Tidal breathing pulmonary function and influencing factors in late preterm and full-term neonates

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ABSTRACT

Neonatal period is the key stage of lung development. However, tidal breathing pulmonary function (TBPF) of late preterm and full-term infants without pathology has rarely been studied. Our research focuses on the early neonatal period and aims to detect the factors influencing PF and implemente effective interventions earlier. **Methods:** This prospective study evaluated the PF characteristics of 142 infants admitted to our neonatology department. Potential explanatory variables for TBPF were analyzed using single-factor and multi-factor linear regression analyses. **Results:** PF characteristics, including tidal volume (VT) and minute ventilation (MV), were significantly lower in late preterm infants compared to full-term infants (*P*<0.01). The ratio of time to peak tidal expiratory flow to total expiratory time (TPTEF/TE) and volume to peak tidal expiratory flow to total expiratory volume (VPTEF/VE) were not significantly different between groups (*P*>0.05). In the single-factor analysis, changes in parameters related to lung volume (VT, VT/kg, MV) were mainly correlated with gestational age (GA), corrected GA, birth weight, weight at examination, weight changes, and serum albumin(SAB). After birth, VT/kg and indicators of airway obstruction (VPTEF/VE and TPTEF/TE) changed significantly with increasing age. In the multiple-factor analysis, the main factors influencing VT, VT/kg, and MV were corrected GA and daily weight change, GA and corrected GA, and corrected GA and SAB, respectively. **Conclusion:** The main difference in PF between full-term and late premature infants was the lung volume. In these newborns PF was associated with GA, corrected GA, daily weight change, and SAB level. These results suggest that an adequate energy supply is critical for PF development in neonates, and especially for premature infants.

1 INTRODUCTION

The neonatal period is critical for the development of pulmonary function. Tests for pulmonary function are of great value in the diagnosis, treatment, severity assessment, and prognosis of respiratory diseases in neonates [1,2]. These tests can be used to identify pathophysiological changes associated with pulmonary diseases, and provide an important reference for the assessment of respiratory system development. However, these evaluations require deep sleep to ensure tidal breathing, which will make examinations difficult and time-consuming, especially as most newborn patients are in critical condition. At present, most studies in this field focus on the effects of fetal intrauterine growth retardation, preterm birth, extremely low birth weight, and bronchopulmonary dysplasia (BPD) on pulmonary function when they are at the pre-school, school, and even adult years [1,3-6]. The majority of pulmonary function research during the neonatal period pertains to the diagnosis and assessment of acute or chronic pulmonary diseases [7,8]. However, tidal breathing pulmonary function in late preterm and full-term neonates without pathology has rarely been studied. Therefore, the objective of this study was to examine tidal breathing pulmonary function changes in late preterm and full-term neonates, and its influencing factors, with the overarching aim of facilitating the implementation of prompt intervention measures for improving long-term pulmonary function levels.

2 MATERIALS AND METHODS

2.1 Research objects

This study included late preterm and full-term newborns who were admitted to the Neonatal Department of the First Affiliated Hospital of Fujian Medical University (Fuzhou, China) from May 2019 to September 2020. Newborns were included if they had a gestational age of ≥34 weeks, and did not receive respiratory support after birth. Exclusion criteria included: (1) pulmonary infection, aspiration pneumonia, apnea, and wet lung; (2) sepsis; (3) abnormal thyroid function; (4) anemia; (5) application of pulmonary surfactant; (6) use of caffeine; (7) nasal feeding; (8) congenital heart disease; (9) various congenital malformations (such as congenital diaphragmatic hernia, esophagotracheal fistula, esophageal atresia, etc.); (10) neuromuscular disease; (11) mother's history of smoking; and (12) a family history of bronchial asthma. Informed consent was obtained from all the researchers involved. The study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical

University，and written parental consent was obtained at enrolment.

2.2 Methods: Pulmonary function tests

2.2.1 Measuring instruments

As suggested by previous studies, the JAEGER MasterScreen equipment was used to examine tidal breathing pulmonary function, and the environmental temperature, humidity, and capacity were calibrated prior to the initiation of each test [9-11].

2.2.2 Measurement methods

The body length and weight of each subject were measured prior to the test, and nasopharyngeal secretions were removed. Each newborn was administered an oral dose of

10% chloral hydrate (0.5 mL/kg). After being orally sedated, the infants were clothed in loosely fitting garments and laid on their backs on baby beds, with their heads placed at the midline. A doctor selected an appropriately sized mask button for each neonate's nose and mouth, and ensured that there were no leakages, and that the infant breathed smoothly. Five consecutive tests were subsequently performed, and 20 tidal breaths were recorded for each test; the average values were then calculated. All tests were conducted between 3 to 5 PM by the doctor, who was a lung function testing professional.

2.2.3 Measurement parameters

The following parameters were assessed: tidal volume (VT); VT per kg of body weight (VT/kg); minute ventilation (MV); ratio of time to peak tidal expiratory flow to total expiratory time (TPTEF/TE); ratio of volume to peak tidal expiratory flow to total expiratory volume (VPEF/VE); and ratio of the expiratory to the inspiratory flow rate when exhaling and inhaling 50% of the tidal breath volume (TEF50/TIF50).

2.3 Statistical analysis

Data analysis was performed using IBM SPSS Statistics v22.0 software. A chi-square test was used to compare the enumeration data. Measurement data were expressed as mean ± standard deviation, and a t-test was employed. $P<0.05$ was considered as statistically significant. Furthermore, lung function factors determined to be significant in the single-factor analyses were used as independent variables in a multi-factor linear regression analysis.

3 RESULTS

3.1 Basic characteristics of the newborns

In all, 142 late preterm and full-term newborns were admitted to the Neonatology Department of the First Affiliated Hospital of the Fujian Medical University from May 2019 to September 2020. They were divided into two groups according to gestational age: late preterm infants (19 males and 15 females; gestational age ≥34 and <37 [i.e., 35.50±1.27] weeks; birth weight [2.50±0.44 kg]) and full-term infants (65 males and 43 females; gestational age ≥37 [i.e. 39.49±0.91] weeks; birth weight [3.40±0.40 kg]).

3.2 Comparison of tidal breathing pulmonary function examination results between late premature and full-term newborns

The VT and MV of late premature infants were significantly lower than those of full-term infants ($P<0.01$). The VT of the former, after weight correction, was higher than that of the latter; however, no significant differences were observed between the two groups for indicators reflecting airway obstruction (VPTEF/VE, TPTEF/TE, and TEF50/TIF50) (see Table 1).

3.3 Influencing factors of tidal breathing pulmonary function in late premature and full-term newborns

3.3.1 Single-factor analysis

Age and corrected gestational age

After birth, the VT/kg increased with age, and the indicators of airway obstruction, VPTEF/VE and TPTEF/TE, showed a statistically significant decrease ($P<0.05$). However, VT, MV, and TEF50/TIF50 showed no significant changes ($P>0.05$), as shown in Table 1.

The VT and MV were significantly lower in newborns with a corrected gestational age of <37 versus ≥37 weeks (*P*<0.01); however, the VT/kg, VPTEF/VE, TPTEF/TE, and TEF50/TIF50 showed no significant differences (*P*>0.05), as shown in Table 1.

Weight

The effects of different weights at birth and examination on the pulmonary function of newborns were evaluated. Newborns with a greater weight at birth and examination had significantly higher VT and MV values (*P*<0.01); the VT/kg decreased gradually after weight correction. However, no significant differences between the three groups were found for indicators of airway obstruction, including VPTEF/VE, TPTEF/TE, and TEF50/TIF50 (%) (*P*>0.05), as shown in Table 2.

To examine the effect of weight change on the lung function of newborns, their weights at examination were compared with those at birth. They were divided into two groups: those who lost weight and those who did not. VT, VT/kg, and MV were significantly higher among newborns who had no weight loss (*P*<0.05). However, no significant differences between the two groups were observed for VPTEF/VE, TPTEF/TE, and TEF50/TIF50 (%) (*P*>0.05), as shown in Table 2.

Auxiliary inspection

In terms of the influence of peripheral blood white blood cell counts on neonatal lung function, newborns with counts of $\geq 10\times10^9$/L had significantly lower VT/kg and higher MV values than newborns with counts of $<10\times10^9$ (*P*<0.05). However, VT, VPTEF/VE, TPTEF/TE, and TEF50/TIF50 were not significantly different (*P*>0.05), as shown in Table 3.

Peripheral blood hemoglobin

Newborns were divided into those with hemoglobin levels of <145 g/L and ≥145 g/L. The results showed no significant differences in VT, VT/kg, MV, VPTEF/VE, TPTEF/TE, or TEF50/TIF50 between the two groups (see Table 3).

Effect of serum albumin on neonatal lung function

Three groups were formed based on serum albumin levels: <30 g/L, 30–35 g/L, and >35 g/L. VT and MV were significantly higher with increasing serum albumin levels ($P<0.05$), while VT/kg, VPTEF/VE, TPTEF/TE, and TEF50/TIF50 showed no significant differences ($P>0.05$), as shown in Table 3.

3.3.2 Analysis of variance for multiple linear regression model

The single-factor analysis indicated that lung volume parameters (VT, VT/kg, and MV) of newborns were affected by birth weight, examination weight, weight change, gestational age at birth, corrected age, and auxiliary examination of serum albumin levels. Variables found to be significant in the single-factor analysis (i.e., gestational age, corrected gestational age, daily birth weight, peripheral blood leukocyte count, peripheral blood hemoglobin levels, and serum albumin level) were entered as independent variables in a multiple dependent variable linear model of variance analysis, with VT, VT/kg, and MV as the dependent variables (α=0.05 and β=0.10; α refers to the significance level or acceptable probability of a Type I error, and β refers to the acceptable probability of a Type II error). It can be observed from the results shown in Table 4 that the main influencing factors of VT were corrected gestational age and daily weight change during examination, while those of VT/kg were gestational age at birth and the corrected gestational age at examination (since VT/kg was negatively correlated with gestational age after birth weight correction). The major factors that influenced MV were the corrected gestational age and albumin levels at the time of examination. Considering VT as the dependent variable, the results of the linear regression of age and daily weight change as the constant during the examination were as follows: F=19.173; P=0.000; and VT regression equation ($VT=-19.241+1.051X_1+14.648X_2$). For the linear regression with VT/kg as the dependent variable, and gestational age at birth and corrected gestational age at examination as the constants, the findings were as follows: F=5.389; P=0.006; and VT/kg regression equation ($VT/kg=10.406-0.695X_3+0.595X_1$). The results of the linear regression with MV as the dependent variable, with corrected gestational age and serum albumin as the constants during examination, were: F=16.989; P=0.000; MV regression equation ($MV=-1.152+0.062X_1+0.072X_4$).

4 DISCUSSION

The measurement of neonatal tidal breathing pulmonary function is highly valuable in assessing neonatal pulmonary development and the severity and future risk of respiratory diseases. Previous studies have confirmed that a family history of asthma and exposure to environmental pollutants, especially a maternal history of smoking, affect neonatal pulmonary function [12,13]. Therefore, it is necessary to exclude their effects when evaluating other factors that may potentially influence neonatal pulmonary function. In this study, we examined late preterm and full-term neonatal pulmonary function changes and its influencing factors. Confounding variables that may have impacted lung function (e.g., receiving respiratory support, respiratory system diseases, sepsis, application of lung surface active substances, caffeine, birth defects, neuromuscular diseases, family history of bronchial asthma, and maternal smoking history) were ruled out. The subjects were neonates with no evident diseases; this better reflected the characteristics and influencing factors of normal neonatal tidal breathing pulmonary function.

Previous studies have confirmed that gestational age is a key factor in neonatal lung development [14,15]. Lombardi et al. examined the pulmonary function of 194 premature infants with gestational ages of less than 32 weeks at birth. At the age of 5 years, 55% of the children had a wheezing history and 21% had been hospitalized due to lower respiratory tract infections; 31% had experienced wheezing in the past 12 months, which was related to the increase of airway resistance parameters, as indicated by lung function test results [16]. Lung function was slightly impaired in BPD as compared with non-BPD patients (24 and 170 cases, respectively); however, this did not reach statistical significance. A multivariate analysis found that low gestational age was associated with poorer lung function. In our study, the pulmonary function characteristics of late preterm and full-term infants were compared, the results of which showed that the VT and the MV of the former were significantly lower than those of the latter. This indicated that gestational age mainly affected lung capacity development, with no significant influence on airway resistance.

In the present study, we investigated factors that potentially influenced neonatal tidal breathing lung function. First, the effects of age and corrected gestational age were compared. A higher corrected gestational age was significantly associated with greater VT and MV values. With an increase in age, the VT/kg and the indicators of airway obstruction (VPTEF/VE and TPTEF/TE) changed significantly, indicating that age and corrected gestational age mainly affect the development of lung capacity. The maturation of the respiratory system after birth also affects changes in pulmonary ventilation function. Jiang et al. conducted a study on infant lung function by dividing newborns below the age of 2 years into four age groups: 1–28 days, and 2–6, 7–12, and 13–24 months [17]. It was found that VT was significantly greater in higher age groups, while VT/kg and TPTEF/TE were not significantly different. These results suggest that with increasing age, lung function maturation is dominated by volume development, which is consistent with the results of our study. However, in contrast with our study, all subjects in this prior study were full-term infants, and those with family histories of tobacco exposure and allergic diseases were not excluded.This is the advantage of our research.

Weight is a factor that influences neonatal pulmonary function. Jiang et al. tested the tidal breathing lung function of 211 healthy full-term newborns, and found that VT was significantly correlated with age and body weight, while the selected lung function parameters showed no significant correlation with gender [17]. Furthermore, body weight was found to be the strongest predictor of neonatal lung function. In our study, the weights at birth and examination of late preterm and full-term infants were grouped. The results indicated that the greater the weight, the higher the indicators of lung volume (i.e., VT and MV); furthermore, VT/kg gradually decreased after weight correction. This suggested that while these weights mainly affect lung volume development, they have no significant influence on lung ventilation function or airway resistance. Previous studies have reported an association between low birth weight and a greater risk of decreased lung function in children, especially among those with a family history of asthma. Brew et al. studied the relationship between birth weight and lung function in 449 8-year-old children with a family history of asthma [12].

They found that low birth weight was associated with asthma attacks. Forced expiratory volume in 1 second(FEV_1) and forced vital capacity(FVC) increased between 165 mL and 205 mL for every kg of weight gained after the administration of bronchodilators. Thus, the authors suggested that low birth weight was a greater risk factor for lung function loss in their study cohort. However, their study utilized a retrospective design to assess the relationship between birth weight and lung function level in school-aged children. In our study, the influence of birth weight on tidal breathing lung function was examined during the neonatal period. This was an important advantage of our study, as assessments conducted at an earlier age are beneficial for the early detection of factors that potentially influence pulmonary function. This in turn facilitates the implementation of effective interventions that aim to improve long-term pulmonary function.

Furthermore, we compared the birth weight with the weight at examination (defined as the change in weight). Newborns were divided into two groups: those who had lost weight, and those who had not. The results showed that the indicators of lung capacity (VT, VT/kg, and MV) were significantly higher among newborns who did not experience a loss in weight. A higher serum albumin level was also associated with a greater VT and MV. These findings suggest that both postnatal weight gain and an increase in serum albumin in late preterm and full-term infants contribute to lung function development. This indicates that an adequate caloric supply is of great importance for lung development, especially in early premature infants, and the improvement of long-term lung function.

The lower VT/kg and higher MV values observed among newborns with white blood cell counts of $\geq 10\times10^9$/L may have been related to the elevation of respiratory frequency. Blood hemoglobin levels did not have any significant effects on lung function parameters; this may have been related to the fact that none of the neonates had evident diseases, including anemia. The effect of auxiliary examination on the pulmonary function of preterm and full-term newborns warrants further investigation.

The results of the single-factor analysis indicated that birth weight, weight at examination, weight changes, gestational age, corrected gestational age, and auxiliary examination of serum albumin had an influence on neonatal pulmonary function, mainly on the indicators of lung capacity (VT, VT/kg, and MV). The results of the multi-factor linear regression analysis indicated that VT, VT/kg, and MV were associated with corrected gestational age and daily weight change, gestational age and corrected gestational age, and corrected gestational age and albumin level, respectively. This suggests that corrected gestational age, daily weight gain, gestational age at birth, and serum albumin are important for early pulmonary function development in neonates. These findings may be used to facilitate the improvement of neonatal pulmonary ventilation function through the early implementation of nutritional interventions to reduce the risk of respiratory diseases.

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