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Dynamic changes of pulmonary arterial pressure in perinatal neonates with pulmonary and extrapulmonary acute lung injury/respiratory distress syndrome

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Abstract

This study aims to explore the dynamic changes of pulmonary arterial pressure (PAP) and its clinical significance in prenatal neonates with pulmonary and extra-pulmonary acute lung injury/respiratory distress syndrome (ALI/ARDS).

A prospective study was conducted in the Neonate Intensive Care Unit (NICU) between May 2015 and April 2017. A total of 78 prenatal neonates with ALI/ARDS were selected and divided into 2 groups: pulmonary group (n = 37) and extra-pulmonary group (n = 41). These neonates were further divided into 3 groups according to the OSI index: mild, moderate, and severe groups. The dynamic changes of PAP were observed in these neonates. In the moderate and severe groups, PAP was significantly higher in neonates with pulmonary ALI/ADDS (ALI/ARDSp) than in neonates with extrapulmonary ALI/ARDS(ALI/ARDSexp) (62.5 ± 5.4 vs 68.0 ± 6.5, 54.7 ± 5.9 vs 64.2 ± 4.9; t = 3.264, 3.123; P = .004,.039). Furthermore, PAP was higher in neonates with ALI/ADDSp in the severe group, compared with those in the moderate group (t = 2.420, $P < .05$). There was significant difference among the 3 subgroups of neonates with ALI/ADDSexp (F = 60.100, P = .000). PAP was positively correlated with the OSI index (r = 0.823). The overall dynamic PAP monitoring results revealed that PAP was higher in the pulmonary group than that in the extrapulmonary group, and this exhibited a gradually decreasing trend as the condition of the subject improved.

PAP in perinatal neonates with ALI/ARDS increases in varying degrees, and its extent was related to the severity of the illness. PAP was significantly higher in neonates with ALI/ADDSp than in neonates with ALI/ADDSexp. This can be used as a monitoring indicator for the severity of illness.

Abbreviations: ALI/ARDS = acute lung injury/acute respiratory distress syndrome, ALI/ARDSexp = acute lung injury/acute respiratory distress extrapulmonary, ALI/ARDSp = acute lung injury/acute respiratory distress pulmonary, ANOVA = analysis of variance, CPAP = continuous positive airway pressure, NICU = neonatal intensive care unit, OSI = oxygen saturation index, PAP = pulmonary arterial pressure, PPHN = persistent pulmonary hypertension of the newborn, SIMV = synchronized intermittent mandatory ventilation.

Keywords: acute lung injure, acute respiratory distress, infant newborn, pulmonary artery pressure

1. Introduction

Respiratory failure caused by neonatal perinatal acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is a condition that severely compromises the health of the new-borns.[1–2] It is clinically characterized by refractory hypoxemia

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and the further development of diffuse pneumonedema. These pathological changes of perinatal acute respiratory distress syndrome can not only occur in patients with severe lung diseases, but also in patients without primary lung diseases. Perinatal ALI/ARDS due to different causes have some differences in terms of pathophysiological mechanisms, respiration mechanics, imaging, treatment responses, and prognosis. Therefore, according to etiology, it can be divided into pulmonary (ALI/ARDSp) and extrapulmonary (ALI/ARDSexp). The classification of respiratory distress syndrome according to the cause of clinical research is the future trend.[3] Neonatal perinatal ALI/ARDSp is mainly caused by neonatal aspiration syndrome and infectious pneumonia, while ALI/ARDSexp is mostly caused by sepsis, severe asphyxia, and circulatory dysfunction. These pathological changes in the lungs can lead to secondary pulmonary hypertension, which in turn makes it more difficult to correct hypoxemia.[4] The early dynamic monitoring of changes in pulmonary artery pressure (PAP) and active treatment can prevent the occurrence of persistent pulmonary hypertension of the newborn (PPHN), and have a certain significance on the prognosis. However, few studies on neonatal lung injury/respiratory distress syndrome by etiology classification have been conducted. The present study was conducted based on the consensus of pediatric acute respiratory syndrome/acute lung

injury recommended by Pediatric Care Medicine in 2015.[5] This was combined with the characteristics of the neonatal perinatal period, which is the diagnostic reference standard of ALI/ADRS. These were conducted with the aim of exploring the dynamic changes and clinical significances of PAP in patients with ARDSp and ARDSexp.

2. Materials and methods

2.1. Research object

The present retrospective study was conducted in the neonatal intensive care unit (NICU) of Yancheng Third people's Hospital (Jiangsu, China) between May 2015 and April 2017. A total of 78 prenatal neonates with ALI/ARDS were included in this study. These patients were divided into 2 groups: pulmonary group and extrapulmonary group. The inclusion criteria in this study were:

1. Acute onset lung disease meet ARDS diagnostic criteria.[5]
2. Average gestational age was ≥34 weeks, birth weight ≥2500 g.
3. There were definite external causes of progressive dyspnea and hypoxemia.
4. Chest imaging indicated new infiltrate(s) that were consistent with the acute pulmonary parenchymal disease.
5. Neonates who needed invasive mechanical ventilation were divided into mild ($5 \leq$ oxygen saturation index (OSI) < 7.5), moderate ($7.5 \leq OSI < 12.3$), and severe ($OSI \geq 12.3$) groups, according to OSI[6] and the neonate who only needed continuous positive airway pressure (CPAP) ventilation was assigned to the mild group.

The exclusions criteria: patients with congenital heart disease and respiratory distress of unknown etiology were not covered in this study. There were 41 neonates in pulmonary group and 38 neonates in extrapulmonary group. In the pulmonary group, the primary disease included 26 cases of aspiration syndrome and 15 cases of infectious pneumonia. In the extrapulmonary group, there were 21 cases of sepsis, 11 cases of severe asphyxia, 3 cases of hemorrhagic shock, and 2 cases of cardiogenic shock. Seventy eight healthy newborns were selected as the control group. The present study was approved by the Ethics Committee of our hospital.

3. Research methods and data collection

3.1. PAP determination

PAP was determined by color Doppler ultrasound examination. The determination method was as follows: the use of pulmonary hypertension in children with tricuspid regurgitation, with continuous flow Doppler measurement regurgitation PAP, and this was calculated using the simplified Bernoulli equation: $PAP = 4 \times (\text{tricuspid regurgitation jet velocity})^2 + CVP$ (central venous pressure, $CVP = 5$ mm Hg). When pulmonary artery systolic pressure was greater than 35 mm Hg, or greater than two-thirds of the systolic blood pressure, pulmonary hypertension can be diagnosed. These were classified as follows: mild pulmonary hypertension, within the range of 40 to 49 mm Hg; moderate pulmonary hypertension, within the range of 50 to 69 mm Hg; severe pulmonary hypertension ≥70 mm Hg.

3.2. Mechanical ventilation

Patients received CPAP or the SLE5000 type of mechanical ventilation once the respiratory distress was clear. The lung

protective ventilation strategy was adopted, and the ventilation mode was synchronized intermittent mandatory ventilation (SIMV). Some patients received a pulmonary surfactant (PS, 100 mg per kilogram each time) according to the needs of the disease and changes in chest imaging.

3.3. Systemic treatment

All patients received treatment for the cause, including anti-shock, anti-infective, improved ventilation, and stable cycle function. Neonates who could not endure the enteral nutrition were given total parenteral nutrition, disturbance of water-electrolyte balance, and acid-base balance were corrected.

3.4. Observation item

1. PAP was evaluated daily before and after respiratory support treatment.
2. The OSI was calculated to monitor the disease progression.
3. Dynamic chest imaging was followed-up, and hospital stay, duration of ventilation support and prognosis were recorded.

4. Statistical analysis

SPSS 16.6 software was used for statistical analysis. The measurement data, which fit the normal or approximately normal distribution, were presented as mean ± standard deviation ($x \pm SD$), compared between 2 groups using independent samples t test, and compared within a group using One-way analysis of variance (ANOVA). Count data were compared using X^2-test, and Pearson's correlation analysis was performed. $P < .05$ was considered statistically significant.

5. Results

5.1. General clinical data of the perinatal neonatal ALI/ARDSp and ALI/ARDSexp groups

There was no statistically significant difference in birth weight between the 2 groups ($P > .05$). The incidence in males, average gestational age were lower in the ALI/ARDSexp group compared with the ALI/ARDSp group, and the difference was statistically significant ($P < .05$). Furthermore, mean airway pressure, the OSI and the utilization rate of pulmonary surfactant were higher in the ALI/ARDSp group than in the ALI/ARDSexp, and the differences were statistically significant ($P < .05$). Moreover, the difference in hospitalization days and the survival rate in both groups were not statistically significant ($P > .05$, Table 1).

5.2. PAP were compared in neonates between the ALI/ARDSp group and the ALI/ARDSexp group according the OSI

In the ALI/ARDSp group, neonates with mild PAP were not observed. However, PAP in neonates with the ALI/ARDSp were higher in the severe group than those in the moderate group, and difference was statistically significant (t = 2.420, $P < .05$). For the ALI/ARDSexp group, the one-way ANOVA revealed that OSI and PAP were higher, and the differences were statistically significant (F = 60.100, $P < .05$). Comparison of the OSI revealed that, the PAP was higher in the ALI/ARDSp group than in the ALI/ARDSexp group ($P < .05$, Table 2).

Table 1

Perinatal ALI/ARDSp was compared to ALI/ARDSexp clinical data.

Project	ALI/ARDSp (n=41)	ALI/ARDSexp (n=37)	t/χ2 (P)
Average gestational age (w)	38.9±1.7	37.5±1.7	3.72 (.000)
Birth weight (g)	3088.5±513.7	3148±465.7	0.54 (.592)
Men/n (%)	31 (75.6%)	16 (43.2%)	8.51 (.000)
OSI index	16.6±5.8	12.0±4.2	3.95 (.000)
Mean airway pressure (cmH$_2$O)	22.8±3.4	18.6±3.0	5.90 (.000)
Utilization rate of pulmonary surfactant (n, %)	32 (78.0%)	5 (13.5%)	32.49 (.000)
Hospitalization days (d)	11.5±4.2	12.1±4.0	0.61 (.550)
The survival rate (%)	82.9%	94.6%	2.594 (.107)

ALI/ARDS = acute lung injury/acute respiratory distress syndrome, ALI/ARDSexp = acute lung injury/acute respiratory distress extrapulmonary, ALI/ARDSp = acute lung injury/acute respiratory distress pulmonary, OSI = oxygen saturation index, PAP = pulmonary arterial pressure.

Table 2

The comparsion of PAP between ALI/ARDSp group and ALI/ARDSexp group according the OSI.

OSI index of the group	ALI/ARDSp (n=41)	ALI/ARDSexp (n=37)	t values	P values
OSI<7.5 (Mild group, n=6)	/	37.8±6.5 (6)	/	
7.5≤OSI<12.3 (The moderate group, n=23)	62.5±5.4 (10)	54.7±5.9 (13)	3.264	.004
≥12.3 (Severe group, n=49)	68.0±6.5 (31)	64.2±4.9 (18)	3.123	.039
Statistics	t=2.42 0	F=60.100		
P values	.021	.000		

ALI/ARDS = acute lung injury/acute respiratory distress syndrome, ALI/ARDSexp = acute lung injury/acute respiratory distress extrapulmonary, ALI/ARDSp = acute lung injury/acute respiratory distress pulmonary, OSI = oxygen saturation index, PAP = pulmonary arterial pressure.

The correlation coefficient between the OSI and PAP by Pearson was 0.823 ($P < .01$).

5.3. Dynamic trend chart of neonatal PAP in the ALI/ARDSp and ALI/ARDSexp groups

The overall dynamic PAP monitoring revealed that the PAP was higher in the ALI/ARDSp group and ALI/ARDSex group than in the control group ($P = .000$). The PAP values were higher in the ALI/ARDSp group than those in the ALI/ARDSexp at different time point (0, 48, 72, and 96 hours). At the 24-hour time point the PAP was significantly lower compared it with that at the 0-hour time point in the ALI/ARDSp group, and PAP was either which were both lower compared with those in the ALI/ARDSexp group ($P < .05$). PAP was rebonded in the ALI/ARDSp group at the 48-hour time point, and before extubation there was no statistically significant difference in the PAP between the 2 groups ($P < .05$). (Fig. 1)

6. Discussion

Perinatal ALI/ARDS is one of the main causes of neonatal respiratory failure, and is also the major cause of neonatal death.[1] Hypoxia hypercapnia and elevated alveolar permeability, and induce pulmonary vasospasm or increase in pulmonary venous pressure, often leading to increased PAP.[7] If PAP continues to exceed the systemic pressure, it would force functionally close off patent ductus arteriosus or foramen ovale to re-open, induce the right-to-left shunt. This would aggravate hypoxemia and acidosis, impair right ventricular function,[8] and even lead to failure in circulatory function. Hence, for perinatal lung injury/respiration distress syndrome, PAP monitoring should be given enough attention. According to its etiology, perinatal ALI/ARDS can be divided into 2 types: pulmonary and extrapulmonary type. This shows that knowing the different causes of respiratory distress and understanding these differences in pathophysiology can be beneficial for the purpose of clinical treatment.[9]

Although the diagnosis of ADRS has no limits of gestational age and birth weight, considering the difference between ARDS and neonatal respiratory distress syndrome, all these neonates with ARDS had clear external causes, the gestational age and birth weight of all subjects were restricted; at the same time neonates with pulmonary hypertension caused by congenital heart disease or pulmonary vascular dysplasia were excluded from the study, so the change of PAP was usually caused by
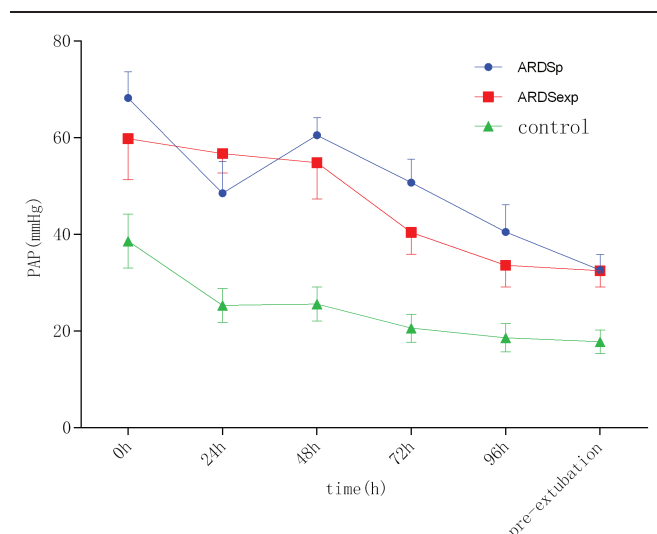

Figure 1. Dynamic PAP changes during the hospitalization of ALI/ARDSp and ALI/ARDSexp.

pulmonary vascular maladaptation, the increase of PAP was often reversible as the primary disease improves.

In this study, there was no statistically significant difference in birth weight between the 2 groups, it may be associated with weight gain slowly in later pregnancy. The gestational age between the ALI/ARDSexp and ALI/ARDSp groups has a significant difference, gestational age in the ALI/ARDSexp group was significantly smaller than it in the ALI/ARDSp group. This may be related to the high incidence of aspiration syndrome in ARDSp group. Aspiration syndrome is more common in post-term infants. In a study conducted by Gattinoni,[10] it was pointed out that there are differences between the 2 aspects of respiratory mechanics and response to treatment vary, and that ventilator parameters for pulmonary ALI/ARDS were significantly higher, when compared with extrapulmonary ALI/ARDS. In this study, it was observed that the mean airway pressure and OSI were significantly higher in the ALI/ARDSp group than those in the ALI/ARDSexp group, so the parameters of ventilator in the ALI/ARDSp group were often higher. The primary disease in neonates with ALI/ARDSexp occurs outside of the lungs. Before onset in the lung itself, it does not induce serious pathological lesions. This is one of the reasons for the relatively low respiratory support parameters.

PAP changes can reflect the severity of lung injury/respiratory distress and prognosis. Elevated PAP can affect right heart function, resulting in reduced right ventricular discharge[11] and the relative reduction in alveolar blood flow, which is due to the alveolar lesions. Partial alveolar collapse or consolidation that affects the ventilation induces ventilation/perfusion defects and leads to hypoxemia that was difficult to correct. Hence, PAP monitoring and reasonable intervention can affect the treatment effect.[12] The secondary PAP increase is mainly due to hypoxia, acidosis, and vasospasm contraction caused by Inflammatory factor, so our clinical management should focus on improving oxygenation and cardiac function, correcting acidosis, expanding the pulmonary vascular smooth muscle, and active treatment of the primary disease. In the present study, it was observed that the expression of PAP was significantly higher in all neonates with lung injury/respiratory distress syndrome, compared with those in the control group. Meanwhile, the increase in PAP was positively correlated with the OSI. Hence, PAP could be used as a monitoring index for ALI/ARDS severity. PAP was significantly higher in the ALI/ARDSp group than in the ALI/ARDSexp group, suggesting that the state of illness in ALI/ARDSp group is more serious and easy to merge PPHN. In the ALI/ARDSexp group, PPHN were not observed, but 4 cases combined with PPHN were observed in the ARDSp group. PPHN obviously affects the prognosis of the disease.[13] There were no significant difference in survival rate between the 2 groups. Greater sample sizes and a longer follow-up period are required to fully determine whether it was associated with the improvement of intensive care treatment technology.

The dynamic PAP monitoring revealed that although normal healthy neonates also had elevated PAP after birth, these mildly increased and rapidly decreased to normal levels within 24 hours after birth. Furthermore, PAP in neonates with perinatal lung injury/respiratory distress syndrome was moderately-severely increased. Neonates combined with ALI/ARDSp had higher PAP compared to those with ALI/ARDSexp. At 24 to 48 hours after admission, PAP monitoring curve in the ALI/ARDSp group exhibited a significantly decline and rebound, while this was not obvious in the ALI/ARDSexp group, this phenomenon was considered to be induced by the high utilization rate of pulmonary surfactants in the ALI/ARDSp group. This indirectly shows that pulmonary surfactants have an effect in improving oxygenation to lung parenchymal injury, thereby reducing PAP and the need for extracorporeal membrane in neonates with PPHN.[14–15] The PAP in neonates with ALI/ARDSp and ALI/ARDSexp exhibited a tendency to gradually decrease with the improvement in their condition. There was no statistically significant difference in PAP before extubation. The treatment of pulmonary hypertension was mainly to control the primary disease. The early treatment of pulmonary hypertension can protect the function of the organ, without having to wait until the occurrence of PPHN; A previous investigations reveal that[10] lung compliance in neonates has differences between ALI/ARDSp and ALI/ARDSexp, the response to treatment of pulmonary surfactant is not the same. This study indicated that PAP was difference between neonates with ALI/ARDSp and ALI/ARDSexp, neonates with ALI/ARDSp easily to develop PPHN because of high PAP, early treatment to reduce PAP can improve right heart function and ventilation/perfusion (V'/Q') mismatch, accordingly make the oxygenation better.[16] However, this study failed to conduct a thorough comparative study of PAP management. In the future, appropriate cases should be chosen in order to be able to present a further in-depth discussion.

In summary, there are different causes in neonates with ALI/ARDSp and ALI/ARDSexp, although the clinical manifestations both types of patients were respiratory function damage, pulmonary inflammation and lung edema, physiological differences are still present in clinic. According to these pathological differences, the management points should be individualized, and dynamic PAP monitoring should be carried out to determine the severity of the disease. Active treatment of primary disease and rational use of drugs to reduce PAP are very importance in improving right heart function and prognosis, thus reducing mortality.

Author contributions

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Methodology: Qi-Jun Yong.
Validation: Tong-jin Yin.
Writing – original draft: Tong-jin Yin, Yu-Sheng Hu, Sheng Cheng.
Writing – review & editing: Tong-jin Yin, Yu-Sheng Hu, Sheng Cheng, Qi-Jun Yong.

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