REVIEW
1761 Cardiac rehabilitation and its essential role in the secondary prevention of cardiovascular diseases
Winnige P, Vysoky R, Dosbaba F, Batalik L

ORIGINAL ARTICLE

Case Control Study
1785 Association between homeobox protein transcript antisense intergenic ribonucleic acid genetic polymorphisms and cholangiocarcinoma

Retrospective Study
1793 Risk factors for post-hepatectomy liver failure in 80 patients
Xing Y, Liu ZR, Yu W, Zhang HY, Song MM
1803 Outcomes of laparoscopic bile duct exploration for choledocholithiasis with small common bile duct
Huang XX, Wu JY, Bai YN, Wu JY, Lv JH, Chen WZ, Huang LM, Huang BF, Yan ML

Observational Study
1814 Three-dimensional finite element analysis with different internal fixation methods through the anterior approach
Xie XJ, Cao SL, Tong K, Zhong ZY, Wang G
1827 Bedside cardiopulmonary ultrasonography evaluates lung water content in very low-weight preterm neonates with patent ductus arteriosus
Yu LF, Xu CK, Zhao M, Niu L, Huang XM, Zhang ZQ

CASE REPORT
1835 Conservative endodontic management using a calcium silicate bioceramic sealer for delayed root fracture: A case report and review of the literature
Zheng P, Shen ZY, Fu BP
1844 Brain magnetic resonance imaging findings and radiologic review of maple syrup urine disease: Report of three cases
Li Y, Liu X, Duan CF, Song XF, Zhuang XH
1853 A three-year clinical investigation of a Chinese child with craniometaphyseal dysplasia caused by a mutated ANKH gene
Wu JL, Li XL, Chen SM, Lan XP, Chen JJ, Li XY, Wang W
1863 Intradural osteomas: Report of two cases
Li L, Ying GY, Tang YJ, Wu H
### Contents

**Thrice Monthly Volume 9 Number 8 March 16, 2021**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1877</td>
<td>Chest pain showing precordial ST-segment elevation in a 96-year-old woman with right coronary artery occlusion: A case report</td>
<td>Wu HY, Cheng G, Cao YW</td>
</tr>
<tr>
<td>1885</td>
<td>Subcutaneous panniculitis-like T-cell lymphoma invading central nervous system in long-term clinical remission with lenalidomide: A case report</td>
<td>Sun J, Ma XS, Qu LM, Song XS</td>
</tr>
<tr>
<td>1893</td>
<td>Imaging findings of primary pulmonary synovial sarcoma with secondary distant metastases: A case report</td>
<td>Li R, Teng X, Han WH, Li Y, Liu QW</td>
</tr>
<tr>
<td>1909</td>
<td>Bilateral common peroneal neuropathy due to rapid and marked weight loss after biliary surgery: A case report</td>
<td>Oh MW, Gu MS, Kong HH</td>
</tr>
<tr>
<td>1940</td>
<td>Computed tomography imaging features for amyloid dacryolith in the nasolacrimal excretory system: A case report</td>
<td>Che ZG, Ni T, Wang ZC, Wang DW</td>
</tr>
<tr>
<td>1946</td>
<td>Epidural analgesia followed by epidural hydroxyethyl starch prevented post-dural puncture headache: Twenty case reports and a review of the literature</td>
<td>Song LL, Zhou Y, Geng ZY</td>
</tr>
<tr>
<td>Year</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>1976</td>
<td>Diabetes insipidus with impaired vision caused by germinoma and periopic meningeal seeding: A case report</td>
<td>Yang N, Zhu HJ, Yao Y, He LY, Li YX, You H, Zhang HB</td>
</tr>
<tr>
<td>1983</td>
<td>Madelung disease: A case report</td>
<td>Chen KK, Ni LS, Yu WH</td>
</tr>
<tr>
<td>2001</td>
<td>Inadvertent globe penetration during retrobulbar anesthesia: A case report</td>
<td>Dai Y, Sun T, Gong JF</td>
</tr>
<tr>
<td>2015</td>
<td>Interstitial lung disease induced by the roots of <em>Achyranthes japonica Nakai</em>: Three case reports</td>
<td>Moon DS, Yoon SH, Lee SI, Park SG, Na YS</td>
</tr>
</tbody>
</table>
ABOUT COVER
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ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/gerinfo/239

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Observational Study

Bedside cardiopulmonary ultrasonography evaluates lung water content in very low-weight preterm neonates with patent ductus arteriosus

Li-Fang Yu, Chen-Ke Xu, Min Zhao, Lin Niu, Xian-Mei Huang, Zhi-Qun Zhang

BACKGROUND

Patent ductus arteriosus (PDA) is a common congenital heart abnormality in preterm neonates with a high incidence in neonates with very low birth weights. When PDA persists, interstitial lung water content increases, which could lead to abnormal circulation hemodynamics and pulmonary edema. It is important to perform early and reliable assessment of lung water content in very low-weight preterm neonates with persistent PDA.

AIM

To evaluate the role of bedside cardiopulmonary ultrasonography in the lung water content assessment in very low-weight preterm neonates with persistent PDA.

METHODS

From January 2018 to March 2020, 69 very low-weight preterm neonates with echocardiography-confirmed PDA were selected as the PDA group. At the same time, 89 very low-weight preterm neonates without PDA were randomly selected as the control group. All neonates underwent echocardiography and 6-segment lung ultrasonography on the fourth day after birth. The clinical characteristics and main ultrasonography results were compared between the two groups. Pearson’s analysis was used to analyze the correlation between lung ultrasonography score (LUS) and other related clinical and ultrasonography results in all neonates. In the PDA group, PDA diameters were recorded, and the correlation with LUS and left...
INTRODUCTION

Patent ductus arteriosus (PDA) is a common congenital heart abnormality in preterm neonates. Neonates with prematurity and low birth weights, especially those with a birth weight less than 1500 g have poorly developed organs and thus a higher incidence of PDA[1]. The direct communication between the aorta and pulmonary artery can result in abnormal pulmonary circulation, left heart overload and poor systemic perfusion[3], which may present with pulmonary edema, pulmonary hemorrhage, left ventricular dysfunction and bronchopulmonary dysplasia[4]. Therefore, it is important to perform an early and reliable lung water content and hemodynamic assessment in very-low-weight preterm neonates with persistent PDA.

With recent advancements in lung ultrasonography, the detection of a variety of
lungs in neonates has improved markedly. Studies have reported that changes in the ratio of fluid in the interstitial or pleural spaces can produce artifacts, making it possible to diagnose pulmonary diseases\cite{5,6}. The B line is an artifact caused by excessive water outside of pulmonary blood vessels, and the number of B lines is related to the severity of pulmonary edema\cite{7}. The lung ultrasonography score (LUS) is a quantitative assessment of B line. In very low birth-weight preterm neonates with PDA, hemodynamic instability mainly manifests as pulmonary edema\cite{8,9}.

Also, PDA has a characteristic performance in echocardiography. For typical PDA cases, the diagnostic accuracy of echocardiography can be 100%, and the structure and function of the heart can be simultaneously evaluated. At present, the diagnostic criteria for hemodynamically significant PDA include clinical symptoms and echocardiographic indicators, of which the left atrium to aortic (LA/AO) dimension ratio and PDA diameter are important ultrasonic indicators for hemodynamically significant PDA. A ratio of LA/AO ≥ 1.5 suggests the possibility of hemodynamic changes in persistent PDA\cite{10,11}. Therefore, we performed cardiopulmonary ultrasonography in neonates with or without PDA and compared their ultrasonography results to explore the differences, evaluate lung water content and predict hemodynamic changes in very low-weight preterm neonates with PDA.

**MATERIALS AND METHODS**

**Study population and data collection**

A total of 69 very low-weight preterm neonates with echocardiography-confirmed PDA screened fetal congenital heart defects who were admitted to the neonatal intensive care unit of the Hangzhou First People’s Hospital from January 2018 to March 2020 were enrolled in this study. During the same period, 89 cases without PDA were included as the control group. The inclusion criteria were: Gestational age less than 37 wk; birth weight less than 1500 g; and admission to the neonatal intensive care unit of our hospital within 24 h of birth. The exclusion criteria were: Congenital malformations and other chromosomal abnormalities identified before birth; and lung diseases caused by definite pathogenic factors (including meconium aspiration syndrome, pulmonary hemorrhage, and pneumonia, etc.). The study protocol was approved by the Ethics Committee of the Hangzhou First People’s Hospital in China (approval no. 2018-30-1) and conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from the guardians of the neonates prior to inclusion.

**Ultrasonic examination instrument**

Ultrasonic examination was performed with the use of Philips IE33 and Philips CX50 United States instruments (Philips Healthcare, Best, the Netherlands). Neonatal cardiac ultrasound probe (12 MHz), high-frequency shallow probe (12 MHz) and micro-convex probe (8 MHz) were used to evaluate the heart and lung functions.

**Ultrasonic examination techniques**

Ultrasonic examinations were completed on the fourth day after birth. Echocardiography was performed to measure the left ventricular ejection fraction, LA and AO in M-mode with standard planes. Lung ultrasonography was carried out to evaluate lung function in horizontal and vertical scans. Each lung was divided into three regions, namely anterior superior, anterior inferior and lateral. According to the method of Brat et al\cite{12}, we scored the lungs as follows (Figure 1): Lung sliding with line A or slight line B, 0 point; more than three B lines with a gap between B lines and no fusion, 1 point; diffuse B lines and fusion between B lines with moderate subpleural lung consolidation, 2 points; and extensive consolidation, 3 points. Each region with the most severe performance was scored, the final LUS value was the sum of the scores, and the highest score was 18 points. All ultrasonography examinations were performed by the same sonographer who was well-experienced in cardiopulmonary ultrasonography examination. All images were saved and stored in the picture archiving and communication system.

**Statistical analysis**

All statistical analyses were conducted using SPSS 17.0 software for Windows (IBM Corp, Armonk, NY, United States). Measured data were presented as means ± standard deviations and categorical variables as percentages. Differences between the
two groups were determined by Student’s t-test or Chi-square test. Pearson’s analysis was used to analyze the correlation between the LUS and other data in all cases. In the PDA group, Pearson’s analysis was also used to analyze the correlation between the PDA diameter, LUS and LA/AO ratio. A receiver operating characteristic curve was established using the sensitivity of the LUS to predict the possibility of hemodynamic changes in persistent PDA as the ordinate and 1-specificity as the abscissa. P values less than 0.05 were considered statistically significant.

RESULTS

General data
A total of 158 cases were included in this study. There were 69 neonates in the PDA group (33 males and 36 females; 68 of them were ventilator dependent) with an average gestational age of 29.09 ± 2.15 wk, an average birth weight of 1195.14 ± 235.96 g and an average hospitalization length of 41.61 ± 22.76 d. There were 89 neonates in the control group (52 males and 37 females; 84 of them were ventilator dependent) with an average gestational age of 29.26 ± 1.93 wk, an average birth weight of 1165.11 ± 230.04 g and an average hospitalization length of 48.67 ± 16.43 d. There were no statistical differences in any of the parameters between the two groups (P > 0.05).

Ultrasonography results in the two groups
Lung ultrasonography results revealed that all cases had different B line characteristics. The LUS of neonates on a ventilator were 8.00 ± 3.66 points, and those not on a ventilator were 5.83 ± 3.12 points. There were no differences between them (t = 0.58, P = 0.16). The ultrasonography results of the two groups are summarized in Table 1. The PDA group had an average LUS of 9.26 ± 3.21 points, with a minimum of 2 points and a maximum of 15 points, whereas the control group had an average LUS of 6.88 ± 3.66 points, with a minimum of 2 points and a maximum of 18 points. The difference in the LUS between the two groups was statistically significant (P < 0.01). There were two deaths in the PDA group with lung scores of 10 points and 16 points, respectively. The average left ventricular ejection fraction value was not statistically different between the two groups (P = 0.22), while the average LA/AO ratio of the PDA group was higher than that of the control group (P = 0.01). Pearson’s analysis
Table 1 Ultrasonography results in patent ductus arteriosus group and control group

<table>
<thead>
<tr>
<th>Variable</th>
<th>PDA group, n = 69</th>
<th>Control group, n = 89</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUS</td>
<td>9.26 ± 3.21</td>
<td>6.88 ± 3.66</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>LA/AO</td>
<td>1.28 ± 0.24</td>
<td>1.18 ± 0.24</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF</td>
<td>62.70 ± 7.61</td>
<td>64.00 ± 5.86</td>
<td>0.22</td>
</tr>
</tbody>
</table>

LA/AO: Left atrium to aortic ratio; LUS: Lung ultrasonography score; LVEF: Left ventricular ejection fraction.

showed that the LUS was negatively correlated with gestational age \((r = -0.28, P < 0.01)\) and birth weight \((r = -0.36, P < 0.01)\), while positively correlated with the LA/AO ratio \((r = 0.27, P < 0.01)\).

PDA diameter in PDA group

PDA diameter ranged from 0.08 to 0.35 cm, with an average of 0.20 ± 0.06 cm. PDA diameter was positively correlated with the LA/AO ratio \((r = 0.39, P < 0.01)\) and LUS \((r = 0.31, P < 0.01)\). There were 16 cases with an LA/AO ratio ≥ 1.5. The receiver operating characteristic curve results showed that the LUS had moderate accuracy for predicting the possibility of hemodynamic changes in persistent PDA. The area under the curve was 0.741 (95% confidence interval: 0.621–0.839), and sensitivity and specificity were 93.75% and 50.94%, respectively (Figure 2).

DISCUSSION

The lungs were once considered to be blind spots in ultrasonography. Advancements in lung ultrasonography have made it possible to detect a variety of pulmonary diseases, including respiratory distress syndrome, pneumonia, wet lung and pulmonary hemorrhage in neonates\[^{13,14}\]. The 2019 Guidelines for Ultrasound Diagnosis of Neonatal Lung Diseases confirmed that lung ultrasonography had higher sensitivity and accuracy compared with traditional chest X-rays in the diagnosis of pneumothorax, pulmonary edema, pulmonary consolidation and pleural effusion\[^{15–17}\]. Ultrasonography also has many advantages; it produces highly reproducible findings without radiation damage. Scanning can also be performed easily at the bedside, which is especially important for critically ill patients. As such, lung ultrasonography has become increasingly used in the diagnosis of lung diseases in general intensive care and child intensive care units\[^{17–22}\].

Persistent PDA in very low-weight preterm neonates would cause left ventricular enlargement and increase diastolic blood pressure, resulting in congestion of the left atrium and pulmonary vascular bed causing abnormal circulation hemodynamics and pulmonary edema. It was previously reported that the LUS was related to the presence of lung water content\[^{12,23–25}\], while it is still controversial whether the LUS can directly reflect the severity of pulmonary diseases\[^{26–29}\]. The aim of the present study was to evaluate lung water content and predict the possibility of hemodynamic changes in very low-weight preterm neonates with persistent PDA. The results showed that the LUS in the PDA group was statistically higher than in the control group and negatively correlated with gestational age and birth weight, suggesting that neonates with lower gestational age and birth weight would had higher lung water content. This would provide useful information for clinical treatment.

PDA has a characteristic performance in echocardiography, and the LA/AO ratio measured in M-mode is related to the severity of the PDA diameter. The LA/AO ratio and PDA diameter are important ultrasonic indicators for hemodynamically significant PDA, and a LA/AO ratio ≥ 1.5 suggests the possibility of hemodynamic changes in persistent PDA. There were 16 cases with a LA/AO ratio ≥ 1.5 in the PDA group. The receiver operating characteristic curve showed that the LUS had moderate accuracy for diagnosing hemodynamically significant PDA. When the cut-off of the LUS was more than 9 points, its sensitivity and specificity were 93.75% and 50.94%. PDA diameter can be measured and was positively correlated with the LUS and LA/AO ratio. Therefore, it might provide more information for clinicians to determine whether further interventions are needed.

Ultrasonic examinations were completed on the fourth day after birth based on the following reasons: (1) Patent ductus is still present 72 h after birth\[^{30}\]; (2) Pulmonary
blood vessels dilate after birth, and the pulmonary artery pressure decreases rapidly by 72 h\(^2\); and (3) Examinations at different time points may affect the LUS. Currently, there are several different methods for the LUS calculation. The most widely used are the 6-zone and 12-zone methods\(^5\). In the present study, the 6-zone method was used. First, as the body surface area of very low-weight preterm neonates was very low, the 6-zone method can cover all inspection areas. Second, some neonates were on ventilators and moving them would increase the risk of tube removal. Last, the dense B line was mainly located in the anterior chest.

This study has several limitations. First, the LUS is a semi-quantitative evaluation of lung function, and there is no established quantitative standard for the number of B lines and the range of lung consolidation. Second, scores are affected by subjective factors of the operator. Different operators may give different scores for the same neonate. It is also difficult to collect large amounts of data from several centers. However, this study involved one sonographer who scored all the cases. Third, very low birth-weight preterm neonates often have other lung problems, indicating that a variety of complex factors may affect the accuracy of the scoring. Fourth, the number of cases in this study is small, and additional studies with a larger sample are needed.

CONCLUSION
Cardiopulmonary ultrasonography could evaluate lung water content and predict the possibility of hemodynamic changes in very low-weight preterm neonates with PDA. The LUS in lung ultrasonography is higher in PDA neonates and has a moderate accuracy for predicting hemodynamic changes. Echocardiography can detect PDA and indirectly assess left atrial pressure based on LA/AO ratio. The LUS is positively correlated with PDA diameter and LA/AO ratio and comprehensive assessment of the ultrasonic indicators is needed.

ARTICLE HIGHLIGHTS
Research background
Patent ductus arteriosus (PDA) has a high incidence in neonates with very low-birth weights, and abnormal circulation hemodynamics and pulmonary edema may occur in persistent PDA. Lung ultrasonography was reported to be a quantitative method for assessment of lung water content. However, there are few studies reporting its role in neonates with PDA.
Research motivation
With recent advancements in lung ultrasonography, the detection of a variety of lung diseases in neonates has improved markedly. The advantages of bedside, radiation free, relatively cheap and reproducible would make it widely used in clinical work.

Research objectives
To evaluate lung water content and predict the possibility of hemodynamic changes in very low-weight preterm neonates with PDA.

Research methods
In this study, we performed cardiopulmonary ultrasonography in neonates with or without PDA and compared the ultrasonography results including left ventricular ejection fraction, left atrium to aortic dimension ratio and lung ultrasonography score (LUS) between the two groups.

Research results
Results showed that the LUS and left atrium to aortic ratio were higher in neonates with PDA, and the LUS was positively correlated with PDA diameter and left atrium to aortic ratio, indicating that the lung water content was higher in PDA. In addition, the receiver operating characteristic curve showed that the LUS had moderate accuracy for predicting the possibility of hemodynamic changes. The area under the curve was 0.741 (95% confidence interval: 0.621-0.839), and sensitivity and specificity were 93.75% and 50.94%, respectively.

Research conclusions
We conclude that bedside cardiopulmonary ultrasonography can evaluate lung water content and predict the possibility of hemodynamic changes in very low-weight preterm neonates with PDA.

Research perspectives
The LUS is subjective and operator dependent. A more objective and appropriate evaluation method should be identified. In addition, neonatal lungs are complex, different diseases can have the same ultrasound images, the LUS alone cannot reflect its severity, and comprehensive evaluation is needed.

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