


Pulmonary Function Testing in Pediatric Pneumonia Patients With Wheezing Younger Than 3 Years of Age

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Abstract

Background. Wheezing symptoms are one of the risk factors in young pneumonia patients that often leads to asthma development. Infant pulmonary function test (iPFT) is potentially a useful tool to help identify and manage these high-risk pneumonia patients. **Methods.** To examine whether patients with wheezing symptoms are more likely to have poorer pulmonary function and treatment outcomes, and also to explore the clinical benefit of iPFT in young pneumonia patients, we conducted a retrospective analysis of 1005 pneumonia inpatients <3 years of age who had undergone iPFT testing in 2016 at Liuzhou Maternity and Child Healthcare Hospital in Guang-Xi, China. **Results.** We identified from the hospital database 505 pneumonia patients who presented with wheezing and 500 without wheezing. Univariate analysis showed that wheezing symptoms, viral infection, age <1 year, female gender, and prematurity were significantly associated with poorer iPFT results. After adjusting for confounders, patients with wheezing showed significantly poorer pulmonary function. Patients with wheezing had longer length of stay (7.9 ± 3.9 days vs 6.5 ± 2.6 days; $P < .001$) and lower percent with no residual clinical symptoms at discharge (58% vs 98%; $P < .001$) when compared with those of non-wheezing patients. In addition, 81% of patients with viral infection as compared with 43% of patients with nonviral infection presented with wheezing symptoms ($P < .001$). **Conclusion.** Wheezing symptoms were associated with poorer iPFT measures and treatment outcomes for pneumonia inpatients <3 years of age. Patients with wheezing had poorer treatment outcomes. iPFT can be useful in assessing and monitoring young patients with high risk of developing asthma or chronic lung disease later in life.

Keywords

wheezing, infant pulmonary function test, pneumonia, viral infection, chronic lung disease, asthma

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Introduction

Pneumonia continues to be the number one killer of children under 5 years of age worldwide and in China. Although effective interventions have significantly reduced pneumonia mortality,^{1–4} it still accounts for nearly one fifth of childhood deaths worldwide.⁴ Pneumonia is an inflammatory condition of the lung primarily affecting the alveoli. Common symptoms include productive or dry cough, chest pain, fever, and difficulty breathing. Pneumonia is typically caused by viruses and/or bacteria.^{5–7}

The rising incidence of asthma may be partly due to environmental factors such as worsening air pollution. The proportion of pneumonia cases with wheezing in

infants is also increasing.^{8,9} Studies have confirmed that the incidence of bronchial asthma has been rising over the recent years, and that most children with asthma have disease onset before the age of 8 years, while 70% of them have their first wheezing episode before the age of 3 years.¹⁰ This may have a severe impact on these

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children's quality of life as well as an impact on their family's financial and psychological burdens.

Pneumonia with wheezing symptoms (PW) is a class of pneumonia that is accompanied by bronchospasm, which can be appreciated on lung auscultation and can sometimes be audible when severe. It is often caused by a respiratory viral infection.⁸ Viral infection causes the body to produce a large number of cytokines and chemokines, which triggers an immune response. In addition, the damage of epithelial cells and antiviral response lead to edema, increased vascular permeability, and increased mucus production, which leads to airway obstruction and ventilation/perfusion dysfunction mismatch, eventually resulting in shortness of breath.^{10,11} Early childhood PW often results in asthma later in life,¹ which may affect growth and development.⁸ A study published by Morgan et al in 2005¹² followed a group of children from birth who had at least one wheezing lower respiratory illness before the age of 3 years. The authors found that children who had any episode of wheezing lower respiratory illnesses before the age of 3 years, whether transient or persistent, had significantly lower FEF₂₅₋₇₅ (forced expiratory flow between 25% and 75% of forced vital capacity [FVC]), forced expiratory volume in 1 second (FEV₁), and FEV₁-FVC ratio through age 16.

Pulmonary function testing (PFT) is one of the most widely used diagnostic tools in the treatment of chronic lung diseases such as asthma.^{5,6} As a noninvasive and rapid diagnostic tool, PFT is frequently accepted by young patients and their parents. However, before the widespread usage of PFT in young patients with PW can be recommended, more studies should be done to assess the clinical and diagnostic benefit of PFTs in this patient subset.

Infant pulmonary function testing (iPFT) is a very useful tool in both research and clinical settings in young pediatric patients and infants. Major techniques and methods of iPFT include tidal breathing pattern, airway resistance, body plethysmography, and rapid thoracoabdominal compression (RTC). Tidal breathing is the most frequently used component of the test. Other important parameters are TPTEF/TE (ratio of time to peak tidal expiratory flow to total expiratory time) and VPEF/VE (ratio of volume to peak expiratory flow to total expiratory volume) that reflect the obstruction degree and clinical conditions.

So far, few studies have been done to investigate the clinical utility of iPFT in young children in the United States, Europe, and Asia. Peterson-Carmichael et al (2014) conducted a survey to assess the practice and clinical benefits of iPFT.² The authors concluded that the future of iPFT was uncertain due to widely varied

clinical practice, the need for sedation, and the uncertainty regarding the clinical impact of test results.

In China, PFT is commonly used in the management and treatment of young children diagnosed with chronic lung diseases such as asthma, but it is not considered standard practice in small community hospitals. Infant PFT has been widely used in large teaching hospitals in China for the treatment of asthma and other types of lung diseases including pneumonia and PW in children without much evidence-based clinical data. Early detection and proper treatment of PW in young children may reduce their risk of developing bronchial asthma later in life.¹³ Our study explored the potential clinical benefit of iPFT for the treatment of pneumonia in infants and young children <3 years of age in Liuzhou Maternity and Child Healthcare Hospital (LMCHH) in Guang-Xi province, China. We examined whether wheezing symptoms in this patient population were associated with poor pulmonary function as measured by iPFT after adjusting for potential confounders such as viral infection, age, gender, prematurity, and anemia. We hypothesized that young pediatric PW patients have poorer pulmonary function and therefore poorer treatment outcomes than do non-PW patients.

Methods

Study Patients

We conducted a retrospective, observational study in pneumonia patients <3 years of age (0-2.99 years of age) admitted to LMCHH between January 2016 and June 2016. Patients with comorbidities such as congenital heart diseases, diabetes, and so on, were excluded from study. Patients who met the above-mentioned study criteria during patient accrual period but were treated in the pediatric intensive care unit at any time during their hospital stay were also excluded. Sequential sampling method was utilized until approximately 500 patients were accrued in each study group (PW vs non-PW). This study was approved by the ethics committee. We were not provided an approval number; however, the name of the ethics committee is the Liuzhou Maternal and Child Health Hospital Ethics Committee.

Data Collection

The data elements recorded in the study included the following: gender, age, preterm status, hemoglobin (Hb) level (g/L), white blood cell count ($10^9/L$), C-reactive protein (CRP; mg/L), procalcitonin (PCT; ng/L), sputum culture, blood culture, antibiotic use, previous and current wheezing symptoms, 5 PFT

indices (see below in PFT Testing) at baseline, liver and kidney function tests, viral testing, *Mycoplasma pneumoniae* serology test, hospital length of stay (LOS), and discharge outcome (completely cured/improved/worsened/death).

Infant PFT Testing

PFT primarily measures the level of airway resistance and obstruction. The 5 indices of iPFT performed in this study were tidal volume (TV), respiratory frequency (rate), TPTEF/TE, VPEF/VE, and lung compliance (Crs). The machine (MasterScreen PAED) used in PFT testing was manufactured by the German company Jaeger. Tests were performed by physicians trained and certified in the operation of the equipment. Equipment calibration and quality control were performed daily per manufacturer instructions.

Definition of PFT Indices

TV represents the normal volume of air displaced between normal inhalation and exhalation when extra effort is not applied. In a healthy, young adult, TV is approximately 500 mL per inspiration or 7 mL/kg of body mass.¹ In a healthy child, TV is ≥ 6 mL/kg of body mass. TPTEF/TE is the ratio of time to peak tidal expiratory flow (TPTEF) over total expiratory time (TE). VPEF/VE is the ratio of volume to peak expiratory flow (VPEF) over total expiratory volume (VE). Crs measures of the lung's ability to stretch and expand (distensibility of elastic tissue) when lungs are stationary (static compliance). In a healthy child, Crs is normally >10 mL/kPa/kg.

Infant PFT Testing Procedures

- Our testing procedure followed the plethysmography method, and thus no vest was used to determine FEFs.
- During the test, patients were either asleep or sedated using chloral hydrate (0.3-0.5 mL/kg) administered orally.
- Patients were placed in a clear plastic box on their back with mouth and nose covered tightly with a mask appropriate for patient size.
- Mask was connected to the PFT machine's flow sensor before initiation of test.
- At least 5 repetitions of 15 to 20 tidal breathing cycles were recorded.
- Mean values of the PFTs were calculated and reported by a computer connected to the flow sensor.

Laboratory Data Collection

All blood samples used for the study laboratory tests were stored in either venous blood EDTA (ethylenediaminetetraacetic acid) anticoagulant tube or biochemical procoagulant tube.

- *PCT*: A mini-VIDAS, which is a fully automatic immunofluorescence analyzer (Biomérieux, Marcy-l'Étoile, France), was used to measure PCT level.
- *CRP*: CRP level was measured by a fully automatic biochemical analyzer (Hitachi, Tokyo, Japan).
- *Mycoplasma pneumoniae* (MP) detection: An agglutination assay (SERODIA-MYCO II; Fujirebio Inc, Tokyo, Japan) was used to detect *M. pneumoniae*.
- *Sputum culture*: Sputum samples were analyzed using VITEK 2 compact automatic microbial analysis system (Biomérieux).
- *Blood culture*: Blood samples were cultured in the BacT/AlerT 3-dimensional system (Biomérieux).
- *Virus detection*: Nasal secretions collected from study subjects were processed using direct immunofluorescence techniques specifically for respiratory virus detection. All laboratory tests were conducted in accordance with standard laboratory operating procedures. A list of viruses that can be detected by our laboratory tests include human respiratory syncytial virus (RSV), Adenoviridae (RSV), parainfluenza virus (I, II, and III subtypes), influenza A virus, and influenza B virus.

Statistical Analysis

Patient variables analyzed included patient demographic characteristics, clinical characteristics, laboratory test data, LOS, and discharge status. Patients were classified into 2 study groups (PW or non-PW) depending on whether they had wheezing at presentation. Based on sputum culture, blood culture, PCT, and viral test results, pathogens were classified into 2 groups: viral or MP/bacterial infection. Patients tested positive in virus detection tests were classified as "viral" regardless of their results in MP and bacterial test results. Anemia in this study was defined as Hb level <9 g/dL. A premature birth was defined as one that occurred before the start of the 37th week.

Two-sample *t* tests and χ^2 tests were used to compare patient baseline characteristics. *T* tests were also utilized

Table 1. Baseline Characteristics.

Patient Characteristics	PW Patients (N = 505)	Non-PW Patients (N = 500)	P (2-Sided)
Age (months) ^a	10.2 ± 7.4	9.3 ± 8.3	.006*
Gender (male %)	74	63	<.001*
Preterm (%)	7	1	<.001*
Virus infection (positive %)	31	7	<.001*
WBC (10 ⁹ /L) ^a	12.3 ± 5.3	11.8 ± 5.3	.203
Hb (g/L) ^a	113.4 ± 13.8	114.3 ± 13.1	.317
CRP (mg/L) ^a	6.4 ± 14.0	6.2 ± 17.2	.798
Tidal volume (mL/kg) ^a	8.0 ± 1.7	8.1 ± 1.6	.236
TPTEF/TE ^a	23.3 ± 9.2	24.6 ± 9.1	.023*
VPEF/VE ^a	25.3 ± 7.5	26.7 ± 7.2	.002*
Respiratory rate (minutes) ^a	33.7 ± 9.8	33.2 ± 9.3	.401
Crs (mL/kPa/L) ^a	9.7 ± 4.5	13.1 ± 4.6	<.001*

Abbreviations: PW, pneumonia with wheezing symptoms; WBC, white blood cell; Hb, hemoglobin; CRP, C-reactive protein; TPTEF/TE, ratio of time to peak tidal expiratory flow over total expiratory time; VPEF/VE, ratio of volume to peak expiratory flow over total expiratory volume; Crs, lung compliance.

^aMean ± standard deviation.

*P value < .05.

to determine which factors were associated with poorer pulmonary function. Last, generalized linear model analysis was used to compare the 5 indices of PFT between the PW and non-PW study groups while adjusting for confounders such as age (<1 year vs 1-2.99 years), gender, severe anemia, prematurity (yes/no), and infection pathogen (viral vs MP/bacterial). Several potential second-order interaction terms between independent risk factors were examined for statistical significance (eg, PW*viral and PW*age).

Results

Baseline Characteristics

A total of 1005 patients were included in the study. Among them, 505 had wheezing symptoms (PW group) and 500 did not (non-PW group). Comparison of the baseline characteristics of the 2 groups is given in Table 1. Non-PW patients were younger ($P = .006$), while PW group had higher percentage of male patients ($P < .001$). PW patients had significantly poorer pulmonary function in terms of TPTEF/TE, VPEF/VE, and Crs, but not in terms of TV or respiratory rate. Of the patients tested positive for a virus infection, most were positive for RSV except for 2 patients who were positive for parainfluenza virus (type III).

Factors Correlated With Pulmonary Function

Univariate analysis showed that age <1 year, female gender, prematurity, viral infection (vs MP and/or bacterial infection), and wheezing symptoms were negatively

correlated with pulmonary function. Anemia was only negatively correlated with pulmonary function in terms of TV and respiratory rate, but not correlated with TPTEF/TE, VPEF/VE, or Crs. A generalized linear model analysis was performed on each of the 5 iPFT indices adjusting for confounding factors described above. No interaction terms examined were statistically significant (eg, PW*viral, PW*age, viral*age, etc). Differences in least square means (or group means adjusted for all other confounders in multivariate models) as well as their corresponding P values for each of the 5 PFT indices were calculated and presented in Table 2.

It is also worth noting that PW group had a significantly higher percent of viral infection than non-PW patients did (31% vs 7%; $P < .001$), or 81% of patients with viral infection as compared with 43% of patients with nonviral infection presented with wheezing symptoms.

Outcomes

PW patients had an average of 1.4 days longer LOS than non-PW patients (7.9 ± 3.9 days vs 6.5 ± 2.6 days; $P < .001$). Fifty-eight percent of PW patients compared with 98% of non-PW patients were discharged with a “completely cured” discharge disposition ($P < .001$). No deaths nor cases in the “worsened” categories were observed in either patient group.

Discussion

The usefulness of PFT in clinical application is well recognized by clinicians in various adult patient populations. However, the role of iPFT in clinical application in the

Table 2. Least Square Mean Differences Between Groups in PFT Adjusted for Confounders.

Patient Characteristics	Tidal Volume		TPTEF/TE		VPEF/VE		Respiratory Rate		Lung Compliance	
	Difference ^a	P	Difference	P	Difference	P	Difference	P	Difference	P
PW vs non-PW	-0.2	.038*	-1.3	.027*	-1.4	.002*	1.0	.091	-3.6	<.001*
Age <1 year vs age ≥1 year	-1.1	<.001*	-1.3	.048*	-1.1	.032*	5.5	<.001*	-1.9	<.001*
Viral infection vs <i>Mycoplasma pneumoniae</i> /bacterial	-0.5	<.001*	-0.9	.241	-1.2	.048*	1.6	.035*	-2.4	<.001*
Female vs male	-0.2	.049*	0.7	.237	0.5	.294	2.0	.001*	-0.8	.008*
Preterm vs term	-0.2	.555	-4.3	.009*	-3.1	.016*	2.3	.149	0.3	.757
Anemia (Hb < 9) vs others	-0.5	.078	2.0	.209	1.5	.228	3.8	.018*	-0.2	.763

Abbreviations: PFT, pulmonary function test; TPTEF/TE, ratio of time to peak tidal expiratory flow over total expiratory time; VPEF/VE, ratio of volume to peak expiratory flow over total expiratory volume; PW, pneumonia with wheezing symptoms; Hb, hemoglobin.

^aLeast square mean differences between groups (PW vs non-PW, age <1 year vs age ≥1 year, etc.), while least square means are simple group means adjusted for all other covariates.

*P value < .05.

pediatric patient settings is unclear.⁹ Our study explored the clinical use of iPFT in the treatment of pneumonia in children <3 years of age by analyzing the clinical and iPFT data of 1005 pneumonia inpatients treated at LMCHH in Guang-Xi, China, over a 6-month period.

Multivariate analyses adjusting for confounders of iPFT indices showed that wheezing symptoms were significantly associated with poorer pulmonary function based on TV, TPTEF/TE, VPEF/VE, and Crs, but not on respiratory rate. We have also demonstrated that young pneumonia patients with wheezing symptoms had significantly longer LOS and lower percentage of “cure” rate at discharge (no symptoms of fever, coughing, wheezing, and rales). Our study further corroborates with the Tuscon Children’s Respiratory study¹² that wheezing symptoms in early childhood is an important determinant in the development of asthma and chronic airway obstruction later in life.

Having had a viral infection was found to be highly associated with poorer pulmonary function in all iPFT indices except TPTEF/TE in our study. This makes sense because wheezing symptoms were significantly associated with viral infection ($P < .001$). Lung surface active substances and Lung Function Index are 2 well-established indices of lung injury.^{14,15} Lung surface active substances such as SP-A, SP-B, and SP-C, secreted by alveolar type II epithelial cells, are essential for maintaining a healthy level of alveolar tension, Crs, and lung capillary tension. Related studies have shown that pneumonia patients with virus infections had widespread abnormal (low) serum levels of SP-A, SP-B, and SP-C expression. Studies also showed that adult viral pneumonia patients tended to have relatively poorer FVC, PEF₅₀, and MMF lung function indices.¹⁵ These findings are consistent with our clinical observations.

To effectively manage and treat these young and vulnerable patients, it is also important to understand other patient factors that are associated with impaired pulmonary function besides wheezing symptoms and viral infection. In this study, we found that age <1 year was significantly predictive of poorer pulmonary function in all 5 respiratory indices. It is well known that children aged 0 to 3 years grow rapidly in both height and weight. Height and weight are closely related to lung function. Thus, it makes sense that the lung functions of children <1 year of age are poorer than those aged 1 to 2.9 years.^{16,17}

Patients who were born prematurely were also more likely to have impaired pulmonary function in terms of TPTEF/TE and VPEF/VE in our patient sample. A study examining airway microbiome in chronic pediatric lung diseases found that microbiome changes due to prematurity appear to affect the inflammatory response to viral infections postnatally.¹⁸

Our data indicated that female patients in the present study tended to have poorer test results in TV, respiratory rate, and Crs. In the adult population, due to physiologic differences between male and female genders, the male’s lung capacity and Crs are in general better (larger) than those of females.¹⁹

Anemia was defined as Hb < 9 g/dL in our study (generally considered moderate anemia). We found that anemic patients had significantly higher respiratory rate than nonanemic patients but not different in terms all other 4 iPFT indices. It is known that Hb can affect the oxygen carrying capacity of blood in circulation.²⁰ In the case of anemia, the oxygen carrying capacity decreases and the respiratory function changes accordingly. This helps explain our finding of higher respiratory rate in patients with anemia.

Last, RTC, raised volume RTC (RVRTC) technique, and plethysmography are currently 3 of the most common techniques used in iPFT.²¹ At present in China, RTC and RVRTC are only being used in laboratory studies and are not promoted in clinical application due to their relatively more complex technical operation. In contrast, the plethysmography method is relatively simple to execute and is currently widely used in China as well as in LMCHH.

There were a few limitations regarding the sampling procedure in this study due to a logistical issue in a facility that has not yet established a robust research infrastructure. First, sequential sampling instead of random sampling procedure was adopted due to convenience and lack of local biostatistical support. Second, the 2 study groups (PW vs non-PW) were not matched in terms of important clinical confounders such as age, gender, preterm status, and so on. However, because these variables were also correlated with wheezing symptoms, it was not feasible to find 2 comparable study groups. We, however, performed multivariate analyses to adjust for all possible confounders such as age, gender, preterm status, and infection pathogen type to address any imbalance between the 2 study groups. Last, the patients who were admitted to intensive care unit during their hospital stay were not included in the study because their severe condition rendered them unable to go through iPFT testing.

Our future research direction will focus on long-term follow-up of pneumonia patients with wheezing symptoms to see how well iPFT testing at follow-up would help us further identify and manage these high-risk young pneumonia patients with the hope at preventing the development into asthma and other childhood chronic lung diseases.

In conclusion, our data suggest that iPFT testing results were sensitive enough to identify wheezing symptoms, viral infection (vs MP or bacterial infection), age <1 year of age, and prematurity as risk factors for poorer pulmonary function in pneumonia patients <3 years of age. In addition to having had poorer pulmonary function, young pneumonia patients with wheezing symptoms also had significantly higher morbidity as demonstrated by longer LOS and lower percentage of “cure” rate at discharge. It is important to follow-up on this subset of young pneumonia patients who have a higher risk of developing asthma later in life.¹² Infant PFT is a useful tool in identifying and managing high-risk pediatric pneumonia patients who may need closer monitoring and follow-up after hospital discharge, with referral to a pulmonologist and repeat pulmonary function testing.

Author Contributions

JC, XL, WD, EM contributed to the concept and design of the study with JC, XL, WD, JF, MZ, JZ contributing to acquisition of the data and JC, XL, WD, RS and EM contributing to data interpretation. JC, XL, WD, and EM drafted initial versions of the manuscript with critical revisions from JC, XL, WD, RS, JF, MZ, JZ, and EM. All authors gave final approval and ultimately agreed to accuracy and integrity of the work.

Declaration of Conflicting Interests

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