

Bronchial provocation test measured by using the forced oscillation technique to assess airway responsiveness

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ABSTRACT

Background: The bronchial provocation test (BPT) performed by using the forced oscillation technique (FOT) is cooperated without forced expiratory effort. However, a comparison of the application value and safety of BPTs measured by using the FOT and the standardized dosimeter method is lacking, which limits its clinical practice.

Objective: We aimed to analyze the diagnostic value and safety of the BPT as measured by the FOT in patients with asthma and in healthy subjects.

Methods: This was a randomized cross-over clinical study. Airway responsiveness was measured by using the FOT and the aerosol provocation system (APS) dosimeter method in all the participants. The between-test interval was 24 hours. The diagnostic value and safety of the two tests were analyzed.

Results: Asthma control status was assessed based on ACT scores, and patients with asthma (including 27 uncontrolled, 34 partially controlled, and 32 controlled) were collected, and 69 healthy subjects were recruited. Receiver operating characteristic curves revealed slightly superior screening capability of cumulative dose of methacholine causing a 20% decrease (PD₂₀)–forced expiratory volume in the first second of expiration when measured by using the APS-dosimeter method (area under the curve [AUC] 0.981 [95% confidence interval {CI}, 0.952–1.000]) over that of cumulative dose of inhaled methacholine at the inflection point when respiratory resistance began to increase continuously (D_{min}) by using the FOT (AUC 0.959 [95% CI, 0.924–0.994]). The sensitivity and specificity were 98.9% and 98.6%, respectively, with the APS-dosimeter method, and 100% and 87.0%, respectively, with the FOT. It took an average of 9.0 minutes (range, 6.0–11.0 minutes) when using the FOT and an average of 17.0 minutes (range, 14.0–25.0 minutes) when using APS-dosimeter method ($p < 0.01$) in all the participants. The measurement time for the FOT was reduced by 47.1% than the APS-dosimeter. The incidence rate of the adverse events with the FOT was slightly higher than that with the APS-dosimeter method ($p < 0.05$). Both tests were well tolerated. No serious adverse event was found.

Conclusion: The FOT, characterized as being simple, safe, and time saving, could be used to assess airway hyperresponsiveness in patients with asthma and worthy of clinical application.

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Asthma is a common chronic airway disease worldwide.¹ Airway hyperresponsiveness (AHR) is a characteristic feature of asthma, and its measurement is an important tool in the diagnosis of asthma.² The bronchial provocation test (BPT) is used to detect AHR and assess the severity of asthma.³ There are many methods for the BPT, including the five total lung capacity counted breath method, 2-minute tidal breathing method, and dosimeter method as well as the FOT.

In 1999, the American Thoracic Society guideline⁴ outlined two dosing protocols: the five total lung capacity counted breath method and the 2-minute tidal breathing method. Recently, the published European Respiratory Society guideline⁵ recommended a modern dosimeter system that could provide an appropriate dosing protocol. The aerosol provocation system (APS) dosimeter method, characterized as accurate, quantified, safe, and standardized, is most extensively used for clinics and research in China. However, a forced expiratory maneuver, long testing time, and skilled operating technique are required for this method. By contrast, airway responsiveness is determined during continuous tidal breathing with the forced oscillation technique (FOT), which is getting more attention.

The FOT has been applied in the study of the pathogenesis, diagnosis, and evaluation of asthma in Japan.^{6–8} However, there might be several reasons for the FOT not being popularized in China and other countries. First, the application value and safety of the FOT in clinical practice are not yet clear. Second, a

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comparison of BPTs measured by the FOT and the standardized dosimeter method is still lacking. Consequently, the aim of our study was to analyze the diagnostic value and safety of the FOT by comparing it with the APS-dosimeter method in patients with asthma and in healthy subjects.

METHODS

Subjects

Patients with asthma and between 18 and 65 years of age were enrolled from the outpatient clinic of the First Affiliated Hospital of Guangzhou Medical University from September 2018 to June 2019. The diagnosis and control status were defined according to the Global Initiative for Asthma guidelines.⁹ Asthma control status was assessed based on asthma control test (ACT) scores: a score of 20–25 indicates controlled, 16–19 indicates partially controlled, and 5–15 indicates uncontrolled.⁹ Inclusion and exclusion criteria are shown in the Online Supplemental Appendix. The healthy subjects were non-smokers between 18 and 65 years of age, with no history of serious cardiopulmonary or other systemic diseases, no acute upper and lower respiratory tract infections in the past 4 weeks, and with a normal chest physical examination. The study protocol was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University. All the participants gave written informed consent to participate in the study.

Study Protocol

This study had a single-center, randomized, cross-over design. At the first visit, a medical history and physical examination were taken. Spirometry was performed to determine if provocation was contraindicated. After the screening, BPTs by using the APS-dosimeter method and the FOT were performed at a randomized order, with a washout time of 24 hours. Airway responsiveness and adverse events were recorded for analysis.

Spirometry

Spirometry was performed by using a Jaeger Master-scope spirometer (Carefusion Co Ltd, Hoechst, Germany) according to the recommendations of the European Respiratory Society/American Thoracic Society guideline.¹⁰ Preparations of the dilutions are shown in the Online Supplemental Appendix.

Measurement of Airway Responsiveness

FOT. Airway responsiveness was determined by using a Jupiter 21 astograph (Chest, Tokyo, Japan) according to the method of Takishima *et al.*¹¹ Briefly, respiratory resistance (Rrs) was measured by using the FOT (3 Hz)

with a simultaneous examination of AHR by continuous methacholine (MCh) inhalation. Normal saline solution and MCh stepwise incremental concentration were inhaled for 1 minute without an interval until the maximum concentrations had been reached. These procedures were terminated if the Rrs reached twice the baseline value, the cumulative dose of inhaled MCh at the inflection point at which Rrs began to increase (Dmin) is used as the index of airway sensitivity. This variable is presented as 1 unit, defined as continuous inhalation of MCh for 1 minute (1 mg/mL).⁶

PD35 is the cumulative dose of MCh that causes an 35% increase in Rr. PD40 is the cumulative dose of MCh that causes an 40% increase in Rrs. The total cumulative dose of MCh at the end of inhaling the maximum concentration was 50 units. The slope of the MCh respiratory conductance dose-response curve (SGrs) was used as the index of airway reactivity. AHR was assessed by using the Dmin. The BPT measured by using the FOT was defined as a positive result when Rrs reached twice the baseline value, otherwise it was consider a negative result.

APS-Dosimeter Method. Airway responsiveness was measured by using the APS computerized dosimeter (Carefusion, Hoechst, Germany) connected to a jet nebulizer (MedicAid Pro; Carefusion) powered by compressed air. An output of 160 mg/min and a mean mass diameter (MMD) of 3.2 μ m was delivered by APS. The provocation protocol is given in Table 1. When inhalation became steady, subjects were instructed to inhale slowly, hold the breath, and exhale into the mouthpiece. Spirometry was performed within 3 minutes after the inhalations of each concentration, with 5-minute intervals between different concentrations until the maximum cumulative dose (12.5 μ mol) had been reached. The provocation was terminated if forced expiratory volume in the first second of expiration (FEV₁) dropped by $\geq$ 20% of the baseline value. Then subjects were asked to inhale 200–400 μ g of salbutamol administered through a metered-dose container to relieve discomfort. Spirometries were conducted again after 5 or 10 minutes until the FEV₁ recovered to the baseline level. AHR was assessed by using the cumulative dose of MCh that caused a 20% decrease in FEV₁ (PD₂₀-FEV₁).

Adverse Events Assessment

Adverse events were scored by using the visual analog scale.

Statistical Analysis

Statistical analysis was performed by using SPSS version 16.0 (SPSS, Inc., Chicago, IL). Data with normal distribution are expressed as mean $\pm$ standard deviation, otherwise as median (interquartile range). The

Table 1 The aerosol provocation system–dosimeter provocation protocol*

Step No.	Concentration, $\mu\text{mol/L}$	Inhalation Duration, s	Inhalation Times	Dosage, μmol	Cumulative Dosage, μmol
0	0	0.600	5	0	0
1	1.25×10^5	0.260	1	0.13	0.13
2	1.25×10^5	0.520	1	0.26	0.39
3	1.25×10^5	0.585	4	1.17	1.56
4	2.50×10^5	0.671	5	4.69	6.25
5	2.50×10^5	0.696	9	6.25	12.5

*1 μmol is equivalent to 200 μg .

Table 2 The baseline demographics and spirometry of all the study participants

Parameter	Patients with Asthma			Healthy Subjects ($n = 69$)	p
	Uncontrolled ($n = 27$)	Partially Controlled ($n = 34$)	Controlled ($n = 32$)		
Age, y	34.89 ± 10.43	40.62 ± 12.98	36.25 ± 13.71	34.39 ± 9.11	0.063
Weight, kg	62.16 ± 9.22	60.43 ± 10.80	62.23 ± 10.91	61.48 ± 10.97	0.897
Height, cm	164.81 ± 10.92	160.13 ± 8.87	165.47 ± 9.20	163.70 ± 8.15	0.080
FVC, L	3.89 ± 0.96	3.56 ± 0.93	3.92 ± 0.93	3.92 ± 0.73	0.197
FVC % predicted	100.52 ± 10.40	104.22 ± 13.25	101.38 ± 12.05	102.16 ± 10.44	0.610
FEV ₁ , L	2.78 ± 0.74	2.58 ± 0.62	3.07 ± 0.80	3.25 ± 0.58	< 0.001
FEV ₁ % predicted	84.44 ± 9.75	89.60 ± 12.12	93.12 ± 10.46	99.54 ± 8.69	< 0.001
PEF, L	6.98 ± 1.88	6.74 ± 1.54	7.78 ± 1.92	8.31 ± 1.62	< 0.001
PEF, % predicted	89.20 ± 11.85	94.22 ± 14.20	99.42 ± 16.09	107.29 ± 14.19	< 0.001
MMEF % predicted	47.50 ± 18.80	49.21 ± 16.22	63.84 ± 21.29	80.41 ± 19.13	< 0.001

FVC = Forced vital capacity; FEV₁ = forced expiratory volume in the first second of expiration; PEF = peak expiratory flow; MMEF = maximum mid-expiratory flow.

independent sample t -test or the Wilcoxon test was used for the comparison between the two groups. One-way analysis of variance (ANOVA) or the Kruskal-Wallis test was used for the comparison among three or more groups. The row-column table was analyzed with the χ^2 test. The Spearman rank correlation test was used to analyze relationships between variables. Receiver operation characteristic curve analysis, sensitivity, specificity, positive predictive value, and negative predictive value for AHR variables to diagnose asthma were calculated. The PD₂₀-FEV₁, Dmin, PD35, and PD40 values were log-transformed for correlation analysis. The p values < 0.05 were considered significant.

RESULTS

A total of 191 adults underwent the initial screening. Eight were excluded because of not meeting the inclusion/exclusion criterias. Fourteen asthma and seven

healthy were not completed both FOT and APS-dosimeter testings. Ninety-three patients with asthma (27 uncontrolled, 34 partially controlled, and 32 controlled) as well as 69 healthy subjects were included in the final analysis.

Comparison of Spirometric Parameters

Major spirometric parameters in patients with asthma were significantly decreased compared with the healthy subjects ($p < 0.05$), except for forced vital capacity (FVC) ($p = 0.197$) and FVC % predicted ($p = 0.610$). The baseline demographics and spirometry of all the groups are presented in Table 2.

Comparison of BPT Parameters

BPT parameters measured by using the two methods differed significantly between the patients with asthma and the healthy subjects (All $p < 0.01$). The Dmin and PD₂₀-FEV₁ in the patients with asthma were lower, and Rrs, SGrS, SGrS/respiratory conductance (GrS)

Table 3 Comparison of BPT parameters between the patients with asthma and the healthy subjects

Parameter	Patients with Asthma (n = 93)	Healthy Subjects (n = 69)	p
Dmin, units	1.46 (0.51, 4.44)	50.00 (50.00, 50.00)	< 0.001
Rrs, cm H ₂ O/L/s	3.30 (2.60, 4.20)	2.80 (2.40, 3.30)	0.001
SGr _s , L/s/cm H ₂ O/min	0.06 (0.04, 0.08)	0.05 (0.00, 0.08)	< 0.001
SGr _s /Gr _s /min	0.21 (0.16, 0.30)	0.13 (0.00, 0.24)	< 0.001
PD ₃₅ , units	5.62 (1.83, 12.59)	50.00 (33.00, 50.00)	< 0.001
PD ₄₀ , units	5.97 (2.29, 16.18)	50.00 (38.36, 50.00)	< 0.001
PD ₂₀ -FEV ₁ , mg	0.17 (0.06, 0.70)	2.50 (2.50, 2.50)	< 0.001

BPT = Bronchial provocation test; Dmin = cumulative dose of inhaled MCh at the inflection point when Rrs began to increase; MCh = methacholine; Rrs = respiratory resistance; SGr_s = slope of the MCh respiratory conductance dose-response curve; Gr_s = respiratory conductance; PD₃₅ = cumulative dose of MCh that causes an 35% increase in Rrs; PD₄₀ = cumulative dose of MCh that causes an 40% increase in Rrs; PD₂₀-FEV₁ = cumulative dose of MCh that causes a 20% decrease in the forced expiratory volume in the first second of expiration.

Table 4 Comparison of BPT parameters in patients with asthma with different control levels: uncontrolled, partially controlled, and controlled

Parameter	Uncontrolled (n = 27)	Partially Controlled (n = 34)	Controlled (n = 32)	p
Dmin, units	0.64 (0.13, 1.85)	1.54 (0.51, 4.42)	2.78 (1.03, 9.67)	0.004
Rrs, cm H ₂ O/L/s	3.30 (2.60, 4.60)	3.50 (2.60, 4.50)	3.05 (2.60, 3.55)	0.137
SGr _s , L/s/cm H ₂ O/min	0.05 (0.04, 0.08)	0.06 (0.04, 0.09)	0.07 (0.06, 0.09)	0.030
SGr _s /Gr _s /min	0.19 (0.14, 0.25)	0.21 (0.15, 0.32)	0.21 (0.17, 0.31)	0.274
PD ₂₀ -FEV ₁ , mg	0.07 (0.03, 0.15)	0.16 (0.06, 0.52)	0.70 (0.16, 1.00)	< 0.001

BPT = Bronchial provocation test; Dmin = cumulative dose of inhaled MCh at the inflection point when Rrs began to increase; MCh = methacholine; Rrs = respiratory resistance; SGr_s = slope of the MCh respiratory conductance dose-response curve; Gr_s = respiratory conductance; PD₂₀-FEV₁ = cumulative dose of MCh that causes a 20% decrease in the forced expiratory volume in the first second of expiration.

ratio were higher compared with the healthy subjects (Table 3). The patients with asthma with different control levels were analyzed. The major parameters differed significantly among asthma groups ($p < 0.05$), except for Rrs and SGr_s/Gr_s (Table 4). The worse asthma control, the lower the median and interquartile range of Dmin, PD₂₀-FEV₁. Data are presented, with logarithmic transformation, in Fig. 1

Relationship between Variables of Spirometric and BPT Parameters

Log PD₂₀-FEV₁ and log Dmin were moderately positively related to maximum midexpiratory flow (FEF_{25%-75%}) % predicted, followed by the FEV₁/FVC % predicted. In addition, log PD₂₀-FEV₁ was strongly positively correlated with BPT parameters (log Dmin: $r = 0.811$, log PD₄₀: $r = 0.805$, log PD₃₅: $r = 0.797$; all $p < 0.01$). The SGr_s was unrelated to any spirometric parameters. Log Dmin values were not related to the SGr_s.

Diagnostic Value

The receiver operation characteristic curves revealed slightly superior screening capability of the PD₂₀-FEV₁

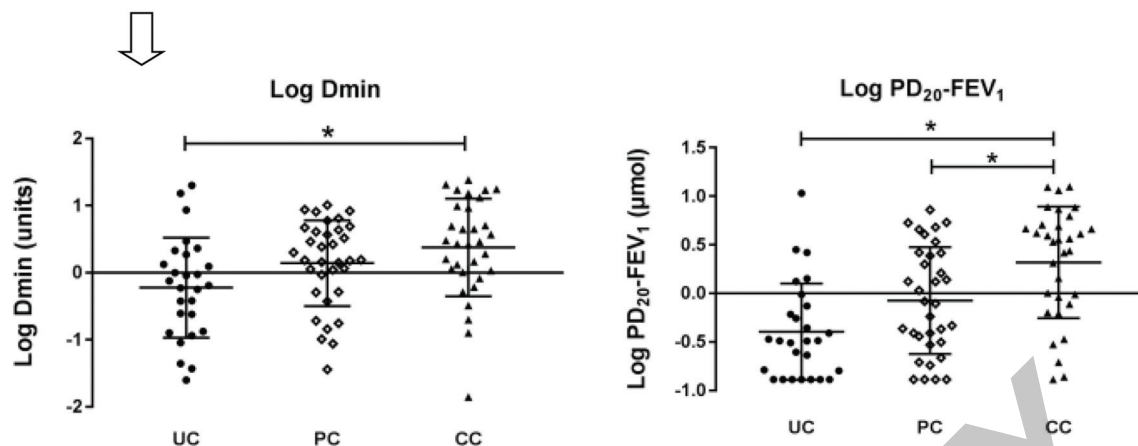
values as measured by using the APS-dosimeter method (AUC 0.981 [95% confidence interval {CI}, 0.952–1.000]) over that of the Dmin value as measured by using the FOT (AUC 0.959 [95% CI, 0.924–0.994]), (Fig. 2).

The patients with asthma and the healthy subjects with positive or negative results to BPT were analyzed. Positive responses measured by the methods of APS and FOT were found in ninety-two and ninety-three out of 93 asthma patients, respectively. Positive responses measured by the methods of APS and FOT were found in one and nine out of 69 healthy subjects, respectively. There was no statistical difference in the positive rate comparison ($\chi^2 = 1.043$; $p > 0.05$). Sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and the Youden index calculated based on relevant equations are shown in Table 5.

Measurement Time of the Two Tests

The measurement time took an average of 9.0 minutes (range, 6.0–11.0 minutes) with the FOT and an average of 17.0 minutes (range, 14.0–25.0 minutes) with the APS-dosimeter method ($p < 0.01$) in all

Before Figure 1



After Figure 1

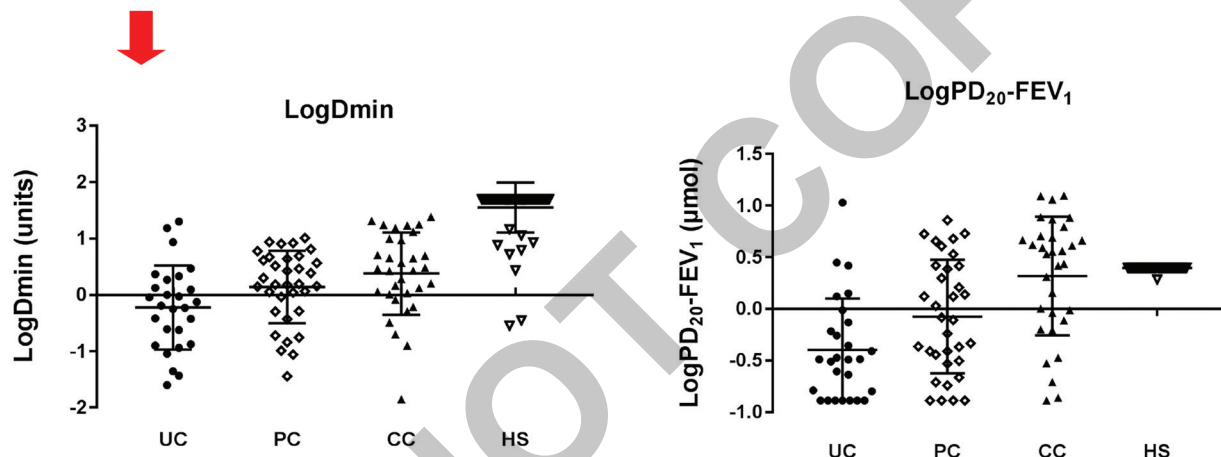


Figure 1. Distribution characters of log Dmin and log PD₂₀-FEV₁ of the patients with asthma with different control levels: log Dmin, between-group comparison, $p < 0.01$; UC compared with CC, $p < 0.01$; UC compared with PC and PC compared with CC, $p > 0.05$; log PD₂₀-FEV₁, between-group comparison, $p < 0.01$; UC compared with CC, $p < 0.01$; PC compared with CC, $p < 0.05$; and UC compared with PC, $p > 0.05$. Dmin = Cumulative dose of inhaled methacholine at the inflection point when respiratory resistance began to increase; PD₂₀ = cumulative dose of methacholine causing a 20% decrease in FEV₁; FEV₁ = forced expiratory volume in the first second of expiration; UC = uncontrolled asthma group; CC = controlled asthma group; PC = partially controlled asthma group.

subjects. The measurement time of the FOT was reduced by 47.1% than the APS-dosimeter.

Adverse Events

Of the 162 participants, 101 (62.3%) when using the APS-dosimeter method and 118 (72.8%) when using the FOT had adverse events ($p < 0.05$). The major adverse events were tightness, tachypnea, coughing, wheezing, and dyspnea. The incidence rate of dizziness and palpitation in the APS-dosimeter method was higher and that of thirst and itching was lower than with the FOT ($p < 0.05$) (Table 6). The incidence rate of the adverse events in the patients with uncontrolled asthma (85.2% versus 88.9%) was greater than

that in patients with partially controlled asthma (79.4% versus 85.3%), followed by that in patients with controlled asthma (46.9% versus 65.6%) and the healthy subjects (52.2% versus 63.8%) with the APS-dosimeter method versus the FOT (APS-dosimeter: $\chi^2 = 16.521$, FOT: $\chi^2 = 9.893$; both $p < 0.05$).

Furthermore, the incidence rate of tightness, tachypnea, wheezing, dyspnea, and coughing differed considerably ($p < 0.01$), and that of thirst, itching, and dizziness was similar in the patients with different asthma control statuses. Short-acting bronchodilator resulted in recovered from bronchoconstriction within 15 minutes for most subjects with the two tests. Both tests were tolerated. No nebulization of bronchodilators or oxygen therapy and hospitalization were needed.

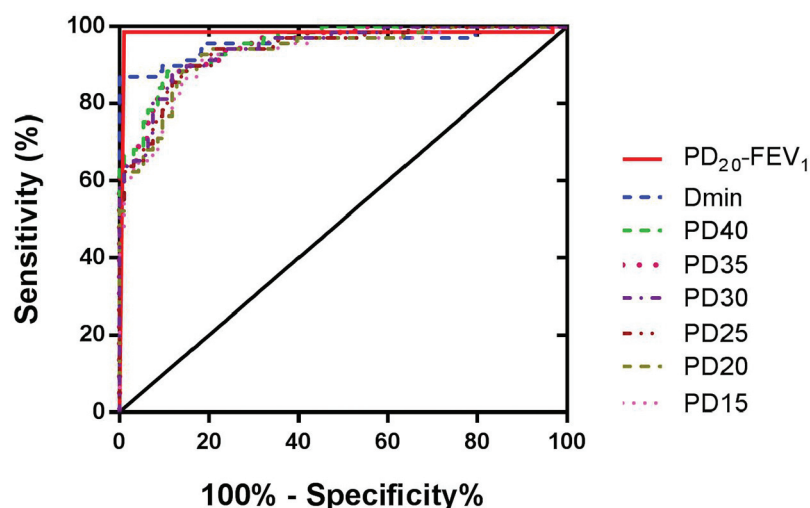


Figure 2. Comparison of the diagnostic value of APS-dosimeter and FOT provocation protocol.

Table 5 Diagnostic parameters of the two methods: APS-dosimeter and FOT

Parameter	APS-Dosimeter Method	FOT
Sensitivity, %	98.9	100.0
Specificity, %	98.6	87.0
PPV, %	98.9	91.2
NPV, %	98.6	100.0
Accuracy, %	98.8	94.4
Youden index	0.98	0.87

APS = Aerosol provocation system; FOT = forced oscillation technique; PPV = positive predictive value; NPV = negative predictive value.

DISCUSSION

The current study showed that there were no significant differences in sensitivity and specificity between the FOT and the APS-dosimeter method. Both methods were valuable in the diagnosis and assessment of asthma. Spirometric parameters in the patients with asthma with different control levels were consistent with the results of Guan *et al.*¹² The worse the control status of asthma, the greater was the decrease of the major spirometric parameters, especially uncontrolled asthma.

Bronchial asthma is an inflammatory airway disease characterized by reversible airway obstruction, AHR, chronic airway inflammation, and airway remodeling.¹ As expected, airway sensitivity, reactivity, and Rrs values in the patients with asthma were greater than those in the healthy subjects, which reflected the pathophysiology of asthma. Based on the comparison of the BPT parameters in the patients with asthma with different control levels, we found that Rrs and SGRs/GRs were similar with the between-group comparison.

An upward trend was presented in the SGRs with better asthma control status, which was contrary to our expectation. The median of the PD₂₀-FEV₁ and Dmin values were greater in the patients with controlled asthma than those in the patients with uncontrolled asthma, which supported the fact that, the better the asthma control status, the milder the AHR. The association between the asthma control status and the AHR was in accord with the study by Gyllfors *et al.*¹³ In addition, although some patients with asthma was well controlled, the PD₂₀-FEV₁ and Dmin values were still low, which indicated that AHR still persisted in patients with totally controlled asthma.

Airway sensitivity and airway reactivity are two major components of AHR.¹⁴ Initially, Orehek *et al.*¹⁵ suggested that there was no significant correlation between the two characteristics of the bronchial response, airway sensitivity was represented as the dose of stimulus that causes a 25% decrease in specific airway conductance, and airway reactivity was measured as the slope of the dose-response curve. Niimi *et al.*¹⁶ came up with the view that airway sensitivity was represented as the Dmin and airway reactivity was represented as the slope of the MCh respiratory conductance dose-response curve (SRs). However, Cockcroft and Berscheid¹⁷ proposed the opposite view, that there was a direct correlation between airway sensitivity and airway reactivity, a strong negative correlation between PC₂₀-FEV₁ and the slope of the dose-response curve ($r = -0.98$), as shown in their study. Based on the tendency and correlation analyze of the SGRs and Dmin in our study, we found that the Dmin was not parallel with the SGRs and that airway sensitivity was not related to airway reactivity.

In the present study, the AUC evaluated by using the Dmin was highest among the variables measured by using the FOT, and Dmin was highly related to

Table 6 Adverse events rates (in percentages) in the two methods: APS-dosimeter and FOT*

	Tightness	Tachypnea	Wheezing	Dyspnea	Coughing	Thirst	Itching	Dizziness	Palpitation
BPT measured by using the APS-dosimeter method									
Asthma (n = 93)	40.9	33.3	19.4	11.8	44.1	29.0	17.2	11.8	8.6
UC (n = 27)	77.8	66.7	44.4	25.9	74.1	33.3	18.5	14.8	11.1
PC (n = 34)	35.3	29.4	14.7	8.8	38.2	32.4	17.6	11.8	5.9
CC (n = 32)	15.6	9.4	3.1	3.1	25	21.9	15.6	9.4	9.4
NS (n = 69)	7.2	10.1	0	1.4	36.2	24.6	17.4	13.0	10.1
BPT measured by using the FOT									
Asthma (n = 93)	48.4	49.5	18.3	14.0	48.4	50.5	30.1	2.2	3.2
UC (n = 27)	85.2	88.9	37.0	29.6	74.1	48.1	33.3	3.7	3.7
PC (n = 34)	50	47.1	17.6	11.8	38.2	55.9	29.4	0	2.9
CC (n = 32)	15.6	18.8	3.1	3.1	37.5	46.9	28.1	3.1	3.1
NS (n = 69)	10.1	18.8	2.9	5.8	39.1	43.5	26.1	0	1.4

APS = Aerosol provocation system; FOT = forced oscillation technique; BPT = bronchial provocation test; UC = uncontrolled asthma group; PC = partially controlled asthma group; CC = controlled asthma group; NS = healthy subjects group.

*The incidence rates of tachypnea, thirst, and itching in the FOT were significantly higher than in the APS-dosimeter method (tachypnea: $\chi^2 = 5.238$, thirst: $\chi^2 = 14.365$, itching: $\chi^2 = 12.199$; all $p < 0.05$); dizziness and palpitation in the FOT method was lower than in the APS-dosimeter method (FOT: $\chi^2 = 15.800$, APS-dosimeter: $\chi^2 = 6.765$, both $p < 0.05$). There was no significant difference in tightness, wheezing, dyspnea, and coughing.

PD₂₀-FEV₁, which suggested that the Dmin was the optimal parameter in the FOT for the assessment of AHR. PD35-Grs (the cumulative dose of bronchoconstrictor that induced a decrease of 35% in Grs) had been used as an indicator of AHR in some studies.^{6,18} In our study, the AUC assessed when using the PD35 was slightly lower than that when using the Dmin. The PD40 was considered to be intermediate between the Dmin and PD35. Nevertheless, the PD40 is rarely reported due to a lack of awareness.

The major adverse events when using the two methods were tightness, tachypnea, coughing, wheezing, and dyspnea. Repetitive forced expiratory maneuvers were performed in the APS-dosimeter method, whereas continuous tidal breathing were performed in the FOT method, which resulted in the difference of the incidence rate of dizziness, palpitation, thirst, and itching. The worse the asthma control status, the higher the incidence rate and the more severe adverse events were shown in the patients with asthma, which was in line with the report of Guan *et al.*¹² The discomfort could be relieved rapidly through inhalation of a short-acting bronchodilator.

Not only does the FOT have some advantages of safety, simplification, and time-saving, it also is more applicable for the elderly, children, and patients who can not perform the forced expiratory maneuver. A shorter appointment time, better patient compliance, and lighter burden of the technicians with large everyday workload make this method more popular. However, cross-infection of patients could be easily be caused due to the lack of filtration devices. In addition, the cumulative dose or concentration measured by the FOT could not be compared with conventional

methods as a result of methodologic differences. In our study, it could be believed that the FOT will have a good prospect and application despite some disadvantages.

Several limitations of the study were considered. First, typical asthma patients were included. It was unclear that these findings are fit for those atypical asthma patients, such as cough variant asthma (CVA), chest tightness variant asthma (CTVA). Therefore, more study population should be taken into account in further studies. Second, the participants were clearly diagnosed, and we did not acquire the cutoff value of the Dmin for the differential diagnosis. It is encouraged to explore the characters in all kinds of asthma, and multicenter clinical research is recommended to establish a more appropriate threshold and standardized evaluation criteria. Third, in the FOT, FEV₁ was not measured repeatedly after the inhalation of bronchodilator in the patients with positive response; we were not sure if FEV₁ had reached the baseline level.

CONCLUSION

There were no significant differences in sensitivity and specificity between the FOT and the APS-dosimeter method. The FOT, characterized by being simple, safe, and time saving, could be used to assess AHR in patients with asthma. As an alternative method of BPT, the FOT is worthy of clinical application.

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