also had a fluid bronchogram (8/47, 17.0%; Figures 3–6); (3) Atelectasis: 19 of these patients had atelectasis (33.3%; Figures 4 and 5); (4) Abnormal pleural lines and A-line disappearance: this was found in all of the patients (100%); (5) Pleural effusion: this was seen in 48 cases (84.2%; Figures 3–7). The fluid was confirmed as bleeding by thoracocentesis. In severe cases with destruction of red blood cells, fibrous protein deposition in the formation of a fibrous cord similar to floating objects were seen with fluid movement under real-time ultrasound (Figure 6, avi-1); and (6) AIS: 7 of the infants had AIS (12.2%) with lung edema (Figure 7).

The sensitivity and specificity of the shred sign in diagnosing PHN

Based on the results of this study, the shred sign was the most common and specific ultrasonic findings of PHN. Therefore, this study used the presence of a shred sign as a parameter for calculating the sensitivity (a/a + c) and specificity (d/b + d) of ultrasonography for diagnosing severe PHN. The results indicated that the shred sign exhibited a sensitivity of 91.2% and a specificity of 100% in diagnosing PHN (Table 2).

Discussion

It was reported that the incidence rate of PHN was 1~12% of live births, and it increased to 50% in infants with high risk factors [19]. The common risk factors included premature birth, intrauterine growth restriction (IUGR), patent ductus arteriosus (PDA), severe birth asphyxia, hypoxia or oxygen toxicity, disseminated intravascular coagulation (DIC), RDS, MAS, hypotension, severe infection or sepsis, polycythemia, mechanical ventilation, multiple births, male gender as well as surfactant therapy [1]. In this study, the main causes of PHN were severe intrauterine infection (33.3%), severe birth asphyxia (21.1%) and RDS (21.1%), which accounted for more than 75% of the patients. MAS and severe postnatal infection accounted for 25% of these patients. PHN often occurred within the first several days after birth. In this study, 40 (71.4%) cases developed PHN within several hours to 24 h after birth, 45 cases (80.4%) developed PHN within three days of life, 50 infants (89.5%) developed PHN within seven days of life, while only six cases (10.5%) developed PHN between 1 to 2 weeks after birth, which means nearly 90% of the NPH cases occurred within the first week of life.

During the early years, the mortality of PHN may be as high as 50%. The survival of infants was affected by several factors contributing to a long-term poor prognosis. For example, the incidence of nerve sensory disturbance doubled in severe PHN patients, the incidence of bronchopulmonary dysplasia, cerebral palsy and cognitive delay increased 2.5 times in premature infants with NPH, and the incidence of seizure periventricular leukomalacia also increased significantly [1]. Recently, mortality decreased significantly with the development of new treatment methods [20–22]. There were only two PHN patients who died in this study, so the mortality rate was 3.51%.
Figure 4. The ultrasonic findings in a severe NPH case. The baby was G1P1 with a gestational age of 39\(+\)6 weeks and had a vaginal delivery with a birth weight of 3180 g. The baby was admitted to the NICU because of NPH caused by severe intrauterine infection. The lung ultrasound showed a large area of lung consolidation with an air bronchogram, a shred sign at the edge of consolidation, pleural effusion in both sides of the lungs (which was confirmed as bleeding by thoracocentesis), a disappeared pleural line and A-lines.

Figure 5. The ultrasonic findings in a severe NPH case. The baby was G1P1 with a gestational age of 38\(+\)6 weeks and had a Cesarean delivery with a birth weight of 3345 g. The baby was admitted to the NICU because of NPH caused by severe birth asphyxia. The lung ultrasound showed a large area of lung consolidation with an air bronchogram, a shred sign at the edge of consolidation, pleural effusion in both sides of the lungs (which was confirmed as bleeding by thoracocentesis), a disappeared pleural line and A-lines.

Figure 6. The ultrasonic findings in a severe NPH case. The baby was G3P1 with a gestational age of 37\(+\)1 weeks and had a Cesarean delivery with a birth weight of 4600 g. The baby was admitted to the NICU because of NPH caused by MAS. The lung ultrasound showed a large area of lung consolidation with an air bronchogram, a shred sign, disappeared pleural line and A-lines in both sides of the lungs, as well as pleural effusion in the right lung. It was found that there was fibrous protein deposition in the formation of fibrous cord-like floating objects with fluid movement under real-time ultrasound.
The key protocol for decreasing PHN mortality is based on early, quick and accurate diagnosis. For a long time, the diagnosis of PHN has been mainly based on medical history, typical clinical presentation and chest X-ray examination. Although chest X-ray is non-specific, it is usually necessary in the diagnosis of PHN, which often manifests with fluffy opacities, focal ground-glass opacities, or even “white out” in severe patients. Lung ultrasound is not usually performed in cases of suspected PHN. In the present study, we therefore investigated the diagnostic value of lung ultrasound for PHN. Through the systemic observation of lung ultrasonic characteristics of 57 PHN patients, we found lung ultrasound can accurately diagnose PHN, which is also useful for dynamic observation, timely understanding of the changes of pulmonary lesions and, thus, helping to guide treatment and improve the prognosis.

According to the results of this study, we found that the major ultrasonic characteristics of PHN are the following: (1) Shred sign: when the border of the aerated lung and consolidated lung is not sharp, a shred sign appears [12]. The shred sign is the most common ultrasonic sign of PHN, and it occurred in more than 90% of the patients. The shred sign is the main ultrasonic finding in mild PHN patients or within the lung on the side with mild bleeding. In addition, the shred sign is often found at the edge of large areas of consolidation. (2) Lung consolidation with an air bronchogram: this is one of the most common ultrasonic signs of PHN and was seen in more than 80% of the patients. We think that the reasons for consolidation were mainly related to the original lung diseases, the lung bleeding itself or the secretions blocking the trachea and bronchus. (3) Pleural effusion: this is another common sign of PHN and it occurred in more than 85% of the PHN cases. Pleural effusion can be found in one or both side of the thorax, but is often seen on the side with more severe bleeding in the lung. The fluid amount was associated with the original diseases and/or the degree of bleeding. The fluid was confirmed as bleeding by thoracentesis. Severe cases are due to the destruction of red blood cells, and fibrous protein depositions result in the formation of fibrous cord like floating objects. These fiber strip floating objects could be observed with fluid movement under real-time ultrasound (avi-1). (4) Pulmonary atelectasis: this was seen in one-third of the patients. In addition to lung consolidation, atelectasis is mainly related to the original lung diseases, such as pneumonia, RDS or MAS, while lung bleeding itself or the secretions blocking the trachea and bronchus are also associated with these pathogenic findings. (5) Abnormal pleural lines and A-line disappearance: both of these signs were the most common and non-specific ultrasonic findings of PHN. (6) AIS: In some cases with mild bleeding, or in the acute stages of some cases with severe bleeding, AIS is the main manifestation.

Lung ultrasound for the diagnosis of PHN has high sensitivity and specificity. According to the results of this study, the shred sign, which had a sensitivity of 91.2% and a specificity of 100%, is especially helpful for diagnosing PHN.

Conclusions

In conclusion, the value and characteristics of ultrasound imaging of PHN were determined in this study. We found that ultrasound had a definitive diagnostic value for NPH. The advantage of ultrasound is it allows observation of changes in the condition of the disease easily, and it is of great significance in guiding treatment and adjusting the treatment plan over time. In addition, it is non-invasive, harmless and can avoid being inspected. Other newborns within the same endemic area and the staff may suffer from radiation damage with other types of imaging techniques. Ultrasound is therefore worth being widely used in neonatal wards and may eventually be able to replace chest X-rays and CT [23,24].

Declaration of interest

Ethical approval and consent to participate: The institutional review board of the Army General Hospital of the Chinese PLA approved the study protocol (number 2011-LC-Ped-01).

Consent for publication: All the coauthors approve the publication of this manuscript.

Availability of supporting data: All the data are available for the editors and reviewers of Critical Care, and will be submitted if required.

This work was supported by the Clinical Research Special Fund of Wu Jieping Medical Foundation (320.6750.15072).

Contributorship statement

Prof. Dr Jing Liu: contributed to the study conception, lung ultrasound examination, data analysis, manuscript preparation, and write and approval of the manuscript.
Dr Xiao-Ling Ren: contributed to lung ultrasound examination, data analysis, manuscript preparation, the baby care, and approval of the final manuscript.

Dr Wei Fu: contributed to data analysis, manuscript preparation, and approval of the final manuscript.

Dr Ying Liu and Rong-Ming Xia: contributed to data analysis, manuscript preparation, and approval of the final manuscript.

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