Impaired Lung Functions Using Tidal Breath Analysis in High-risk Infants with Recurrent Wheezing

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ABSTRACT

Objective: *We aimed to investigate lung functions using tidal breath analysis (TBA) in high-risk infants with recurrent wheezing.*
Methods: *Lung functions measured using TBA in infants with physician-diagnosed recurrent wheezing (≥3 episodes) who applied our institution between 2018-2020, were retrospectively analyzed. Infants were assigned to two groups: high-risk infants with recurrent wheezing (n=30) and wheezy infants without high risk of atopy (n=33).*
Results: *High-risk infants with recurrent wheezing had lower mean values of tPTEF, tPTEF: tE, VPTEF, and VPTEF: VE than that of wheezy infants without high risk of atopy. There was no significant difference between two groups in terms of Vt/kg and respiratory rate. ROC curve analysis showed that tPTEF: tE ratio <26.5 demonstrated 63.3% sensitivity and 63.6% specificity for detection of high risk of atopy.*
Conclusion: *This study showed that high-risk infants with recurrent wheezing have lower lung function than those of wheezy infants without high risk of atopy. TBA might be useful method to evaluate lung function in wheezy infants.*

INTRODUCTION

Wheezing is common in children and more than 30% of children suffer from wheezing before their third birthday.[1] It is not clear how this problem which is seen in early period, will progress to the advanced age of the child. Many wheezing infants have only a transient type of disease, however, approximately 40% of them will demonstrate asthma during school age.[2] Objective tools which could predict prognosis in these infants will assist in making the therapeutic decisions.[3] Tidal breath analysis (TBA) in wheezy infants, has been shown to predict subsequent wheezing illnesses.[4,5]

TBA is a new technique that has been used in a limited number of research centers, especially in measuring respiratory functions in infants. TBA is a repeatable method that allows the measurement of airway obstruction and tidal capacity during effortless spontaneous breathing in infants. This method is (i) noninvasive, (ii) does not require cooperation and (iii) does not require sedation.

The presence of family history of atopy has been accepted as a risk factor for the onset of respiratory symptoms in infants.[6] Although several risk factors for developing asthma in wheezing infants have been identified, the relevance of assessing lung function in these high risk infants remains unclear. Studies are needed to determine the effect of family history on lung function in infants. Accordingly, in

this study we aimed to investigate TBA in wheezy infants with high risk for atopy and to compare their data with wheezy infants without high risk of atopy.

MATERIAL and METHODS

Subjects

This retrospective study was conducted between January 2018 and March 2020 at the outpatient clinic of pediatric allergy and immunology at the Aydın Adnan Menderes University. The study was approved by the Institutional Ethics Committee (No: 2020/228). Infants with recurrent wheezing (≥3 episodes of physician verified wheeze) were assigned to two groups: (i) wheezy infant with positive family history of atopy (high risk group): with at least one parent or sibling with physician-diagnosed asthma, allergic rhinoconjunctivitis, atopic dermatitis, allergic urticaria and food allergy, and (ii) wheezy infant without positive family history of atopy.

The exclusion criteria were as follows: Prematurity (<370/7 weeks), small for gestational age, known history of bronchopulmonary dysplasia, major congenital anomalies, neuromuscular diseases, infants delivered to mothers who gave a history of smoking, congenital heart diseases, any chronic lung disease, any previous non-respiratory infection, immunodeficiency, exposure of passive smoking, chronic disease, respiratory infection within 3 weeks, infants who received corticosteroid or bronchodilator treatment before three weeks.[7]

Tidal breath analysis measurements

Tidal breath flow obtained with a commercially available portable pediatric lung function device (MasterScreen PAED, CareFusion, Germany). The flow was measured by a non-heated pneumotachograph with a flow range of 0-10 L/min (Hans Rudolph Inc, USA). The system was checked for leakage after the transparent facemask (Rendell-Baker, Soucek) was placed on the face.[8,9] A thin sealing ring of silicon putty was effective in prevention of air leaks. Dead space for the pneumotachograph and system was 1.66 mL and 2.4 mL, respectively. Standard calibration of the system was performed by the experienced practitioner with a 100 mL calibration syringe before each recording session. All the measurements were performed in the early morning time (between 09:00-12:00 am) after 30 minutes of feeding during natural and quiet sleep. Any sedative drugs such as chloral hydrate and triclofos sodium solutions were not given. The face mask was placed and recordings began after quiet sleep which defined as regular respirations, no eye movement, and no overt motions. Recording was stopped when any movement of the body, rapid eye movements, hiccups, or impaired rhythm of breathing is observed. The ambient temperature was maintained at 22-25°C. Recording was made after a sufficient adaptation period (for 2-3 minutes) had been allowed to regular respiration.[10,11] Depending on the variability of the breathing pattern, at least 60 inspiratory and expiratory breath cycles were measured as the flow-volume curve considered as an epox.[8,9] The respiratory pattern in which at least 20 regular epox cycles were evaluated. All epox values were recorded and averages were calculated separately by two different researchers. The parameters were measured with each breath of the infant and a diagram consistent with the breath was formed. The average value was measured after at least 20 consecutive artifact-free breaths and the best three values were selected.[12] Parents were always accompanied their infants during the measurement.

The main parameters of tidal breath include; time to peak tidal expiratory flow (tPTEF), peak tidal expiratory flow (PTEF), expiratory time (TE), time to reach peak tidal expiratory flow to total expiratory time (tPTEF:tE), tidal volume (VT), inspiratory time (Ti), expiratory flow when %75, 50% and 25% of tidal volume remains in the lungs (TEF75, TEF50, and TEF25), respiratory rate (RR), exhaled volume to peak tidal expiratory flow (VPTEF), the volume until peak tidal expiratory flow to total expiratory volüme (VPTEF:VE) and total expiratory volume (VE). All parameters were calculated by the tidal breath analyze device computer.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Categorical data were presented with n and %, and numerical data with mean±standard deviation if normally distributed, and median (IQR) if non-normally distributed. Descriptive statistics

(kurtosis and skewness), visual methods (histogram), and analytical tests (Shapiro-Wilk test) were used to determine the normal distribution of numerical variables. Chi-square tests were used for comparison of categorical data. In the comparison of independent 2 groups, student t test was used if the data was normally distributed, and Mann Whitney U test was used if the data were non-normally distributed. Spearman correlation test was used for the associations between numeric data. Receiver Operating Curve (ROC) analysis was used for some breath parameters in predicting presence of high risk. When a significant cut-off value was detected the sensitivity, specificity and area under curve statistics were presented. A linear regression model was used to identify independent predictors of tPTEF:tE. Type I error was determined as 5% and a p value was<0.05 was considered statistically significant.

RESULTS

a. Patient Characteristics

A total of 63 wheezy infants aged 8–23 months were included in this study. The characteristics of the wheezy infants are summarized in Table 1. There was no significant difference between two groups in terms of age, gender, weight, and height.

Table 1. Demographic characteristics of the infants*

Gender	
Female	27 (42.9)
Male	36 (57.1)
Age (month)	16.0 (11.0-23.0)
Weight (kg)	10.6±2.8
Height (cm)	78.8±9.1
Mother Astma	
Yes	47 (74.6)
No	16 (25.4)
Non-Asthmatic Atopy in the Mother	
Yes	57 (90.5)
No	6 (9.5)
Father Astma	
Yes	57 (90.5)
No	6 (9.5)
Non-Asthmatic Atopy in the Father	
Yes	61 (96.8)
No	2 (3.2)
Sibling Astma	
Yes	58 (92.1)
No	5 (7.9)
Stove Heating at Home	
Yes	53 (84.1)
No	10 (15.9)
Household Pets	
Yes	60 (95.2)
No	3 (4.8)

Data were presented as n (%) or mean±standard deviation if normally distributed, and median (IQR) if non-normally distributed
Abbrevations: kg, kilogram; cm, centimeter; IQR, interquartile range

b. Measurement of lung function

The comparison of TBA parameters between high-risk infants with recurrent wheezing and wheezy infants without high risk of atopy are shown in Table 2. The parameters of tPTEF, tPTEF:tE, VPTEF, VPTEF:VE were significantly lower in infants with high risk when compared with the infants with no risk (p< .05). Although VT/kg was lower in infants with high risk than no risk, the difference was not significant (p= .11).

Age was positively correlated with tPTEF, tPTEF:tE and VPTEF [(r= 0.448, p< 0.001), (r= 0.310, p= 0.014) and (r= 0.709, p< 0.001) respectively] (Table 3).

Table 2. Comparison of high-risk infants with recurrent wheezing and wheezy infants without high risk of atopy*

	High Risk (n=30)	No Risk (n=33)	p†
Gender			
Female	11 (40.7)	16 (59.3)	
Male	19 (52.8)	17 (47.2)	0.344‡
Age (month)	15.5 (8.0-22.0)	17 (12.0-23.0)	0.347§
Weight (kg)	11.0±3.4	10.3±2.1	0.350
Height (cm)	77.7±10.4	79.7±7.7	0.389
tPTEF	0.2 (0.2-0.3)	0.4 (0.3-0.4)	0.002§
tPTEF:tE	24.0±9.9	31.4±12.3	0.011
VPTEF	21.55 (16.5-31.7)	31.8 (22.0-41.9)	0.030§
VPTEF:VE	27.3±7.9	32.8±10.3	0.022
MV	2.3 (2.0-3.9)	2.6 (2.2-3.4)	0.826§
VT/kg	8.8±2.1	9.6±2.1	0.110
IT/ET	0.7±0.1	0.7±0.1	0.490
RR	30.6 (24.3-42.6)	26.7 (23.4-32.4)	0.280§
TEF75	128.9±41.2	115.9±45.1	0.240
TEF50	112.6±39.5	108.9±44.0	0.731
TEF25	69.0 (54.0-98.0)	75.0 (61.0-103.0)	0.545§

**Data were presented as n (%) or mean±standard deviation if normally distributed, and median (IQR) if non-normally distributed*
†Data analysis was held by Student's t test
‡Data analysis was held by Pearson chi-square test
§Data analysis was held by Mann Whitney U test
Abbrevations: kg, kilogram; cm, centimeter; tPTEF, time to peak tidal expiratory flow; tPTEF:tE, rate of time to reach peak tidal expiratory flow; VPTEF, volume expired before PTEF was attained; VPTEF:VE, ratio of volume until peak tidal expiratory flow to total expiratory volume; MV, minute ventilation; VT, tidal volume; IT, inspiratory time; ET, expiratory time; RR, respiratory rate; TEF75, TEF50, and TEF25, expiratory flow when 75%, 50%, and 25% of tidal volume remain in the lungs; IQR, interquartile range

Table 3. Correlation between breath parameters and age*

Parameter	Age	tPTEF	tPTEF:tE	vPTEF
1. Age	–			
2. tPTEF	0.448 (<0.001)	–		
3. tPTEF:tE	0.310 (0.014)	0.667 (<0.001)	–	
4. vPTEF	0.709 (<0.001)	0.766 (<0.001)	0.686 (<0.001)	–
5. vPTEF:vE	0.243 (0.055)	0.642 (<0.001)	0.945 (<0.001)	0.699 (<0.001)

**Data were presented as Spearman's rho (p value)*
Abbrevations: *tPTEF, time to peak tidal expiratory flow; tPTEF:tE, rate of time to reach peak tidal expiratory flow; VPTEF, volume expired before PTEF was attained; VPTEF:VE, ratio of volume until peak tidal expiratory flow to total expiratory volume*

Table 4. Predictors of tPTEF:tE

Parameter	β	95% CI	t	p
Constant	10.116	-0.098 – 20.329	1.981	0.052
Age	0.477	0.086 – 0.869	2.440	0.018
Risk	6.586	1.087 – 12.086	2.396	0.020

F=6.687, p=0.002, adj. R^2:

A multiple linear regression was calculated to predict tPTEF:tE based on their age and risk. A significant regression equation was found (F(2,60)=6.687, p=0.002) with an R2 of 0.182. Participants' predicted tPTEF:tE is equal to 10.116+0.477 (age) + 6.586 (risk), where risk is coded as 1=high risk, 2=no risk, and age is measured in months. Participant's tPTEF:tE increased 0.477 for each month of age, and no risk is 6.586 more than high risk. Both age and risk were significant predictors of tPTEF:tE (Table 4).

According to the ROC curve analysis to estimate optimal cut-offs to predict being wheezy infant with high risk for atopy: (a) tPTEF ≤ 0.27 demonstrated 70.0% sensitivitiy and 69.7% specificity with an AUC:0.723 (CI:0.595-0.851, p=0.002), (b) tPTEF:tE <26.5 demonstrated 63.3% sensitivitiy and 63.6% specificity with an AUC:0.687 (CI:0.556-0.817, p=0.011), (c) VPTEF <23.0 demonstrated 60.0% sensitivitiy and 69.7% specificity with an AUC:0.659 (CI:0.523-0.795, p=0.030), and (d) VPTEF:VE <29.0 demonstrated 63.3% sensitivitiy and 63.6% specificity for detection of high risk with an AUC:0.670 (CI:0.537-0.803, p=0.020) (Table 5).

DISCUSSION

In the present study, we demonstrated a significant lung function impairment in wheezy infants with high risk for atopy than that of wheezy infants without high risk of atopy. The airflow tPTEF, tPTEF:tE) and lung volumes (VPTEF, VPTEF:VE) were lower in wheezy infants with high risk for atopy compared to those wheezy infants without high risk of atopy. However, there was no significant difference between two groups in terms of Vt/kg and respiratory rate. Additionally, ROC curve analysis showed that tPTEF:tE ratio <26.5 demonstrated 63.3% sensitivity and 63.6% specificity for detection of high risk.

The TBA parameter of tPTEF:tE is associated with the initial portion of tidal breath expiration, until the point of peak flow. A few studies have reported that

Table 5. Cut-off criterion values and coordinates of the ROC curve of high risk and no risk groups

Parameter	Cut-off	Sensitivity	Specificity	AUC	95% CI	p
tPTEF	≤0.27	70.0	69.7	0.723	0.595-0.851	0.002
tPTEF:tE	<26.5	63.3	63.6	0.687	0.556-0.817	0.011
VPTEF	<23.0	60.0	69.7	0.659	0.523-0.795	0.030
VPTEF:VE	<29.0	63.3	63.6	0.670	0.537-0.803	0.020

Abbrevations: *AUC, area under curve; CI, confidence interval; tPTEF, time to peak tidal expiratory flow; tPTEF:tE, rate of time to reach peak tidal expiratory flow; VPTEF, volume expired before PTEF was attained; VPTEF:VE, ratio of volume until peak tidal expiratory flow to total expiratory volume*

a decrease in tPTEF:tE ratio which indicates obstructive airway diseases. Dezateux et al.[13] demonstrated that the mean value of tPTEF:tE was lower in wheezy infants than healthy infants. Zedan et al.[7] demonstrated that, wheezy infants with positive parental history of asthma and high eosinophilic percentage showed a significant decrease in tPTEF:tE compared to healthy infants. Carlsen et al.[14] found that VPTEF:VE was significantly lower in asthmatic children compared to healthy infants before bronchodilator administration. Also, Morris et al.[15] demonstrated that, the ratio of tPTEF:tE and VPTEF:VE were significantly lower in children with obstructive airway disease. In the present study, in the high-risk group the mean tPTEF:tE (0.24) was the same as reported by Martinez et al.[16] in the group of (sedated) infants who subsequently developed wheezing.

We speculate that, decreased tPTEF:tE ratio in high-risk infants might be related to narrowing of the airway size. The increase of these parameters after bronchodilator inhalation in children with obstructive airway diseases supports this hypothesis.[17] Several studies have observed an increase in tPTEF:tE ratio after bronchodilators inhalation in infants[18,19], so this improvement may be a result of the bronchial hyperreactivity. Consequently, in wheezy infants with high risk, a decrease in tPTEF:tE may be a valuable finding in predicting the development of asthma.

In the present study, the wheezy infants with high risk for atopy had no clinically detectable bronchial obstructionat the physical examination with a normal range of respiratory rate. Additionally, there was no correlation between the respiratory rate and other TBA parameters.

Thus, it was demonstrated by the TBA method that wheezy infants with high risk for atopy in this study had a subclinical bronchial obstruction despite normal respiratory rate.

The strengths of our study include well defined high-risk infants that were not exposed to smoke, the collection of data using meticulous methodology by the same experienced staff under the same conditions, which adhered to international guidelines and tight quality control during the study. The major limitations of the present study were the relatively small sample size and the lack of long-term follow up of the infants. Although, maternal or paternal history of atopy was recorded, its effect on TBA could not be evaluated due to small sample size.

In this study, subclinical bronchial obstruction was accurately demonstrated by the TBA technique in wheezy infants with high risk of atopy compared to wheezy infants without a high risk of atopy. Thus, it has been shown that being at high risk for atopy in the early years of life is associated with bronchial obstruction. Therefore, we suppose that obtaining a more detailed history of atopy from the parents and/or siblings may help us to predict the risk of early asthma development in this particular population. Additionally, TBA is a non-invasive, repeatable, easy method for assesment of lung function at an early age and is a potential candidate for subsequent asthma prediction. Further studies conducted with a long follow-up period will be helpful to demonstrate the association between wheezy infants with high-risk for atopy and lung function abnormalities.

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