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Diagnostic value of the hypertonic saline bronchial provocation test in children with asthma using the high-power aerosol provocation system

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ABSTRACT

Objective: This study aimed to evaluate the diagnostic value of the modified hypertonic saline bronchial provocation test (HS-BPT) for children with asthma by using the high-power Aerosol Provocation System (APS).

Methods: A total of 330 children suspected of having asthma and receiving HS-BPT-APS were included in this prospective survey conducted in Guangzhou, China from February 2017 to September 2018. The positive rate of HS-BPT-APS and the volume and types of adverse reactions were observed. There was also a retrospective cohort of 123 children with suspected asthma who underwent a methacholine BPT from 2015 to 2017. Using the method of nearest neighbor matching, a comparison was made of the positive rate and adverse reaction between the methacholine BPT group and HS-BPT-APS group.

Results: The total positive rate of HS-BPT-APS was 43.9%. Common adverse reactions included cough, wheezing and chest tightness. There were no serious adverse reactions. Results of nearest neighbor matching showed a difference in the positive rate between the methacholine BPT group and HS-BPT-APS group (8.1% vs 18.2%, $p = 0.026$), but there was no statistically significant difference between the age groups in patients who received the methacholine BPT or HS-BPT-APS. There was a similar adverse reaction rate in the two groups ($p = 0.609$).

Conclusions: HS-BPT-APS is simple, safe, and time-saving, with few adverse reactions. The positive rate of HS-BPT-APS was higher than that of methacholine BPT in children with asthma. HS-BPT-APS may be a valuable tool in the diagnosis of children with asthma, and further study is required.

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Introduction

Early diagnosis is particularly important in the treatment and prognosis of children with asthma. For children over age six, asthma is diagnosed by testing the airway hyperresponsiveness with a pulmonary function test. The most common way to diagnose asthma in children six years of age and younger is by questionnaire (1).

The bronchodilator test, which measures changes in lung capacity after inhaling a short-acting bronchodilator drug (2), has lower operational risks than the

bronchial provocation test (BPT), and is also less likely to induce asthma. The Global Initiative for Asthma (3) and guidelines for asthma prevention and treatment in China (4), Japan (5), Korea (6), Britain (7), India (8) and Spain (9) each recommend the bronchodilator test for asthma diagnosis, and if that result is negative, a BPT is performed. However, asthma diagnoses are often overlooked due to false-negative results on bronchodilators tests because of normal pulmonary function and reversible airways. Therefore, in China, the BPT is very common and crucial for the diagnosis of asthma (10).

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Methacholine and histamine remain the gold standard substances for bronchial challenge tests (4), but since 2017, these commonly used inhalation aerosols have been difficult to obtain in China because they must be imported. Moreover, they are yet to be approved by the State Food and Drug Administration (SFDA). As a result, to diagnose asthma, an indirect bronchial provocation activator, such as hypertonic saline, is being used in clinical practice again, and with positive results.

The hypertonic saline bronchial provocation test (HS-BPT) is safe, inexpensive and easy to perform, however the traditional ultrasonic atomization step is not only time-consuming, but also inaccurate for calculating inhalation doses. The aerosol provocation system (APS) is generally used in methacholine and histamine BPT (11). In our previous study, APS and a high power cup were combined and added to HS-BPT, allowing patients to accurately and quickly inhale adequate hypertonic saline (12). This modified method of challenge testing is also known as the quantitative hypertonic saline challenge test. As there are no studies of its use in children, it is necessary to compare the differences between the modified HS-BPT-APS and the traditional methacholine BPT in the diagnosis of childhood asthma, and to analyze whether there are differences amongst various age groups of children with asthma. Our study evaluated the diagnostic value and safety of HS-BPT using the high-power APS cup in children with asthma.

Materials and methods

Patients and study design

A hospital-based cross-sectional study was undertaken at Guangdong Provincial Hospital of Chinese Medicine in Guangzhou, China. The study was approved by the hospital's ethics committee. According to the WHO classification criteria for age groups, patients 0–17 years of age are considered minors. Ages were grouped according to the school years of compulsory education in China—the early childhood group (six years old and younger); the lower-grade group (seven to nine years old); and the higher-grade group (10 years old and older). Minor patients visiting the outpatient clinic were invited to participate in this study. Patients were recruited based on their respiratory symptoms (cough/wheezing/shortness of breath), chest imaging, eczema, and allergic family history. Eligible minor patients were between ages four and 17 years with a clinical diagnosis suggestive of asthma (typical asthma or cough variant asthma) and who had a BPT using

quantitative nebulization inhalation of hypertonic (4.5%) saline. All patients had a normal spirometry [FEV_1/FVC ratio > lower limit of normal (LLN)] without significant reversibility, which justified additional pulmonary function testing with a BPT. When the test was completed, the patient, or parents, grandparents, or a guardian received a questionnaire. All the tests were administered by the same trained researchers to ensure standardization of the questionnaire results.

There was also a retrospective cohort of minor patients with suspected asthma who underwent a methacholine BPT in Guangdong Provincial Hospital of Chinese Medicine from 2015 to 2017. All subjects had detailed outpatient medical histories and pulmonary function test records.

Baseline pulmonary function

All patients received spirometry to obtain baseline values using a pulmonary function instrument (Diffusion PFT System/Master Screen PFT System with APS - JAEGER Company, Germany), and following international recommendations (13,14). Detection indicators, such as forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC , peak expiratory flow (PEF) and maximal voluntary ventilation (MVV) were conducted using a standard spirometric method. The best of three forced expiratory volume curves was used to determine the FVC and FEV_1 values. To avoid the influence of sex, age, height or weight on patients' pulmonary function values, indicators were expressed as the percentage of measured values/predicted values.

Quantitative nebulization inhalation of HS-BPT-APS

A modified HS-BPT-APS was performed using the Master Screen MS plus APS quantitative nebulization drug delivery system (JAEGER Company, Germany). In this system, the patient inhales hypertonic saline through a Devilbiss 99 high power cup, and with this inhalation, the system is automatically triggered to release the stimulant (4.5% sodium chloride solution). The system was set to start administering drug 0.1 s after inhalation, and each inspiratory administration time was 0.6 to 0.8 s. The system automatically calculated the cumulative dose of the patient's cumulative inhalation (see Table 1 for standard procedures and settings). The dose-response slope (DRS) was defined as the percentage fall in FEV_1 divided by the final cumulative dose of hypertonic saline administered. The spear metric measurement was detected after

Table 1. Procedures and settings for hypertonic saline provocation quantitative nebulization inhalation test.

Step	Concentration	Single dose	Atomization power	Each inhalation time	Each inhalation dose	Inspiratory frequency	Cumulative dose
1	4.5%	15 mg	900 mg/min	0.8 s	12 mg	2	15 mg
2	4.5%	30 mg	900 mg/min	0.8 s	12 mg	3	45 mg
3	4.5%	60 mg	900 mg/min	0.8 s	12 mg	5	105 mg
4	4.5%	120 mg	900 mg/min	0.8 s	12 mg	10	225 mg
5	4.5%	240 mg	900 mg/min	0.8 s	12 mg	20	465 mg

each inhalation for 60 to 90 s, and two repeatable values were obtained and recorded. The results of lung function testing needed to meet quality control standards put forth by the Chinese Thoracic Society's Guide to Pulmonary Function Test (15). If not, the studies were redone and completion was attempted within three minutes. If the FEV₁ fell between 10% and 15%, the next stimulant inhalation dose was the same, and the patient was asked to re-inhale hypertonic saline immediately through the Devilbiss 99 high power cup. If the FEV₁ fell by more than 15%, or the maximum dose had been reached and the FEV₁ had fallen to less than or equal to 15%, the provocation test was terminated. Dose-response curves were plotted for each inhalation period.

BPT result analysis

Efficacy was analyzed using sensitivity and specificity of HS-BPT-APS and a clinical assessment. A positive BPT was defined as a decline of greater than 15% in FEV₁ after hypertonic saline inhalation. A reduction range of 10% to 15% in FEV₁ was considered suspicious. Patients who reached the end of a challenge with <10% reduction in FEV₁ were considered to have had a negative response. The results of the methacholine BPT were judged according to Chinese guidelines, as described in a publication by the Pulmonary Function Professional Group of the Chinese Thoracic Society (16).

Adverse reaction questionnaire

A questionnaire assessed adverse events after HS-BPT-APS. Contents of the questionnaire included basic information, namely symptoms, clinical signs, diagnosis, duration, treatment methods and recovery time. Patients were asked if they had experienced symptoms such as shortness of breath or cough during the test. If so, it had to be determined whether these symptoms were related to the test. Common adverse reactions to BPT include cough, chest tightness, shortness of breath, wheezing, itchy throat, hoarseness, palpitations, hand tremors, vomiting, dizziness, headache, blushing and numbness in the fingertips. The treatment methods

were: (1) rest; (2) inhaled short-acting bronchodilator; (3) oxygen therapy; (4) other treatments.

Statistical analysis

Statistical analyses were performed using the Predictive Analytics Software (PASW) Statistics 18.0 software package (SPSS Inc. IBM Corporation, Armonk, New York, USA) and STATA software 11.0 (Stata Corp. College Station, Texas, USA). Measurement data were expressed as means $\pm$ SD or median, and the significance of differences in continuous variables between groups was tested using ANOVA or a Rank Sum Test. Categorical data were expressed as rates or percentages, and a comparison between groups was conducted using either Chi-square analysis or the Fisher's exact test. To control for potential confounding between the methacholine BPT group and HS-BPT-APS group, nearest neighbor propensity-score matching based on logistic regression was applied using a 1:2 ratio according to four baseline variables: gender, age, height and weight. In order to match more patients, the caliper definition was set at 0.5. *p*-Values were derived from two-tailed tests. A significant difference was defined as a *p*-values < 0.05.

Results

Positive and adverse reactions of HS-BPT-APS subjects

Between February 2017 and September 2018, 506 patients (156 in the early childhood group, 214 in the lower-grade group and 136 in the higher-grade group) were invited to participate in this study. Of the 506 patients, 176 were excluded and 330 were enrolled in the study. The main reasons for exclusion were: inability to complete the lung function test, and failure to meet the test's quality control standards. For example, in the early childhood group, 18 patients failed to perform the basic lung function test and seven failed to complete HS-BPT-APS, 15 completed the basic lung function, but did not meet the quality control requirements of the lung function test. Another two patients requested voluntary withdrawal.

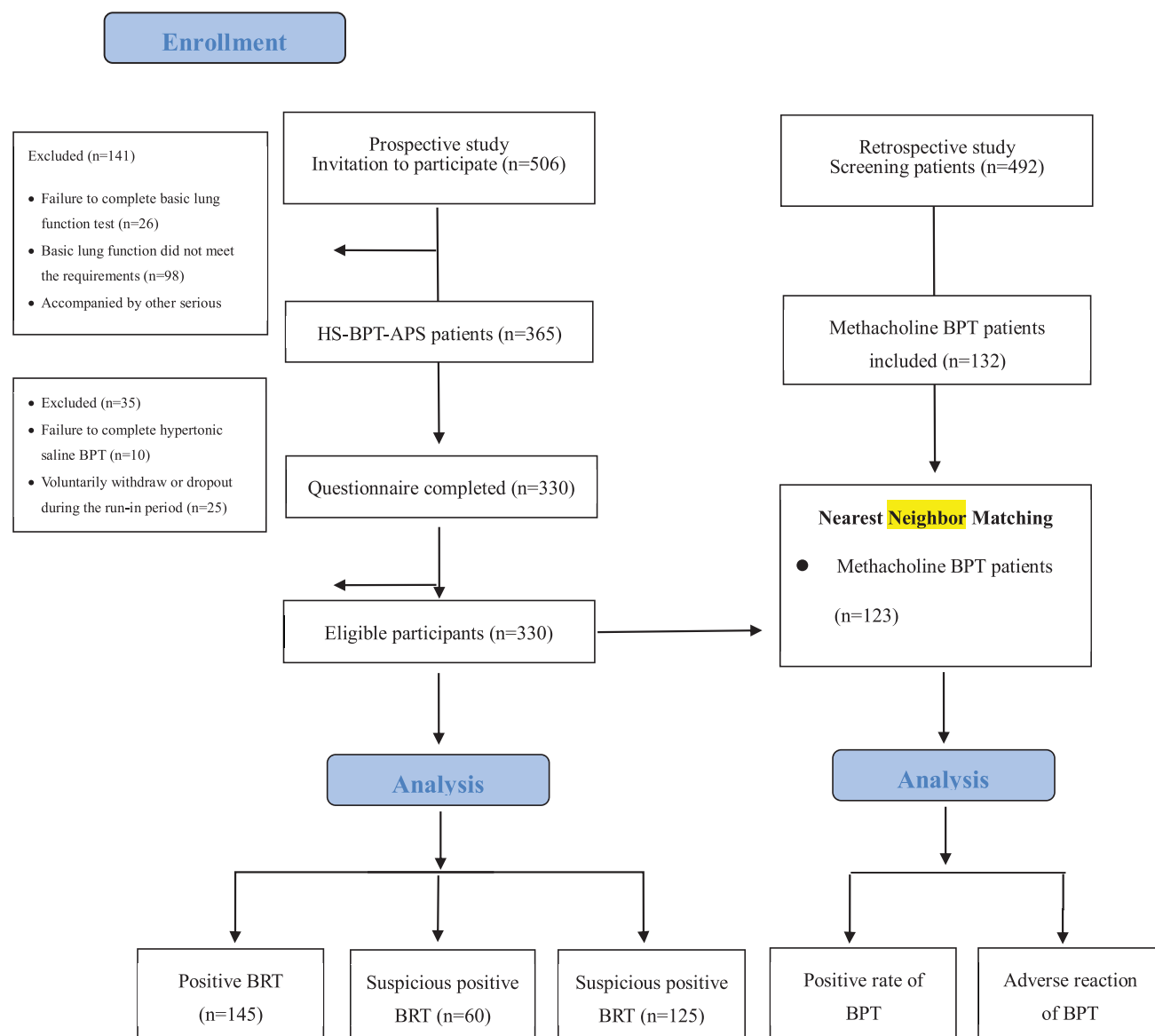


Figure 1. Flow diagram of study enrollment.

A recruitment flowchart and retention data are presented in [Figure 1](#).

The mean age of study participants was 7.93 ± 2.47 years and most participants were male (70.9%). There were significant differences in height and weight, but not sex, between the three age groups. Patient demographics and characteristic data at baseline are shown in [Table 2](#).

Of the 330 participants, BPT results showed a positive rate of 43.9% and a suspicious positive rate of 18.18%. The positive rate was 47.4% in the early childhood group, 45.7% in the lower-grade group, and 35.9% in the higher-grade group ([Table 3](#)).

Sixty-two (62) participants reported adverse reactions, the most common being cough (34 cases), tightness (21 cases), chest tightness (26 cases), and itchy

and dry throat (10 cases). Adverse reactions for all participants were relieved after rest or inhalation of relief medication (e.g. albuterol). No serious adverse reactions were reported.

Comparison of positive BPT rates between the HS-BPT-APS and methacholine BPT groups

492 minor patients who underwent a methacholine BPT between 2015 and 2017 were retrospectively screened, and of this group, 132 met the criteria and were included. We compared the differences in positive BPT rates between the HS-BPT-APS and methacholine BPT groups. In order to satisfy nearest neighbor propensity-score matching between two groups, some patients were excluded. This resulted in

Table 2. HS-BPT-APS patient demographics and baseline characteristics.

Characteristics	Early childhood group (n = 114)	Lower-grade group (n = 138)	Higher-grade group (n = 78)	p
Male (%)	81(71.1)	94(68.1)	59(75.6)	0.504
Height (cm)	117.2 ± 8.1	129.0 ± 8.7	148.4 ± 11.8	<0.001
Weight (kg)	20.8 ± 5.4	26.4 ± 8.4	40.5 ± 13.8	<0.001
FEV ₁ (L)	1.3 ± 0.3	1.6 ± 0.3	2.5 ± 0.5	<0.001
FVC (L)	1.5 ± 0.3	1.9 ± 0.4	2.9 ± 0.6	<0.001
PEF (L/s)	2.9 ± 0.6	3.6 ± 0.7	5.4 ± 1.0	<0.001
FEF ₅₀ (L/s)	1.6 ± 0.6	1.9 ± 0.5	3.0 ± 0.8	<0.001
FEF ₇₅ (L/s)	0.7 ± 0.3	0.8 ± 0.3	1.3 ± 0.6	<0.001

Table 3. Pulmonary function results of HS-BPT-APS patients.

Group	Positive rate	Suspicious positive rate	Negative rate	χ^2	p-Value
Early childhood group	54 (47.4)	18 (15.8)	42 (36.8)	10.416	0.034
Lower-grade group	63 (45.7)	32 (23.2)	43 (31.2)		
Higher-grade group	28 (35.9)	10 (12.8)	40 (51.3)		

123 cases in the methacholine BPT group paired with 214 cases in the HS-BPT-APS group being enrolled in the analysis. Patient demographics of two groups are presented in Table 4. The height of patients in the HS-BPT-APS group was significantly higher than methacholine BPT group ($p < 0.020$), but there was no difference in gender, age, weight and FEV₁ reduction between the two groups.

The positive rate was 18.2% in the HS-BPT-APS group and 8.1% in the methacholine BPT group. This difference in positive rates between the two groups was statistically significant ($p = 0.026$) (Table 5).

There were no statistically significant differences among the different age groups in patients who received the methacholine BPT, or the HS-BPT-APS test. However, the positive rate of the early childhood group and lower-grade group was higher than that of the high-grade group, and the positive rate of different age stages was higher in the HS-BPT-APS group than in the methacholine BPT group (Table 6).

Comparison of adverse reactions rate between the HS-BPT-APS and methacholine BPT groups

Forty-seven (47) patients reported adverse reactions in the HS-BPT-APS group and 30 in the methacholine BPT group, but no serious adverse reactions were reported in either group. There were no statistically significant differences in adverse reaction rate between the two groups ($p = 0.609$) (Table 7).

Discussion

In our study, BPT results showed a positive rate of 43.9% and a suspicious positive rate of 18.18%. The positive rate was 47.4% in the early childhood group, 45.7% in the lower-grade group, and 35.9% in the higher-grade group. In the HS-BPT-APS group, the

positive rate was 18.2%, while in the methacholine BPT group, the positive rate was 8.1%. This difference in positive rate between the two groups was statistically significant ($p = 0.026$).

BPT plays a significant role in asthma diagnosis. As an indirect BPT, hypertonic saline limits airflow by targeting inflammatory cells and nerve cells, rather than smooth muscle in the airway. It is a powerful physiological stimulation for asthmatic patients, with only a slight reaction in non-asthmatic people. These cells release inflammatory mediators and cytokines to induce airway contraction. Therefore, the sensitivity and positive rate are lower than that of direct bronchial provocation tests, especially after medication by budesonide or other drugs.

Due to its practicality as a bronchial provocation test in the clinic, there is a long history of research with hypertonic saline. In 1981, Schoeffel et al. first reported that inhalation of saline at different concentrations could lead to airway contraction in asthmatic patients (17). Research by Eschenbacher et al. not only confirmed that hypertonic saline could induce airway contraction in asthmatic patients, but also speculated that it may induce airway spasms and cough by changing the osmotic pressure in the airway (18). Smith and Anderson established the standard operating protocol by ultrasonic atomization in Australia (19,20). The protocol has been approved by the European Respiratory Society since 1993 (21), as hypertonic saline is inexpensive, safe, easy to obtain, and has high levels of patient compliance. Also, it has been widely used in epidemic investigations of asthma in children and adults.

The standard operating protocol uses ultrasonic vibration to convert hypertonic saline into aerosol particles, which are inhaled into the terminal bronchus and alveoli as patients deeply and slowly inhale.

Table 4. Demographics of populations (Nearest Neighbor Matching).

Characteristics	Methacholine BPT group (n = 123)	HS-BPT-APS group (n = 214)	p
Male (%)	87 (70.7)	158 (73.8)	0.539
Age, (years)	9.0 ± 2.7	8.5 ± 2.6	0.086
Height (cm)	132.1 ± 13.8	135.9 ± 16.3	0.020
Weight (kg)	31.9 ± 14.5	29.5 ± 11.3	0.103
FEV ₁ reduction(%)	19.9 ± 10.9	19.9 ± 3.6	0.994

Table 5. Pulmonary function results of different groups (Nearest Neighbor Matching).

Group	Positive rate	Suspicious positive rate	Negative rate	χ^2	p-Value
Methacholine BPT	10 (8.1)	55 (44.7)	58 (47.2)	7.297	0.026
HS-BPT-APS	39 (18.2)	95 (44.4)	80 (37.4)		

Table 6. Association analysis between different age groups (Nearest Neighbor Matching).

Group	Positive rate	Suspicious positive rate	Negative rate	χ^2	p-Value
Methacholine BPT					
Early childhood group	4 (13.3)	11 (36.7)	15 (50.0)	–	0.245*
Lower-grade group	3 (7.3)	15 (36.6)	23 (56.1)		
Higher-grade group	3 (5.8)	29 (55.8)	20 (38.5)		
HS-BPT-APS					
Early childhood group	11 (18.3)	28 (46.7)	21 (35.0)	8.081	0.089
Lower-grade group	19 (22.6)	41 (48.8)	24 (28.6)		
Higher-grade group	9 (12.9)	26 (37.1)	35 (50.0)		

*Calculated by Fisher exact test.

Table 7. Adverse reactions in different groups (Nearest Neighbor Matching).

Group	No adverse reaction	Adverse reactions	χ^2	p-Value
Methacholine BPT	93 (75.6)	30 (24.4)	0.261	0.609
HS-BPT-APS	167 (78.0)	47 (22.0)		

The aerosol particles produced by ultrasonic atomization are large, with a diameter of 3.7–10.5 μm (20).

It is worth noting that patient compliance is a challenge, as they are required to maintain deep inhalation for the sake of depositing aerosol particles into the lower respiratory tract. Also, it is impossible to calculate the amount of drug that a patient inhales into the bronchus, or to evaluate (either quantitatively or qualitatively) patients' airway hyperresponsiveness. This reflects the fact that the ultrasonic nebulizer is a continuous nebulization output, and each subject's inhalation amount is related to respiratory frequency and tidal volume. In addition, the process is time-consuming, and the continuous output of atomized particles disperses into the air, impacting both the operator and other subjects.

To address these challenges, we have been developing an independent technique since 2016 to apply to indirect bronchial provocation tests called HS-BPT-APS. It uses the high-power APS, and hypertonic saline can be easily purchased. The quantitative nebulization is driven by compressed air, and the drugs are broken into tiny particles by airflow pressure through a nebulization cup. When the subject inhales, the particles are released by the trigger device, with an

average diameter of 4.5 μm . This diameter disperses the drugs so that they may enter the lungs with the airflow. They are deposited into the bronchus and lung tissues by gravity deposition and Brownian movement and have wide contact surfaces with the lung tissues. The HS-BPT-APS only requires tidal breathing when inhaling, therefore it is especially suitable for children who have low lung capacity. Moreover, the cumulative provocation inhalation dose can be calculated by a computer. Unlike continuous ultrasonic atomization, it can economize on drug disbursement by calculating the quantity of inhaled drugs and avoiding the diffusion of atomized particles into the test room—thus affecting the operator and other subjects. After many attempts and improvements, we have established a set of regulations for HS-BPT-APS (16).

In our previous exploratory research, we counted 1,097 cases of HS-BPT-APS among different age groups (11,12). The statistical analysis showed that the positive rates for the older group, the younger group, and the middle-aged group were low, while that of the junior group was high, thus the results for this group may have more clinical value. Also, the positive rate for HS-BPT in asthmatic children was 47–67%, based on the research reports from different countries (21,23,24). In this study, the positive rate for asthmatic children was 43.9%, which aligns with results from our earlier research. Considering the narrow diameter of the bronchial tree, soft bronchial cartilage ring, poor scaffold function and loose mucosal tissue in children, the provocation of hypertonic saline is

easy because of the changes in tracheal osmotic pressure (25). This explains why the positive rate of HS-BPT-APS in children is higher than that of adults.

It is recommended that asthma in children under six years of age be diagnosed by questionnaires rather than pulmonary function tests, as suggested by the guidelines for asthmatic children both in China and abroad. Although the ability of preschool children to understand and comply with the test is significantly lower than that of elementary school age children, some preschool children between ages four and six years were included in our study. After the operator's patience and careful guidance, the majority of the preschool children were able to complete the pulmonary function test with forced exhalation of at least one second. However, some children still could not comply with a pulmonary function test, and thus needed to take an airway resistance provocation test instead.

Hypertonic saline is a physiological activator in the BPT, which produces fewer pharynx and larynx irritation symptoms. It is safe and readily accepted by both pediatric patients and their parents. The test produces fewer common adverse reactions than other activators for bronchial provocation tests, and produces no serious adverse reactions (26). When considering safety and test quality, we recommend HS-BPT-APS for the diagnosis of asthma in children with suspected asthma. It not only has a high positive rate and good quality control, but also is easily followed by patients.

Thanks to the innovation and practicality of HS-BPT-APS in the diagnosis of asthma in children, we were invited by the Chinese Medical Association to give special reports at the National Respiratory Annual Conference in 2017 and 2018. At present, many hospitals are applying our methods and regulations in clinics across China, and we also look forward to establishing more comprehensive standards in the future. However, there are still some limitations in our research. We did not explore whether the HS-BPT-APS results predict the clinical course, including response to therapy, and whether the children who respond to methacholine also respond to hypertonic saline. Also, we still do not know if HS-BPT-APS can detect different patterns of asthma, just as the application of methacholine BPT does in adults. Whether the results of HS-BPT-APS can be reproduced over time remains a challenge.

Conclusion

HS-BPT-APS is simple and safe for asthmatic children. It produces few adverse reactions and has a

high positive rate. HS-BPT-APS may offer an important diagnostic value in children with asthma, which is worth popularizing, but further study is needed.

Declaration of interest

The authors report that they have no conflicts of interest.

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References

1. Bao YX. The establishment of diagnostic criteria for asthma in children aged < 6 years. *Chin J Pract Pediatr*. 2018;33(11):870–876.
2. Sim YS, Lee J-H, Lee W-Y, Suh DI, Oh Y-M, Yoon J-S, Lee JH, Cho JH, Kwon CS, Chang JH, et al. Spirometry and bronchodilator test. *Tuberc Respir Dis*. 2017;80(2):105–112.
3. Becker AB, Abrams EM. Asthma guidelines: the Global Initiative for Asthma in relation to national guidelines. *Curr Opin Allergy Clin Immunol*. 2017;17(2):99–103. doi:10.1097/ACI.0000000000000346.
4. Asthma group of Chinese Thoracic Society. Bronchial asthma prevention and treatment guide (2016 edition). *Chin J Tuberc Respir Dis*. 2016;39(9):675–697.
5. Ohta K, Ichinose M, Nagase H, Yamaguchi M, Sugiura H, Tohda Y, Yamauchi K, Adachi M, Akiyama K. Japanese Guideline for Adult Asthma 2014. *Allergol Int*. 2014;63(3):293–333. doi:10.2332/allergolint.14-RAI-0766.
6. Kim DK, Steering and Scientific Committee of Asthma Study Group and Guideline Control Committee in The Korean Academy of Tuberculosis and Respiratory Diseases (KATRD), Park YB, Oh Y-M, Jung K-S, Yoo JH, Yoo K-H, Kim KH. Korean Asthma Guideline 2014: Summary of Major Updates to the Korean Asthma Guideline 2014. *Tuberc Respir Dis*. 2016;79(3):111–120. doi:10.4046/trd.2016.79.3.111.
7. BCGuidelines.ca. Asthma in Adults-Recognition, Diagnosis and Management [EB/OL]. Available from: <https://www2.gov.bc.ca/gov/content/health/practitioner-professionalresources/bc-guidelines/asthma-adults>.
8. Agarwal R, Dhoria S, Aggarwal AN, Maturu VN, Sehgal IS, Muthu V, Prasad KT, Yenge LB, Singh N, Behera D, et al. Guidelines for diagnosis and management of bronchial asthma: joint recommendations of National College of Chest Physicians (India) and

- Indian Chest Society. *Indian J Chest Dis Allied Sci*. 2015;57:Spec No: 5
9. Plaza Moral V, Alonso Mostaza S, Alvarez Rodríguez C, Gomez-Outes A, Gómez Ruiz F, López Vina A, Molina París J, Pellegrini Belinchón FJ, Plaza Zamora J, Quintano Jiménez JA, et al. Spanish guideline on the management of asthma. *J Investig Allergol Clin Immunol*. 2016;26(Suppl. 1):1–92. doi:[10.18176/jiaci.0065](https://doi.org/10.18176/jiaci.0065).
10. Yin SM, Chen YB, Zheng YC, et al. Comparison of diagnostic value in different pulmonary function tests in the guidelines of bronchial asthma. *Chin Gen Pract*. 2018;21(32):3911–3914.
11. Schulze J, Rosewich M, Riemer C, Dressler M, Rose MA, Zielen S. Methacholine challenge—comparison of an ATS protocol to a new rapid single concentration technique. *Respir Med*. 2009;103(12):1898–1903. doi:[10.1016/j.rmed.2009.06.007](https://doi.org/10.1016/j.rmed.2009.06.007).
12. Yang JY, Chen YB, Ouyang WW, et al. Preliminary clinical evaluation of quantitative atomizer with improved hypertonic saline bronchial provocation. *J Jinan Univ (Natural Science & Medicine Edition)*. 2018;39(05):419–425.
13. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005; 26(2):319–338. [PMID: 16055882] doi:[10.1183/09031936.05.00034805](https://doi.org/10.1183/09031936.05.00034805).
14. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CPM, et al. Standardisation of the measurement of lung volumes. *Eur Respir J*. 2005; 26(3):511–522. [PMID: 16135736] doi:[10.1183/09031936.05.00035005](https://doi.org/10.1183/09031936.05.00035005).
15. Pulmonary function professional group of Chinese Thoracic Society. Guide to Pulmonary Function Test (Part 2) - Spirometry. *Chin J Tuberculosis Respir Dis*. 2014;37(7):481–486.
16. Pulmonary function professional group of Chinese Thoracic Society. Guide to Pulmonary Function Test (Part 3) - histamine and methacholine bronchial challenge testing. *Chin J Tuberculosis Respir Dis*. 2014; 37(7):566–571.
17. Schoeffel RE, Anderson SD, Altounyan RE. Bronchial hyperreactivity in response to inhalation of ultrasonically nebulised solutions of distilled water and saline. *Br Med J. (Clin Res Ed.)* 1981;283(6302): 1285–1287. doi:[10.1136/bmj.283.6302.1285](https://doi.org/10.1136/bmj.283.6302.1285).
18. Eschenbacher WL, Boushey HA, Sheppard D. Alteration in osmolarity of inhaled aerosols cause bronchoconstriction and cough, but absence of a permeant anion causes cough alone. *Am Rev Respir Dis*. 1984;129(2):211–215.
19. Smith CM, Anderson SD. Inhalational challenge using hypertonic saline in asthmatic subjects: a comparison with responses to hyperpnoea, methacholine and water. *Eur Respir J*. 1990;3(2):144–151.
20. Rodwell LT, Anderson SD, Seale JP. Inhaled clemastine, an H1 antihistamine inhibits airway narrowing caused by aerosols of non-isotonic saline. *Eur Respir J*. 1991;4(9):1126–1134.
21. Riedler J, Reade T, Dalton M, Holst D, Robertson C. Hypertonic saline challenge in an epidemiologic survey of asthma in children. *Am J Respir Crit Care Med*. 1994;150(6):1632–1639. doi:[10.1164/ajrccm.150.6.7952626](https://doi.org/10.1164/ajrccm.150.6.7952626).
22. Lis G, Pietrzyk JJ. Response-dose ratio as an index of bronchial responsiveness to hypertonic saline challenge in an epidemiological survey of asthma in Polish children. *Pediatr Pulmonol*. 1998;25(6):375–382. doi:[10.1002/\(SICI\)1099-0496\(199806\)25:6<375::AID-PPUL4>3.0.CO;2-G](https://doi.org/10.1002/(SICI)1099-0496(199806)25:6<375::AID-PPUL4>3.0.CO;2-G).
23. Araki H, Sly PD. Inhalation of hypertonic saline as a bronchial challenge in children with mild asthma and normal children. *J Allergy Clin Immunol*. 1989;84(1): 99–107. doi:[10.1016/0091-6749\(89\)90183-8](https://doi.org/10.1016/0091-6749(89)90183-8).
24. Riedler J, Gamper A, Eder W, Oberfeld G. Prevalence of bronchial hyperresponsiveness to 4.5% saline and its relation to asthma and allergy symptoms in Austrian children. *Eur Respir J*. 1998;11(2):355–360. doi:[10.1183/09031936.98.11020355](https://doi.org/10.1183/09031936.98.11020355).
25. Zhou MJ. Relationship between the adverse reaction and age in bronchial provocation test. *Chin J Pract Intern Med*. 2015;35(07):610–613.
26. Zhou MJ. Value of small airway disease on predicting asymptomatic in children with chronic cough. *J Appl Clin Pediatr*. 2011;26(04):244–249.