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Original Article

Forced oscillation technique as a predictor for loss of control in asthmatic children

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Background: A reliable objective tool using as a predictor of asthma control status could assist asthma management.
Objective: To find the parameters of forced oscillation technique (FOT) as predictors for the future loss of asthma symptom control.
Methods: Children with well-controlled asthma symptom, aged 6–12 years, were recruited for a 12-week prospective study. FOT and spirometer measures and their bronchodilator response were evaluated at baseline. The level of asthma symptom control was evaluated according to Global Initiative for Asthma.
Results: Among 68 recruited children, 41 children (60.3%) maintain their asthma control between 2 visits (group C-C), and 27 children (39.7%) lost their asthma control on the follow-up visit (group C-LC). Baseline FOT parameters, including the values of respiratory resistance at 5 Hz (R5), respiratory resistance at 20 Hz (R20), respiratory reactance at 5 Hz, area of reactance, %predicted of R5 and percentage of bronchodilator response (%Δ) of R5 and R20 were significantly different between C-C and C-LC groups. In contrast, only %Δ of forced vital capacity, forced expiratory volume in 1 second (FEV_1), and $FEF_{25\%-75\%}$ (forced expiratory flow 25%–75%) were significantly different between groups. Multiple logistic regression analysis revealed that %predicted of R5, %ΔR5, %predicted of FEV_1 and %ΔFEV_1 were the predictive factors for predicting the future loss of asthma control. The following cutoff values demonstrated the best sensitivity and specificity for predicting loss of asthma control: %predicted of R5=91.28, %ΔR5=21.2, %predicted of FEV_1=89.5, and %ΔFEV_1=7.8. The combination of these parameters predicted the risk of loss of asthma control with area under the curve of 0.924, accuracy of 83.8%.
Conclusion: Resistance FOT measures have an additive role to spirometric parameter in predicting future loss of asthma control.

Keywords: Resistance; Reactance; Spirometry; Frequency of resonance; Asthma

INTRODUCTION

Asthma is the most common chronic respiratory disease in children. Global Initiative for Asthma (GINA) guideline had classified level of asthma control according to clinical

Author Contributions

Conceptualization: Piyawut Kreetapirom, Wasu Kamchaisatian, Suwat Benjaponpitak, Wiparat Manuyakorn. Data curation: Piyawut Kreetapirom, Potjanee Kiewngam, Wanlapa Jotikasthira. Formal analysis: Piyawut Kreetapirom, Wiparat Manuyakorn. Funding acquisition: Piyawut Kreetapirom, Wiparat Manuyakorn. Methodology: Wiparat Manuyakorn. Project administration: Wiparat Manuyakorn. Visualization: Wiparat Manuyakorn. Writing - original draft: Piyawut Kreetapirom. Writing - review & editing: Wiparat Manuyakorn, Suwat Benjaponpitak, Wasu Kamchaisatian.

symptoms into controlled, partly controlled and uncontrolled asthma [1]. Poor control in childhood asthma was associated with numerous consequences; increased medical expense [2], increase exacerbation [3], and decrease quality of life [4]. Consequently, evaluation of level of asthma symptom control and finding the predictor to identify patient who is at risk for subsequent loss of asthma control are considered to be crucial. Pediatric patients may have difficulties in explaining their symptoms or may have poor perception for the change of their respiratory status [5]. Objective measurement including spirometry and exhaled nitric oxide levels may not be an accurate prediction for loss of asthma control [6, 7].

Forced oscillator technique (FOT) is a noninvasive objective measurement of lung physiology. FOT is a simple, noninvasive method requiring only passive patient cooperation and possibly be a useful tool for pulmonary function assessment in patients especially children who cannot perform acceptable spirometry maneuver [8, 9]. The parameters measured by FOT consist of resistance (Rrs), reactance (Xrs), and area of reactance (ALX). Rrs at 5 Hz (R5) represents the obstruction in the small and large airways airway while Rrs at 20 Hz (R20) reflects the obstruction of the large airways. Xrs at 5 Hz (X5) is a representative of the elastic and inertial properties of the lungs [10]. A previous study with FOT revealed that the value of R5 could effectively predict asthma exacerbation in children [11]. Bronchodilator response was shown to be a marker of poor asthma control in adolescent and adult asthmatic patients [12, 13]. The higher bronchodilator response as a risk factor for exacerbations was also documented in a recent GINA guideline [1]. We hypothesized that FOT parameters and their bronchodilator response may have a role in prediction of the future loss of asthma symptom control in clinically well-controlled asthmatic children.

MATERIALS AND METHODS

Asthmatic children aged 6–12 years, followed-up at least 12 months at Pediatric Allergy Clinic, Ramathibodi Hospital were recruited. Asthma diagnosis was done by pediatric allergist according to GINA guideline as follow (1) recurrence of clinical of airflow limitation including wheezing, cough or difficult breathing and (2) these clinical symptoms were responded well to bronchodilator therapy or inhaled corticosteroid assessing by the improvement of forced expiratory volume in 1 second (FEV_1) more than 12% or improvement of clinical symptoms in case that spirometry could not be performed. All enrolled children were prescribed inhaled corticosteroids. Children evaluated having well-controlled asthma according to GINA were enrolled. Children who had chronic pulmonary disease other than asthma, cardiovascular disease, history of smoking, lower respiratory tract infection in the past 4 weeks, or unable to performed spirometer or FOT were excluded. Written informed consents were obtained from children and their guardians. The study protocol was approved by the ethic committee of Faculty of Medicine, Ramathibodi Hospital, Mahidol University (ID 01-59-06).

Study protocol

Two visits of evaluation in 12 weeks interval were performed. At the first visit, history of diagnosis of asthma, step of asthma treatment, and evidence of aeroallergen sensitization were reviewed. Asthmatic symptoms were assessed. FOT and spirometer, pre- and postbronchodilator with 400 μg of salbutamol inhalation were evaluated in the first visits. Percentage of bronchodilator response (%Δ) was calculated from the difference absolute value obtained before and after salbutamol inhalation then divided by the absolute values before salbutamol and the result was multiplied by 100. Because of the possible effects of forced expiratory maneuvers

on the bronchial motor tonus [14], first FOT and then spirometry was performed. FOT, using MostGraph-01 (Chest M.I., Co. Ltd., Tokyo, Japan), was performed according to European Respiratory Society criteria [15]. FOT was performed during spontaneous tidal breathing. During data acquisition, pressure and flow traces were graphically displayed in real time. Measurements were accepted when the tracings showed uninterrupted breathing during data acquisition. Measurements were rejected if disturbed by coughing, breath holding, swallowing, or vocalization. Measurement Parameters including R5, R20, and X5, were measured. The spirometry, using Spiromaster PC-10 (Chest M.I., Co. Ltd.), was then performed. Forced vital capacity (FVC), FEV_1, FEV_1/FVC ratio, and forced expiratory flow at 25%–75% of FVC ($FEF_{25\%–75\%}$) were measured. At the end of study, the children who still had well-controlled asthma as GINA were identified as "maintained-controlled group" (C-C group). The children who did not meet the criteria of well-controlled asthma were classified as "lost-controlled group" (C-LC group).

Statistical analysis

R ver. 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA) were used for statistical analysis. Comparison of baseline characteristics was performed by chi-square test or *t* test and Fisher exact test or Wilcoxon rank sum test in normal and nonnormal distribution respectively. Difference of parameters of FOT and spirometer in 2 groups was detected by *t* test and Wilcoxon rank-sum test. Pearson correlation coefficient was used to establish associations between parameters. The receiver operating characteristic (ROC) method and area under the curve (AUC) were used to estimate the optimal cutoff point of parameters of FOT to predict lost-controlled status. Multivariate stepwise logistic regression analysis was performed to identify the independent predictive factors for lost-asthma control status. All variables were added to the model/prediction and non-significant variables were removed.

RESULTS

Sixty-eight well-controlled asthmatic children were enrolled to the study: 45 children (66.2%) were male. The mean age was 9.5 years. At 12-week follow-up, 41 subjects (60.3%) were stable at their well-controlled level (C-C group) while 27 of them (39.7%) were identified having loss of asthma symptom control (C-LC group). Sex, weight, aeroallergen sensitization status, incidence of allergic rhinitis, history of environmental tobacco smoke exposure, age of asthma diagnosis, duration of asthma, and the dosage of inhaled corticosteroid were not significantly different between the 2 groups. However, the subjects in C-LC group were statistically younger and shorter ($P<0.005$) (**Table 1**).

Comparison of FOT parameters

The comparison of FOT parameters between the 2 groups was showed in **Table 2**. The value of R5, R20, X5, and ALX in C-C group were significantly lower than C-LC group. However, only %predicted of R5 was significantly difference between C-C and C-LC groups. The percentage of bronchodilator response (%Δ) in the following parameters: R5 and R20 in C-LC group were significantly higher than those in C-C group (**Table 2**).

Comparison of spirometric parameters

The comparison of spirometric measurement was presented in **Table 3**. There is no significant difference in all spirometric measurement between C-C and C-CL groups. The percentage of bronchodilator response (%Δ) in the following parameters: FVC, FEV_1, and $FEF_{25\%–75\%}$ in C-LC group were statistically significant higher than in C-C group (**Table 3**).

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Table 1. Baseline characteristics

Variable	C-C group (n = 41)	C-LC group (n = 27)	*p* value
Sex			0.74
Male	26 (63.4)	19 (70.4)	
Female	15 (36.6)	8 (29.6)	
Age (yr)	9.93 ± 1.85	8.93 ± 2.0	0.04
Height (cm)	137.07 ± 13.44	128.37 ± 13.45	0.01
Weight (kg)	37.59 ± 13.99	31.78 ± 13.81	0.10
Aeroallergen sensitization	31 (75.6)	22 (81.5)	0.79
Allergic rhinitis	3 (85.4)	22 (81.5)	0.81
Tobacco exposure	8 (19.5)	5 (18.5)	0.08
Age of asthma diagnosis (yr)	5.83 ± 2.71	4.96 ± 2.02	0.16
Duration of asthma (yr)	3.86 ± 2.13	3.71 ± 1.99	0.77
Inhaled corticosteroid dosage (μg)*	218.79 ± 185.15	203 ± 140.72	0.95

Values are presented as number (%) or mean ± standard deviation.
C-C group, group of children who maintained their level of asthma well-controlled; C-LC group, group of children who lost their level of asthma well-controlled at the end of the study.
*Beclomethasone equivalent dose/day.

Table 2. Comparison forced oscillation technique measures between C-C and C-LC groups

Variable	C-C group	C-LC group	*p* value
Prebronchodilator			
R5 (cmH_2O/L/sec)	6.98 ± 2.11	9.98 ± 2.42	<0.001
R5 (% predicted)	89.28 ± 18.44	114.91 ± 23.39	<0.001
R20 (cmH_2O/L/sec)	5.83 ± 1.52	7.82 ± 1.61	<0.001
R20 (% predicted)	118.84 ± 38.85	126.56 ± 34.27	0.405
X5 (cmH_2O/L/sec)	−0.63 ± 0.47	−0.93 ± 0.61	0.03
X5 (% predicted)	27.95 ± 21.70	27.46 ± 20.53	0.9
ALX	2.54 ± 2.22	4.19 ± 4.04	0.03
Bronchodilator response			
ΔR5 (%)	12.92 ± 10.48	30.28 ± 11.32	<0.001
ΔR20 (%)	13.96 ± 10.4	24.65 ± 11.52	<0.001
ΔALX (%)	14.58 ± 62.45	26.43 ± 64.4	0.45

Values are presented as mean ± standard deviation.
C-C group, group of children who maintained their level of asthma well-controlled; C-LC group, group of children who lost their level of asthma well-controlled at the end of the study.
R5, resistance at 5 Hz; R20, respiratory resistance at 20 Hz; X5, respiratory reactance at 5 Hz; ALX, area of reactance; Δ, percentage of bronchodilator response.

Table 3. Comparison spirometric measures between C-C and C-LC groups

Variable	C-C group	C-LC group	*p* value
Prebronchodilator			
FVC (% predicted)	92.5 ± 10.0	98.7 ± 16.6	0.06
FEV_1 (% predicted)	89.7 ± 13.3	96 ± 19.4	0.11
FEV_1/FVC (%)	88.5 ± 6.6	87.6 ± 5.5	0.58
$FEF_{25\%-75\%}$ (% predicted)	95 ± 29.3	92.3 ± 29.3	0.71
Bronchodilator response			
ΔFVC (%)	1.3 ± 5.9	4.3 ± 4.5	0.03
ΔFEV_1 (%)	3.7 ± 5.9	7.9 ± 5.4	0.004
ΔFEV_1/FVC (%)	2.4 ± 3.4	3.5 ± 3.4	0.18
Δ$FEF_{25\%-75\%}$ (%)	15.1 ± 15.4	23.3 ± 15.9	0.04

Values are presented as mean ± standard deviation.
C-C group, group of children who maintained their level of asthma well-controlled; C-LC group, group of children who lost their level of asthma well-controlled at the end of the study.
FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; $FEF_{25\%-75\%}$, forced expiratory flow 25%–75%; Δ, percentage of bronchodilator response.

Loss of asthma symptom control predictors

To find the independent predictive factors for predicting future loss of asthma symptom control in previously well-controlled subjects. Multivariate ordered logistic regression

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Table 4. Logistic regression to predict loss of asthma control

Predictor variable	Regression coefficient	AUC (95% CI)	*p* value
R5 (% predicted)	0.059	0.810 (0.700–0.920)	<0.001
R5 (% predicted)	0.049	0.859 (0.770–0.950)	<0.001
ΔR5 (%)	0.069	-	-
ΔFEV_1 (%)	0.278	0.910 (0.840–0.980)	<0.001
R5 (% predicted)	0.044	-	-
ΔR5 (%)	0.124	-	-
FEV_1 (% predicted)	0.059	0.924 (0.860–0.990)	<0.001
ΔFEV_1 (%)	0.302	-	-
R5 (% predicted)	0.045	-	-
ΔR5 (%)	0.144	-	-

AUC, area under the curve; CI, confidence interval; R5, resistance at 5 Hz; FEV_1, forced expiratory volume in 1 second.

analysis was demonstrated that %predicted of R5, %Δ R5, %predicted of FEV_1, and %Δ FEV_1 were the significant predictive factors for predicting future of asthma control (**Table 4**). ROC was calculated to make an optimal cutoff point for predicting the loss of asthma control. The %predicted of R5 at 91.28 predicts the future loss of asthma with a sensitivity of 82% and a specificity of 56% (AUC = 0.8; $p < 0.001$). The %ΔR5 of 21.2% predicts the future loss of asthma with a sensitivity of 70% and a specificity of 70% (AUC = 0.79; $p < 0.001$). The %ΔFEV_1 of 7.8% predicts the future loss of asthma with a sensitivity of 52% and a specificity of 76% (AUC = 0.69; $p < 0.008$) and %predicted of FEV_1 of 89.5% predicts the future loss of asthma with a sensitivity of 52% and a specificity of 52% (AUC = 0.54; $p = 0.55$) (**Table 5**). The combination of these parameters demonstrated the best regression coefficients with AUC (0.924; $p < 0.001$) and the accuracy of 83.8%. The predictive equation is regression coefficients = -15.308 + 0.059%predicted of FEV_1 0.177 + 0.302%ΔFEV_1 + 0.045%predicted of R5 + 0.144%ΔR5.

DISCUSSION

Our study demonstrates that 40% of asthmatic children who had well-controlled asthma according to GINA lost their asthma symptom control in the next 12 weeks. Significant

Table 5. Cutoff points in predicting of loss of asthma symptom control on a follow-up visit

Variable	Cutoff points	AUC (95% CI)	Sensitivity	Specificity	*p* value
FOT parameters					
R5 (% predicted)	91.28	0.812 (0.702–0.922)	0.821	0.56	<0.001
R20 (% predicted)	122.23	0.55 (0.41–0.69)	0.59	0.52	0.48
X5 (% predicted)	21.16	0.47 (0.33–0.61)	0.48	0.44	0.72
Spirometric parameters					
FVC (% predicted)	96.4	0.60 (0.44–0.75)	0.52	0.66	0.176
FEV_1 (% predicted)	89.5	0.54 (0.387–0.699)	0.52	0.52	0.55
FEV_1/FVC (%)	88.99	0.43 (0.29–0.57)	0.52	0.44	0.32
$FEF_{25\%-75\%}$ (% predicted)	91.65	0.46 (0.32–0.60)	0.48	0.59	0.57
Postbronchodilator response					
ΔR5 (%)	21.2	0.79 (0.68–0.90)	0.70	0.70	<0.001
ΔR20 (%)	24.8	0.74 (0.62–0.86)	0.52	0.90	<0.001
ΔFVC (%)	2.75	0.67 (0.54–0.80)	0.70	0.59	0.018
ΔFEV_1 (%)	7.8	0.69 (0.57–0.81)	0.52	0.76	0.008
ΔFEV_1/FVC (%)	3	0.59 (0.45–0.72)	0.52	0.63	0.21
$\Delta FEF_{25\%-75\%}$ (%)	15.2	0.65 (0.52–0.79)	0.70	0.57	0.035

FOT, forced oscillation technique; AUC, area under the curve; CI, confidence interval; R5, resistance at 5 Hz; R20, respiratory resistance at 20 Hz; X5, respiratory reactance at 5 Hz; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; $FEF_{25\%-75\%}$, forced expiratory flow 25%–75%; Δ, percentage of bronchodilator response.

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difference in baseline FOT measures between children who maintained their level of controlled asthma and those who lost their asthma level of control were demonstrated but there were no significant differences in spirometric measures between the 2 groups. FOT measures were shown to have more clinical value in distinguishing asthmatics from nonasthma children than spirometric measures [16, 17]. Marotta et al. [16] have shown that percentage of bronchodilator response of resistance FOT measures were different between children who have asthma and those who did not have asthma while spirometric parameters were not different between the 2 groups. Similar result was also demonstrated in Korean asthmatic children [17]. However, studies in adolescent and adult asthmatic and healthy subjects have shown the equality informative of resistance FOT measures and spirometry measures for asthma diagnosis and as a potential marker of asthma control [18, 19]. FOT measurement was suggested to be more sensitive than spirometry in detecting subtle changes of lung function in children [20].

Spirometric parameters especially FEV_1 was proposed to be a predictor for asthma exacerbation. Low FEV_1 especially less than 60%predicted is a strong predictor of asthma exacerbation [21]. In the present study, we found that FEV_1 alone might not be good enough to predict future loss of asthma control in clinically well-controlled asthmatic children and all of our enrolled children had FEV_1 more than 60%predicted. We have proposed the following cutoff values for predicting future loss of asthma control: % predicted of R5 = 91.28 (AUC = 0.81), %R5 = 21.1 (AUC = 0.79) and %Δ FEV_1=7.8 (AUC = 0.69). We also have demonstrated that combination between FOT measured resistance at 5 Hz and FEV_1 provided the best AUC and accuracy for predicting future loss of asthma control in well control asthmatic children. These findings would highlight the ability of using FOT resistance measure as a predictor for loss of asthma control.

Even though, we found the significant differences in all FOT measures between children who could maintain their asthma clinical controlled and those who lost control of asthma. From logistic regression analysis adjusted for all parameters which were significant differences between controlled and lost-controlled groups, only %predicted of R5, %Δ R5, %predicted of FEV_1, and %ΔFEV_1 showed significantly associated with the status of asthma control at 12 weeks. This result can be explained form the high association between R5 and R20.

In the present study, there was no significant differences in baseline spirometric parameter between children who could maintain their level of asthma control and those who lost their asthma control. However, percentage of bronchodilator response of $FEV_{1\%}$ and FVC % were significant higher in those who lost of their asthma control. These results were consistent with a recent study in children and adolescents which shown that FEV_1 bronchodilator response is better than $FEV_{1\%}$predicted in distinguishing difficult-to-control from easy-to-control asthma [22]. As a result, higher FEV_1 bronchodilator response should be one of the predictor for future loss of asthma control especially in children with normal FEV_1. We have purposed to use the cutoff value for postbrochodilator response (%Δ) of FEV_1 = 7.8% as a prediction for future of loss of asthma control. However, %ΔFEV_1 has less sensitivity and specificity in predicting loss of asthma control than %ΔR5.

FOT measures were associated with height and age [15]. In the present study, there were significant differences in age and height of children who could maintain their asthma control (C-C) and those who lost their asthma control (C-CL). These differences should have effects on FOT measures. However, after the stepwise multiple logistic regression analysis, age and

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height were eliminated from the model. As a result, the differences in age and height in C-C and C-CL should not have significant effect on the analysis of the present study.

To the best of our knowledge, our study is the first prospective study using the percentage of bronchodilator response of FOT measures in predicting loss of control in asthmatic children. No patient was reported as lost to follow-up. However, our study still has some limitation. First, this study is the preliminary study in a small number of asthmatic children. The result may not be able to generalize to all asthmatic children. Further study with a larger sample size is required to confirm the usefulness of FOT measure in prediction future loss of asthma control. Second, the longer follow-up period might be required to observe the symptoms of future loss of control in the patients who remained controlled at 12-week visit.

In conclusion, we have shown that baseline FOT measured resistance at 5 Hz and its percentage of bronchodilator response were the better predictor for the future of loss of asthma control in those previously well control than spirometric measures. However, the combination with spirometric measure increased the accuracy as demonstrated by AUC in a logistic regression model. While standard spirometric parameters cannot well distinguish asthmatic children who will lost their asthma control from those who can maintain asthma well control. FOT parameters could play an additive role in predicting loss of control in the subsequent 12 weeks with a high predictive value.

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