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Comparative Diagnostic Value of Astograph and APS Methods for Chest Tightness Variant Asthma in Children: a prospective randomized crossover study

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Comparative Diagnostic Value of Astograph and APS Methods for Chest Tightness Variant Asthma in Children: a prospective randomized crossover study

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Abstract

Background: The Astograph technique, based on forced oscillation technique, allows real-time monitoring of airway resistance during tidal breathing with better patient cooperation than conventional methods. However, its diagnostic utility for chest tightness variant asthma (CTVA) in children remains unclear. This study compared the performance and safety of Astograph and APS methods in diagnosing pediatric CTVA.

Methods: Children aged 6–17 years with chest tightness were enrolled from October 2023 to December 2024. Participants underwent both Astograph- and APS-based bronchial challenge testing in a randomized crossover design with 24–48 hour

intervals. Subjects with airway hyperresponsiveness received anti-asthmatic treatment, and responses were monitored. Participants were categorized into CTVA or control groups based on final diagnosis.

Results: Of 132 enrolled children, 125 met criteria (CTVA: 51; controls: 74). CTVA patients showed significantly lower FEV1/FVC ratios and small airway parameters ($p<0.05$), lower Dmin values, and higher SGrs and SGrs/Grs values ($p<0.05$). ROC analysis revealed higher AUC for Astograph (0.777) versus APS (0.709). Diagnostic accuracy was superior for Astograph (83.2% vs. 80.0%). Astograph demonstrated lower adverse reaction rates (46.4% vs. 65.6%, $p<0.05$) and shorter testing time.

Conclusions: Astograph method demonstrates superior diagnostic accuracy, safety, and efficiency compared to APS for pediatric CTVA diagnosis. PD25 represents the most valuable diagnostic parameter and is recommended for clinical implementation.

Keywords:

Children; Chest Tightness Variant Asthma; Airway Hyperresponsiveness; Astograph; APS; Diagnostic Performance

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Introduction

Bronchial asthma is one of the most common chronic respiratory diseases in children, with a steadily increasing global prevalence that significantly impacts health and healthcare systems[1, 21]. Classical asthma is typically characterized by wheezing, coughing, and shortness of breath. However, in recent years, clinicians

have recognized a subset of pediatric patients who lack these typical symptoms and instead present primarily with chest tightness[9, 10]. In 2013, Professor Shen's team first proposed the concept of chest tightness variant asthma (CTVA) to describe this phenotype[11]. Due to its subtle and non-specific symptoms, CTVA is often misdiagnosed or overlooked in clinical practice[12].

A hallmark feature of asthma, including atypical forms like CTVA, is airway hyperresponsiveness (AHR). Thus, objective assessment of AHR is critical in suspected CTVA cases[17,19]. Bronchial challenge testing (BCT) remains the most accurate and widely used method for evaluating AHR[2,18]. In China, the most commonly applied direct challenge method is the APS (Aerosol Provocation System) technique, which is well standardized and yields reliable results[20]. However, APS testing requires repeated forced expiratory maneuvers and active patient cooperation, which may induce respiratory fatigue or bronchospasm, increasing the risk of false-positive results, particularly in children[29,30].

The Astograph method, in contrast, is based on the forced oscillation technique (FOT), allowing continuous monitoring of airway resistance during quiet breathing[13,14]. It generates a dose-response curve and is less demanding in terms of patient cooperation, making it particularly suitable for pediatric populations[15]. Nevertheless, data on the diagnostic sensitivity, specificity, and safety profile of Astograph in evaluating pediatric AHR are limited.

This study aims to assess and compare the diagnostic performance of the Astograph and APS methods in identifying AHR among children presenting with chest tightness.

By evaluating parameters such as sensitivity, specificity, efficiency, and safety, we seek to provide evidence to improve diagnostic strategies and support broader clinical adoption of suitable techniques in pediatric CTVA evaluation.

Subjects and Methods

1.1 Study Population

This cross-sectional study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies. Children aged 6–17 years presenting with chest tightness to the Department of Respiratory Medicine at the Children's Hospital of Soochow University between October 2023 and December 2024 were prospectively enrolled. Based on comprehensive diagnostic criteria, participants were categorized into CTVA or non-CTVA control groups. Written informed consent was obtained from parents or legal guardians of all participants. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board/Ethics Committee of the Children's Hospital of Soochow University (approval number: 2023CS315). Sample size was determined based on feasibility constraints and study duration. A minimum of 100 participants was targeted to provide adequate statistical power for comparing diagnostic accuracy between methods, accounting for an expected AUC difference of 0.1, with $\alpha=0.05$ and $\beta=0.20$. A total of 132 participants were recruited to account for potential dropouts and incomplete testing.

1.2 Study Procedure

Diagnostic criteria for chest tightness variant asthma (CTVA)[4]:(1) Chest tightness or

prolonged sighing as the sole or predominant clinical manifestation, persisting for >4 weeks; (2) absence of wheezing on pulmonary auscultation during episodes of chest tightness; (3) no organic abnormalities on chest radiography; (4) pulmonary function testing demonstrating airway hyper-responsiveness (AHR); (5) exclusion of chest tightness attributable to cardiovascular, gastrointestinal, or psychiatric disorders; and (6) documented efficacy of anti-asthmatic therapy.

All children underwent standardized screening using predetermined criteria and completed structured questionnaires and physical examinations. Clinical data collection included demographic information, medical history, comorbidities, medication history, and allergy history. Each participant subsequently underwent both Astograph-based and APS-based bronchial challenge testing (BCT) using a randomized crossover design with 24–48 hour washout intervals between tests.

Children demonstrating airway hyperresponsiveness by either method received standardized anti-asthmatic treatment and were monitored for 4 weeks to assess therapeutic efficacy. Treatment response was classified as good if chest tightness symptoms showed significant improvement, otherwise as no treatment response. Children with good treatment response were classified as the chest tightness variant asthma group, while those without airway hyperresponsiveness and those with no treatment response comprised the control group.

To minimize potential sources of bias, a randomized crossover design with 24-48 hour washout periods was used to control for order effects and carry-over bias; standardized protocols and equipment calibration were applied for both testing

methods; inclusion and exclusion criteria were applied consistently by trained personnel; statistical analysis was blinded where feasible to minimize interpretation bias; and objective, quantitative outcome measures were used to reduce measurement bias.

Participants were eligible if they met all of the following inclusion criteria: age 6-17 years, regardless of sex; recurrent chest tightness or frequent sighing as the sole or main symptom lasting >4 weeks; no respiratory tract infection within the past 4 weeks; baseline pulmonary function with FEV1 at least 70% of the predicted value and no contraindications to bronchial provocation testing; no recent use of medications that might affect test results; and clinical features of (1) no wheezing on auscultation during episodes, (2) no structural abnormalities on chest radiograph, and (3) exclusion of cardiovascular, gastrointestinal, and other causes of chest tightness.

CTVA Group Criteria:

(1) Presence of AHR confirmed by pulmonary function testing;

(2) Effective response to 4-weeks of anti-asthmatic treatment. In this study, both positive and borderline BCT results were considered indicative of AHR.

Control Group Criteria:

No AHR detected by pulmonary function testing and/or no response to 4-weeks of anti-asthmatic treatment.Children were closely monitored during provocation testing for vital signs and symptoms. All data were collected and analyzed by a unified research team. The study was approved by the Ethics Committee of Soochow University.

1.3 Diagnostic Criteria

APS Method:

Pulmonary ventilation was assessed using the MasterScreen™ pneumotachograph system (Jaeger, Höchberg, Germany); predicted baseline forced spirometric values were computed with the Global Lung Initiative 2012 (GLI-2012) multi-ethnic reference equations.For the quantitative aerosol challenge, the APS (Aerosol Provocation System) method was employed[3]. This integrated, automated dosimeter triggers a single inspiratory-phase nebulisation pulse only when the preset inspiratory flow rate is achieved; aerosol generation is instantaneously suspended during expiration. Detailed operating procedures are provided in the Appendix.

The APS system is an inspiratory-triggered nebulisation device: it releases a precisely controlled aerosol bolus at each inspiration, enabling accurate delivery of every inhaled dose and automatic calculation of the cumulative dose administered. In subjects with airway hyperresponsiveness, inhalation of progressively increasing doses of methacholine induces airway narrowing and a fall in FEV1; a decrease in FEV1 of 20% or more relative to the baseline value is regarded as a positive challenge, indicating airway hyperresponsiveness. In the present study, the routine (standard) methacholine administration protocol was applied to all participants; the two simplified alternative protocols listed in the administration table are provided in the Supplementary Material for reference only.

For the APS method, the bronchial challenge test was interpreted as positive when

FEV1 decreased by 20% or more from baseline after the maximum concentration/dose of methacholine (MCh); negative when FEV1 decreased by less than 15% from baseline; and borderline when (1) new or worsened symptoms and wheezing on auscultation occurred after MCh but the FEV1 decline was less than 20%, or (2) FEV1 decreased by 15-20% without evident symptoms.

Astograph Method: The Astograph (continuous-breathing forced-oscillation) technique is based on the forced oscillation technique: a low-frequency pressure oscillation is superimposed on spontaneous tidal breathing, and respiratory resistance (Rrs) is computed continuously, providing a real-time assessment of bronchoconstriction throughout the test. Testing was performed with the Astograph J-21 system (Chest Co., Tokyo, Japan); aerosol generation is initiated automatically and maintained throughout the procedure, and the subject is required only to maintain quiet tidal breathing [2,5]. Detailed experimental procedures are provided in the Appendix. The test was interpreted as positive when Rrs increased to 2 times the baseline value or more after methacholine (MCh); negative when Rrs remained below 2 times baseline after the maximum MCh dose; and borderline when (1) new or worsened symptoms and wheezing occurred without meeting the objective threshold, or (2) Rrs increased by more than 50% but to less than 2 times baseline, with a subsequent decrease after bronchodilator [2,7].

To facilitate interpretation, the main outcome parameters were defined as follows. For the Astograph method: Dmin (minimum dose) is the cumulative dose of methacholine required to induce the first sustained decrease in respiratory

conductance (Grs), reflecting airway sensitivity; Cmin (minimum concentration) is the lowest inhaled methacholine concentration at which Rrs begins to rise continuously, reflecting the response threshold; SGrs is the slope of the linear decrease in Grs per unit cumulative dose of methacholine, reflecting airway reactivity; and PDx is the cumulative dose of methacholine at which Rrs reaches x% of its baseline value (e.g., PD15, PD20, PD25). For the APS method, PD20-FEV1 is the cumulative dose of methacholine producing a decrease in FEV1 of 20% or more from the baseline value. All result variables reported in the Results section are defined at first use in the text.

1.4 Statistical Analysis

Statistical analysis was performed using SPSS Statistics 27.0. Categorical variables were expressed as percentages and compared using chi-square tests. Normally distributed continuous variables were expressed as mean ± standard deviation and analyzed using t-tests. Non-normally distributed data were reported as median (interquartile range) and analyzed using Wilcoxon rank-sum tests. Correlation analyses utilized Pearson or Spearman coefficients depending on data distribution. Receiver operating characteristic (ROC) curves evaluated diagnostic performance. Statistical significance was set at $p<0.05$.

Complete case analysis was performed for all primary outcomes. Participants unable to complete both testing methods were excluded from comparative analyses but included in descriptive statistics where data were available. No imputation methods

were employed for missing data. Given the robust crossover design and minimal missing data, formal sensitivity analyses were not performed. However, subgroup analyses within the CTVA group based on pulmonary function status assessed consistency across different disease severity levels Within the CTVA group, patients were classified a priori into normal and impaired pulmonary function subgroups: pulmonary function impairment was defined as any conventional spirometry parameter (FEV1/FVC, FEV1, or FVC) below the lower limit of normal (LLN), or two or more small airway parameters (MEF50, MEF25, MMEF75/25) below the LLN; normal pulmonary function was defined as not meeting these criteria.

2. Results

2.1 Comparison of General Characteristics

A total of 132 children were initially recruited. Three were unable to complete APS testing and four were unable to complete Astograph testing. Thus, 125 children (CTVA group: 51; control group: 74) met the inclusion criteria. There were no significant differences between the two groups in sex, age, weight, height, BMI, or age distribution (all $p>0.05$), indicating good comparability. All 125 included participants had complete demographic data and baseline pulmonary function measurements. Seven participants (5.6%) were unable to complete both provocation tests: 3 could not complete APS testing due to inadequate cooperation, and 4 could not complete Astograph testing due to technical difficulties. All participants who completed both tests had complete data for primary outcome measures.

2.2 Comparison of Pulmonary Ventilation Function

Baseline pulmonary function testing revealed no moderate or severe ventilatory impairment in any participants. However, the CTVA group exhibited significantly lower FEV_1/FVC ratios and percent predicted values compared to the control group ($p<0.01$), indicating mild obstructive ventilatory dysfunction. Additionally, small airway parameters including MEF_{50}, MEF_{25}, $MMEF_{75/25}$, and their respective percent predicted values were significantly reduced in the CTVA group ($p<0.05$), while no significant differences were observed in large airway indices[24,25,26]. These findings suggest that children in the CTVA group had more pronounced small airway dysfunction compared to controls(Table 1).

2.3 Comparison of Bronchial Provocation Test Indicators

According to the APS test, PD20-FEV1 in the CTVA group was significantly lower than in the control group [2.33 (0.99, 2.50) vs. 2.50 (2.50, 2.50) mg; $p < 0.001$], indicating a higher airway hyperresponsiveness, though mostly at a very mild level.In the Astograph test, the CTVA group had significantly lower Dmin values ($p < 0.001$), indicating increased airway sensitivity. Furthermore, both SGrs and SGrs/Grs were significantly elevated ($p < 0.001$), reflecting heightened airway reactivity and responsiveness.A detailed analysis of the provocation dose indicators (PD5 through PD50) showed significantly lower values in the CTVA group than in the control group (all $p < 0.001$), with PD25 showing the most prominent intergroup difference, suggesting its high diagnostic discriminative power(Table 2).

2.4 CTVA Subgroup Analysis

Within the CTVA group, patients were divided into normal and impaired pulmonary

function subgroups according to the predefined criteria described in the Methods section.The results showed that the impaired group had significantly lower SGrs and SGrs/Grs compared to the normal group, while PD_{45} was significantly higher in the impaired group, with statistically significant differences ($P < 0.05$). For other parameters including Rrs, Dmin, Cmin, and PD_{15}, no statistically significant differences were observed between the two groups ($P > 0.05$).

2.5 Correlation Analysis of Astograph Parameters

After logarithmic transformation of Dmin, we found that LogDmin showed strong negative correlations with SGrs and SGrs/Grs ($r \approx -0.92$ to -0.93, $P < 0.001$), and high positive correlations with PD_{15}, PD_{20}, PD_{25}, and other parameters ($r \approx 0.97$ to 0.99, $P < 0.001$). These correlations were consistently observed across parameters (Table 3).

2.6 Correlation Analysis Between Astograph and APS Methods

After logarithmic transformation of PD_{20}-FEV_1 from the APS method, correlation analysis was performed with main parameters of the Astograph method. The results showed that LogPD_{20}-FEV_1 had moderate negative correlations with SGrs and SGrs/Grs ($r \approx -0.78$ to -0.79, $P < 0.001$), and strong positive correlations with Dmin, PD_{15}, PD_{25}, and other parameters ($r \approx 0.81$ to 0.82, $P < 0.001$), further demonstrating good consistency between the two methods in core diagnostic indicators（Table 3）.

2.7 ROC Curve Analysis: Diagnostic Performance Comparison

ROC curves showed that PD_{25} in the Astograph method had the best diagnostic performance, with an AUC of 0.777 (95% CI: 0.697–0.850), which was higher than

Dmin (AUC = 0.772), PD_{15} (AUC = 0.774), and PD_{20} (AUC = 0.774)(Figures 1). In comparison, PD_{20}-FEV_1 in the APS method had an AUC of 0.709 (95% CI: 0.637–0.792), showing slightly lower diagnostic performance than the Astograph method[27,28].

2.8 Comparison of Diagnostic Value of Provocation Tests

In the CTVA group, the positive rate of the Astograph method was 43.2%, while the APS method was 44.8%, with no statistically significant difference ($P > 0.05$), suggesting that both methods have comparable consistency levels in detecting airway hyperresponsiveness (AHR). According to the airway reactivity grading systems of both methods[2] (Table 4), the distribution of the CTVA group was described (Figures 2).

2.9 Detection Time Comparison

In this study, detection time for provocation testing was defined as the duration from test initiation to either positive provocation determination or test completion, excluding the time required for bronchodilator inhalation by subjects. In the CTVA group, the median detection time for the Astograph method was 12 minutes (IQR: 11–12 minutes), which was significantly shorter than that of the APS method at 15 minutes (IQR: 15–18 minutes) ($p<0.001$). A similar trend was observed in the control group, with the Astograph method demonstrating superior operational efficiency.

2.10 Adverse Reaction Comparison

The incidence of adverse reactions with the Astograph method was 46.4%, which was significantly lower than that observed with the APS method (65.6%, $p<0.05$) . All

adverse reactions were mild in severity for both testing methods. Common symptoms included cough, chest tightness, and throat irritation. No moderate to severe adverse events were documented in either group. Overall, the Astograph method demonstrated superior safety profile and better pediatric tolerance compared to the APS method.

Discussion

The pathogenesis of chest tightness variant asthma (CTVA) resembles typical asthma, characterized by airway hyperresponsiveness (AHR) and inflammation [1,17,18]. In the present study, CTVA patients demonstrated significantly enhanced airway sensitivity (lower Dmin) and reactivity (elevated SGrs and SGrs/Grs) compared to controls, supporting the concept that despite subtle clinical manifestations, CTVA patients exhibit underlying AHR comparable to typical asthma. Notably, the CTVA group showed reduced PD20-FEV1 with predominantly very mild airway reactivity, indicating that the severity of AHR is generally lower than that seen in typical asthma.In terms of baseline pulmonary function, CTVA patients exhibited significantly impaired FEV1/FVC and small airway parameters (MEF50, MEF25, MMEF75/25) compared to controls, indicating airway obstruction primarily affecting small airways [19,20,21]. This aligns with previous studies demonstrating underlying airway dysfunction in CTVA patients despite absent typical symptoms [22]. Subgroup analysis revealed that patients with impaired lung function showed weaker reactivity (lower SGrs, SGrs/Grs, higher PD45) compared to those with normal function.

With respect to diagnostic performance, the Astograph technique provides comprehensive reactivity assessment parameters, among which PD25 showed the highest diagnostic performance (AUC=0.777), outperforming PD20-FEV1 derived from the APS method (AUC=0.709) [23,24]. Multiple Astograph parameters showed favorable diagnostic performance and significant correlations with PD20-FEV1. Although the two methods had comparable positive rates (Astograph: 43.2%; APS: 44.8%), supporting consistent identification of AHR, they are not simply interchangeable.

From the perspective of testing efficiency and safety, Astograph significantly outperformed APS with shorter detection times, better pediatric tolerance, and lower adverse reaction incidence [25,26]. All adverse reactions were mild, with no moderate-to-severe events reported, demonstrating favorable safety profiles.

Our findings are broadly consistent with, and extend, previous evaluations of bronchial provocation testing in pediatric populations. Conventional dosimeter-based protocols such as the APS method require repeated spirometric maneuvers after each dose increment, which can be difficult for young children and may underestimate provoked bronchoconstriction when forced maneuvers are not reproducible [13,14,15]. In contrast, the Astograph technique monitors airway resistance continuously during tidal breathing and captures methacholine-induced bronchoconstriction in real time, which likely contributes to the shorter testing time and better tolerability observed in our cohort [15,25,26]. The diagnostic performance of PD25 (AUC = 0.777) in the present study falls within the moderate-to-good range reported for Astograph-derived parameters in previous pediatric and adult studies [23,24,27,28]. Moreover, the moderate-to-strong correlations between LogPD20-FEV1 and key Astograph parameters suggest that the two tests largely reflect the same underlying AHR phenotype, rather than being straightforward substitutes for one another.

These results also have practical implications for the diagnostic workup of pediatric CTVA. First, for children who cannot reliably perform forced spirometry, Astograph may be the preferred first-line provocation method, whereas the APS method remains a validated alternative when oscillometry is unavailable. Second, the strong performance of PD25, together with the dose-response slope parameters, suggests that a combined interpretation of airway sensitivity (Dmin) and airway reactivity (SGrs, SGrs/Grs), rather than reliance on a single cutoff value, may improve diagnostic

confidence in borderline cases. Third, because all adverse reactions in both groups were mild and self-limited, both procedures can be safely performed on an outpatient basis with standard monitoring and immediate access to bronchodilators [25,26].

The strengths of this study include its randomized crossover design with a 24-48 hour washout interval, which allowed a within-participant comparison of the two methods and minimized between-method confounding, as well as the enrollment of a relatively large pediatric CTVA cohort, for which prospective comparative data remain scarce.Study limitations include: (1) a single-center design with potential selection bias; (2) limited stratified analyses across age groups or CTVA phenotypes; (3) the absence of inflammatory biomarkers limiting mechanistic understanding.

In conclusion, Astograph demonstrates superior diagnostic efficacy, operational efficiency, and safety for pediatric CTVA diagnosis. PD25 represents the most valuable diagnostic parameter for clinical implementation. Future research should explore associations between Astograph parameters and inflammatory biomarkers to refine individualized CTVA assessment protocols.

Table 1. Comparison of Pulmonary Function Parameters Between the CTVA and Control Groups

Parameter	CTVA group (n=51)	Control group (n=74)	*Z/t* value	*P* value
FEV_1, L	2.12 (1.73, 2.67)	2.25 (1.87, 2.86)	*-1.02*[a]	*0.310*
FEV_1 % predicted, %	102.03 ± 10.87	105.56 ± 12.94	*1.56*[b]	*0.121*
FVC, L	2.80 (2.10, 3.36)	2.68 (2.23, 3.42)	*-0.11*[a]	*0.914*
FVC % predicted, %	104.82 ± 11.06	104.37 ± 12.85	*-0.20*[b]	*0.842*
FEV_1/FVC, %	82.29 ± 7.03	85.55 ± 5.55	*2.90*[b]	*0.004**
FEV_1/FVC % predicted	97.64 ± 8.25	101.32 ± 6.76	*2.68*[b]	*0.008**
PEF, L/s	4.46 (3.75, 5.83)	4.73 (3.90, 5.53)	*-0.43*[a]	*0.669*
PEF % predicted, %	93.01 ± 11.13	94.61 ± 12.42	*0.72*[b]	*0.474*
MEF_{75}, L/s	3.97 (3.20, 5.13)	4.27 (3.56, 5.19)	*-1.13*[a]	*0.257*
MEF_{75} % predicted, %	92.66 (83.54, 101.69)	96.48 (88.49, 106.61)	*-1.56*[a]	*0.118*
MEF_{50}, L/s	2.45 (1.91, 3.06)	2.83 (2.36, 3.49)	*-2.71*[a]	*0.007**
MEF_{50} % predicted, %	79.79 ± 17.31	92.12 ± 20.03	*3.49*[b]	*0.001**
MEF_{25}, L/s	1.05 (0.80, 1.49)	1.28 (0.91, 1.67)	*-1.99*[a]	*0.047**
MEF_{25} % predicted, %	72.17 ± 22.61	82.95 ± 25.31	*2.38*[b]	*0.019**
$MMEF_{75–25}$, L/s	2.13 (1.74, 2.75)	2.53 (1.95, 3.16)	*-2.17*[a]	*0.030**
$MMEF_{75–25}$ % predicted, %	79.90 ± 18.67	91.38 ± 20.61	*3.01*[b]	*0.003**
MVV, L/min	61.46 (49.01, 74.27)	63.40 (48.05, 78.02)	*-0.46*[a]	*0.648*
MVV % predicted, %	138.39 ± 33.94	141.17 ± 31.73	*0.45*[b]	*0.656*

Note: Data are presented as median (interquartile range) for non-normally distributed variables and mean ± standard deviation for normally distributed variables. aMann-Whitney U test; bIndependent samples t-test. *P < 0.05 indicates statistical significance. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; MEF_{75}, maximal expiratory flow at 75% of FVC; MEF_{50}, maximal expiratory flow at 50% of FVC; MEF_{25}, maximal expiratory flow at 25% of FVC; $MMEF_{75–25}$, maximal mid-expiratory flow; MVV, maximal voluntary ventilation; CTVA, chest tightness variant asthma.

Table 2. Comparison of Airway Reactivity Parameters Between the CTVA and Control Groups

Parameter	CTVA group (n=51)	Control group (n=74)	*Z* value	*P* value
Baseline respiratory mechanics				
RrS, cmH_2O/L/sec	5.20 (3.90, 6.30)	5.00 (4.18, 6.03)	*-0.41*	*0.684*
Grs, L/sec/cmH_2O	0.19 (0.16, 0.26)	0.20 (0.17, 0.24)	*-0.41*	*0.684*
Sensitivity parameters				
Dmin, units	4.55 (2.36, 50.00)	50.00 (50.00, 50.00)	*-6.12*	*< 0.001**
Cmin, mg/mL	3.13 (1.56, 25.00)	25.00 (25.00, 25.00)	*-6.10*	*< 0.001**
Reactivity slope parameters				
SGrS, L/sec/cmH_2O/min	0.03 (0.00, 0.04)	0.00 (0.00, 0.00)	*-5.20*	*< 0.001**
SGrs/Grs, /min	0.13 (0.00, 0.21)	0.00 (0.00, 0.00)	*-5.55*	*< 0.001**
Provocative doses				
PD_5, units	5.09 (3.02, 50.00)	50.00 (50.00, 50.00)	*-6.10*	*< 0.001**
PD_{10}, units	6.08 (3.58, 50.00)	50.00 (50.00, 50.00)	*-6.07*	*< 0.001**
PD_{15}, units	6.96 (4.24, 50.00)	50.00 (50.00, 50.00)	*-6.06*	*< 0.001**
PD_{20}, units	9.72 (4.90, 50.00)	50.00 (50.00, 50.00)	*-6.08*	*< 0.001**
PD_{25}, units	12.83 (5.74, 50.00)	50.00 (50.00, 50.00)	*-6.18*	*< 0.001**
PD_{30}, units	17.17 (6.59, 50.00)	50.00 (50.00, 50.00)	*-6.11*	*< 0.001**
PD_{35}, units	23.76 (7.80, 50.00)	50.00 (50.00, 50.00)	*-6.19*	*< 0.001**
PD_{40}, units	36.55 (9.06, 50.00)	50.00 (50.00, 50.00)	*-6.24*	*< 0.001**
PD_{45}, units	50.00 (11.01, 50.00)	50.00 (50.00, 50.00)	*-5.77*	*< 0.001**
PD_{50}, units	50.00 (12.16, 50.00)	50.00 (50.00, 50.00)	*-5.43*	*< 0.001**
PD_{20}-FEV_1, mg	2.33 (0.99, 2.50)	2.50 (2.50, 2.50)	*-5.43*	*< 0.001**

Note: Data are presented as median (interquartile range). Mann-Whitney U test was used for all comparisons. *P < 0.001 indicates statistical significance. RrS, respiratory system resistance; Grs, respiratory system conductance; Dmin, minimal dose causing response; Cmin, minimal concentration causing response; SGrS, slope of conductance change; $PD_{5–50}$, provocative dose causing 5%-50%

decrease in conductance; PD_{20}-FEV_1, provocative dose causing 20% decrease in FEV_1; CTVA, chest tightness variant asthma.

Table 3. Correlation Analysis Between Astograph Parameters and APS Method ($LogPD_{20}$-FEV_1)

Astograph Parameter	Correlation coefficient (*r*)	*P* value
Baseline respiratory mechanics		
RrS, cmH_2O/L/sec	0.315	< 0.001
Grs, L/sec/cmH_2O	-0.315	< 0.001
Reactivity slope parameters		
SGrS, L/sec/cmH_2O/min	**-0.780**	**< 0.001**
SGrs/Grs, /min	**-0.794**	**< 0.001**
Sensitivity and provocative doses		
LogDmin, units	**0.817**	**< 0.001**
$LogPD_{15}$, units	**0.822**	**< 0.001**
$LogPD_{20}$, units	**0.822**	**< 0.001**
$LogPD_{25}$, units	**0.814**	**< 0.001**
$LogPD_{30}$, units	**0.796**	**< 0.001**
$LogPD_{35}$, units	**0.786**	**< 0.001**
$LogPD_{40}$, units	**0.776**	**< 0.001**
$LogPD_{45}$, units	0.633	< 0.001
$LogPD_{50}$, units	0.610	< 0.001

Note: Pearson correlation analysis was performed between $LogPD_{20}$-FEV_1 (APS method) and Astograph parameters. Correlation coefficients are color-coded: **strong positive correlation ($r \geq 0.8$)**, **moderate positive correlation ($0.7 \leq r < 0.8$)**, **moderate negative correlation ($-0.8 < r \leq -0.7$)**, and weak correlation ($|r| < 0.7$). All correlations were statistically significant at $P < 0.001$. APS, acetylcholine provocative spirometry; $LogPD_{20}$-FEV_1, logarithmic transformation of provocative dose causing 20% decrease in FEV_1; RrS, respiratory system resistance; Grs, respiratory system conductance; SGrS, slope of conductance change; LogDmin, logarithmic transformation of minimal dose causing response; $LogPD_{15–30}$, logarithmic transformation of provocative doses causing 15%-30% decrease in conductance.

Table 4. Diagnostic Performance Characteristics of Two Bronchial Provocation Test Methods

Parameter	APS Method	Astograph Method	*P* Value[b]
Sensitivity, %	80.39 (67.2-90.1)	82.35 (69.7-91.6)	*0.774*
Specificity, %	79.73 (68.8-88.2)	83.78 (73.4-91.3)	*0.490*
PPV, %	73.21 (60.4-83.7)	77.78 (64.9-87.6)	*0.571*
NPV, %	85.51 (74.7-93.1)	87.32 (77.3-94.0)	*0.751*
Accuracy, %	80.00 (71.9-86.7)	83.20 (75.5-89.2)	*0.521*
PLR	3.97(2.4-6.6)	5.08(2.9-8.9)	*0.428*
NLR	0.25(0.1-0.4)	0.21(0.1-0.4)	*0.649*

[b] *P* values calculated using McNemar's test for paired proportions. PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio. Values in parentheses represent 95% confidence intervals.

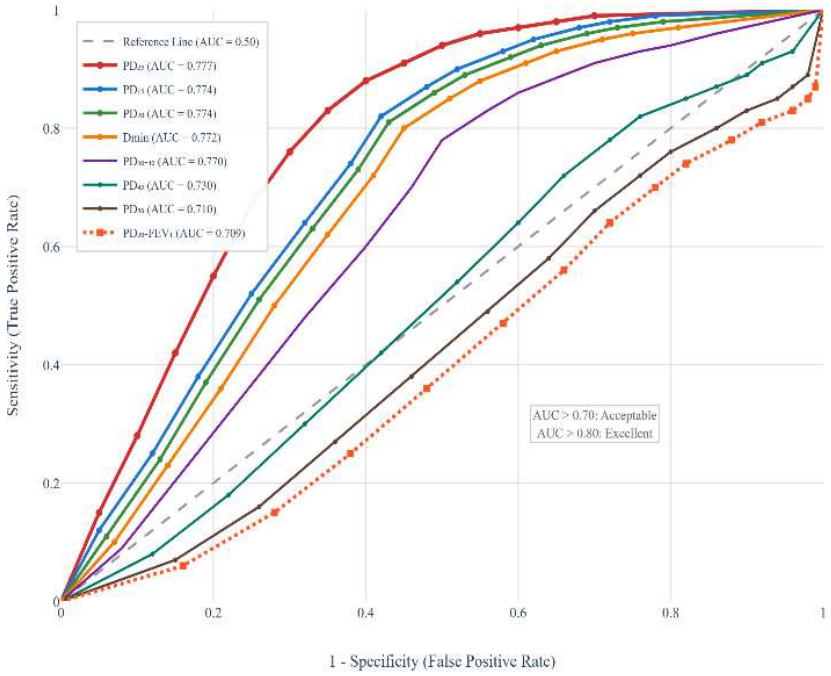

Figure 1. ROC Curve Analysis for Airway Reactivity Parameters

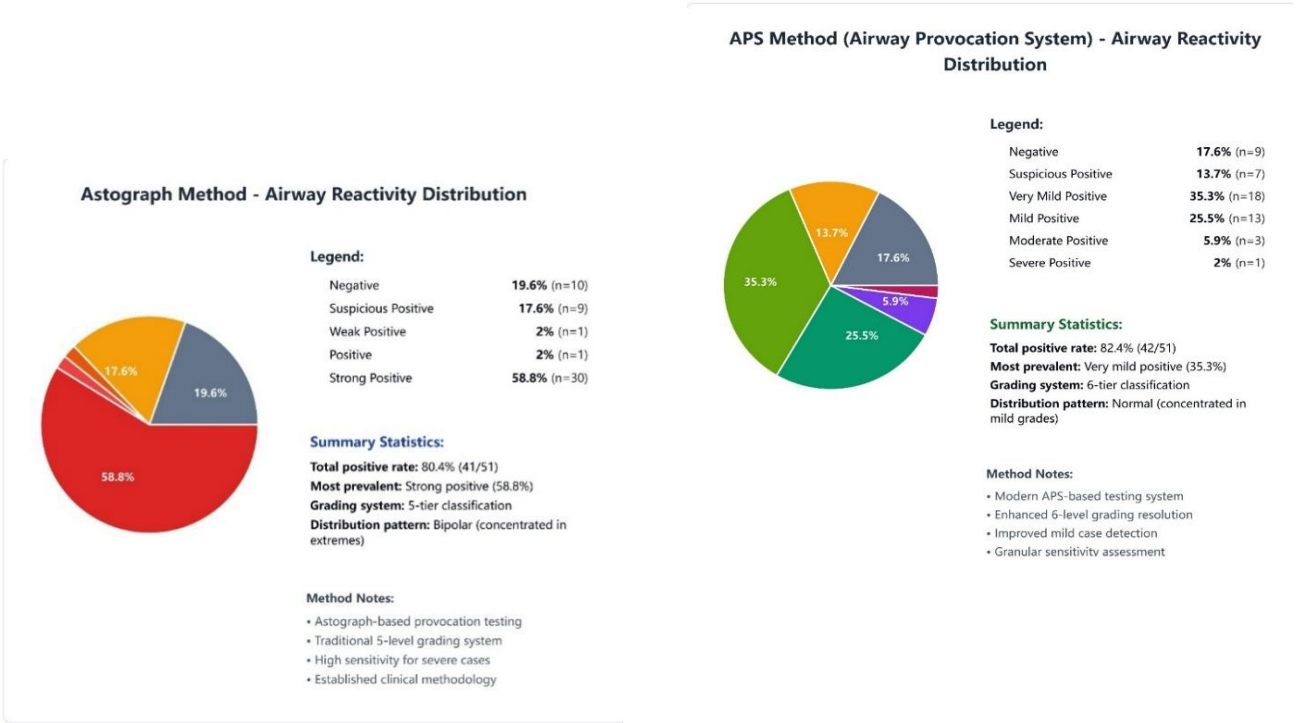

Figure 2. Distribution of Airway Reactivity Grading in CTVA Group

Ethics approval and consent to participate: The study was approved by the Institutional Review Board/Ethics Committee of the Children's Hospital of Soochow University (approval number: 2023CS315). Written informed consent to participate was obtained from the parents or legal guardians of all participants.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Available from: https://ginasthma.org/2024-report/
2. Pulmonary Function and Clinical Respiratory Physiology Committee of Chinese Association of Chest Physicians, Chinese Thoracic Society, Pulmonary Function Group of Respiratory Branch of Chinese Geriatric Society. Standard technical specifications for methacholine chloride (Methacholine) bronchial challenge test (2023). Zhonghua Jie He He Hu Xi Za Zhi. 2024;47(2):101-119.
3. Guan W, Zheng J, Gao Y, Jiang C, Xie Y, An J, Yu X, Liu W, Zhong N. Leukotriene D4 and methacholine bronchial provocation tests for identifying leukotriene-responsiveness subtypes. J Allergy Clin Immunol. 2013 Feb;131(2):332-8.e1-4. doi: 10.1016/j.jaci.2012.08.020. Epub 2012

Oct 4. PMID: 23040886.

4. Subspecialty Group of Respiratory, the Society of Pediatrics, Chinese Medical Association; Editorial Board, Chinese Journal of Pediatrics; China Medicine Education Association Committee on Pediatrics. [Guidelines for the diagnosis and optimal management of asthma in children (2025)]. Zhonghua Er Ke Za Zhi. 2025 Mar 17;63(4):324-337. Chinese. doi: 10.3760/cma.j.cn112140-20250124-00074. Epub ahead of print. PMID: 40090909.
5. Zhang T, Xu L, Zhang Y, Zhen L. The diagnostic value of bronchial provocation testing combined with fractional exhaled nitric oxide (FeNO) in children with chest tightness-variant asthma (CTVA). Respir Med. 2024 Mar;223:107543. doi: 10.1016/j.rmed.2024.107543. Epub 2024 Jan 28. PMID: 38286340.
6. Coates AL, Wanger J, Cockcroft DW, Culver BH; Bronchoprovocation Testing Task Force: Kai-Håkon Carlsen; Diamant Z, Gauvreau G, Hall GL, Hallstrand TS, Horvath I, de Jongh FHC, Joos G, Kaminsky DA, Laube BL, Leuppi JD, Sterk PJ. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J. 2017 May 1;49(5):1601526. doi: 10.1183/13993003.01526-2016. PMID: 28461290.
7. China Asthma Group of Chinese Thoracic Society. [Chinese expert consensus on the clinical applications of bronchial provocation test (2024 edition)]. Zhonghua Yi Xue Za Zhi. 2024 Jun 11;104(22):2031-2040. Chinese. doi: 10.3760/cma.j.cn112137-20240202-00252. PMID: 38858213.
8. Rajvanshi N, Kumar P, Goyal JP. Global Initiative for Asthma Guidelines 2024: An Update. Indian Pediatr. 2024;61(8):781-786.
9. Zhu W, Liu C, Sha L, et al. Atypical asthma in children who present with isolated chest

tightness: risk factors and clinical features. J Asthma. 2022;59(10):1952-1960.

10. Feng Y, Zhang S, Shang Y, Chen N. The Use of Exercise Challenge Testing and Fractional Exhaled Nitric Oxide in Diagnosis of Chest Tightness Variant Asthma in Children. Int Arch Allergy Immunol. 2022;183(7):762-769.
11. Chen JL, Song X, Zhu WJ, et al. Analysis of clinical characteristics and risk factors of chest tightness variant asthma in children. Zhonghua Yu Fang Yi Xue Za Zhi. 2024;58(6):815-822.
12. The diagnostic value of bronchial provocation testing combined with fractional exhaled nitric oxide (FeNO) in children with chest tightness-variant asthma (CTVA). Respir Med. 2024;205:107179.
13. Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J. 2003;22(6):1026-1041.
14. Skylogianni E, Douros K, Anthracopoulos MB, Fouzas S. The Forced Oscillation Technique in Paediatric Respiratory Practice. Paediatr Respir Rev. 2016;18:46-51.
15. Kreetapirom P, Kiewngam P, Jotikasthira W, et al. Forced oscillation technique as a predictor for loss of control in asthmatic children. Asia Pac Allergy. 2020;10(1):e3.
16. Kostorz-Nosal S, Jastrzębski D, Błach A, Skoczyński S. Window of opportunity for respiratory oscillometry: A review of recent research. Respir Physiol Neurobiol. 2023;316:104135.
17. Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J. 2017;49(5):1601526.
18. Nazemiyah M, Ansarin K, Nouri-Vaskeh M, et al. Comparison of spirometry and impulse oscillometry in methacholine challenge test for the detection of airway hyperresponsiveness in

adults. Tuberk Toraks. 2021;69(1):1-8.

19. Liem JJ, Kozyrskyj AL, Cockroft DW, Becker AB. Airway hyperresponsiveness to methacholine in 7-year-old children: sensitivity and specificity for pediatric allergist-diagnosed asthma. Pediatr Pulmonol. 2011;46(7):632-639.

20. Andregnette-Roscigno V, Fernández-Nieto M, Del Potro MG, et al. Methacholine is more sensitive than mannitol for evaluation of bronchial hyperresponsiveness in children with asthma. J Allergy Clin Immunol. 2010;126(4):869-871.

21. Lizzo JM, Goldin J, Cortes S. Pediatric Asthma. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.

22. Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. Lancet. 2011;377(9766):650-657.

23. Beyhan-Sagmen S, Eraslan BZ, Demirer E, et al. Small airway disease and asthma control. J Asthma. 2023;60(9):1761-1766.

24. Yi L, Zhao Y, Guo Z, et al. FEF25-75% Is a More Sensitive Measure Reflecting Airway Dysfunction in Patients with Asthma: A Comparison Study Using FEF25-75% and FEV1. J Allergy Clin Immunol Pract. 2021;9(7):2718-2725.

25. Zhang L, Fu Z, Deng H, et al. Identification and treatment of persistent small airway dysfunction in paediatric patients with asthma: a retrospective cohort study. BMC Pulm Med. 2024;24(1):94.

26. Cottini M, Lombardi C, Passalacqua G, et al. Small Airways: The "Silent Zone" of 2021 GINA Report? Front Med (Lausanne). 2022;9:884679.

27. Evaluation of the Diagnostic Accuracy of Non-Specific Bronchial Provocation Tests in the Diagnosis of Asthma: A Randomized Cross-Over Study. Arch Bronconeumol. 2023;59(11):736-742.

28. Chen W, Yang Z, Liu CH, et al. The cutoff value of small airway dysfunction in children with bronchial asthma. Zhonghua Er Ke Za Zhi. 2024;62(3):245-249.

29. Wang J, Mochizuki H, Muramatsu R, et al. Evaluation of bronchial hyperresponsiveness by monitoring of transcutaneous oxygen tension and arterial oxygen saturation during methacholine challenge in asthmatic children. J Asthma. 2006;43(2):145-149.

30. Bohadana AB, Rokach A, Wild P, Izbicki G. Asthma-like symptoms induced by the methacholine challenge test: do they predict a negative-to-positive switch in the test result? J Thorac Dis. 2018;10(10):E716-E720.

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