

The Use of Exercise Challenge Testing and Fractional Exhaled Nitric Oxide in Diagnosis of Chest Tightness Variant Asthma in Children

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Keywords

Chest tightness variant asthma · Children · Diagnosis · Exercise challenge testing · Fractional exhaled nitric oxide

Abstract

Background: Chest tightness variant asthma (CTVA) in children presents with chest tightness as the sole manifestation. Diagnostic tests are needed given the lack of typical asthma symptoms. The present study aimed to investigate the diagnostic value of exercise challenge testing (ECT) and fractional exhaled nitric oxide (FeNO) in pediatric CTVA. **Methods:** We included 98 children aged 6–13 years with chest tightness as the sole symptom for >4 weeks. All subjects underwent FeNO measurement, spirometry and ECT, and received 4-week budesonide/formoterol treatment. According to treatment responses, children were categorized into CTVA ($n = 12$) and non-CTVA ($n = 86$) groups. Differences in clinical characteristics and FeNO, spirometry, and ECT results were compared between the two groups. The FeNO and ECT diagnostic performances were determined using receiver operating characteristic (ROC) curve analysis. **Results:** Children with CTVA exhibited significantly higher *Mycoplasma pneumoniae* IgG, total IgE, and FeNO values; greater post-ECT forced expiratory volume in 1 s (FEV₁) fall; and more frequent sensitization to mites and pets than those without CTVA. Further logistic regression revealed that higher FEV₁ fall (OR, 1.39; 95% CI: 1.11–1.74; $p = 0.004$) and higher FeNO values (OR, 1.04; 95% CI: 1.01–1.08; $p = 0.014$) were risk factors as-

sociated with CTVA. FEV₁ fall and FeNO had similar areas under the ROC curve (AUCs) (0.79 vs. 0.78; $p = 0.924$), and their optimal CTVA-prediction cutoff values were 9.9% and 15.0 ppb, respectively. The AUC of FEV₁ fall and FeNO combination was higher at 0.86 (95% CI: 0.78–0.93); however, no difference was observed using the single test ($p > 0.05$). Their combination exhibited a relatively higher sensitivity than that of FEV₁ fall alone (0.75 vs. 0.67) and higher positive predictive value than that of FeNO alone (0.60 vs. 0.29). **Conclusion:** CTVA is a cause of unexplained recurrent chest tightness in children. FeNO ≥ 15.0 ppb and post-ECT FEV₁ fall $\geq 9.9\%$ are diagnostically valuable for CTVA in children, with their combination potentially contributing to greater diagnostic accuracy.

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Introduction

Chest tightness is a common complaint among school-age children. The subjective description of chest tightness varies considerably. Older children often report chest discomfort, heavy chest sensation, or poor breathing, without actual tachypnea or dyspnea. Younger children cannot describe the feeling accurately; instead, they attempt to relieve the symptoms by deep or sighing breathing, which is observable by caregivers. The etiology of chest

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tightness in children remains unclear [1–3]. In 2013, Shen et al. [4] described a novel asthma phenotype in adults, chest tightness variant asthma (CTVA), with chest tightness as the sole presenting clinical manifestation. CTVA has been reported in children and is a known cause of chest tightness [2, 3]. Owing to lacking typical asthma symptoms, such as cough, wheezing, or dyspnea, CTVA diagnosis is difficult, and diagnostic tests are warranted.

Patients with CTVA demonstrate airway hyperresponsiveness and favorable response to asthma treatment [2, 4, 5]. Exercise challenge testing (ECT) is an indirect bronchoprovocation test for airway hyperresponsiveness [6], exercise-induced bronchoconstriction (EIB) [6], and asthma diagnosis [7]. The incidence of EIB in children with CTVA remains unclear; nevertheless, the episodes of chest tightness in some children are more frequent during exercise. The fractional exhaled nitric oxide (FeNO) is a noninvasive biomarker of airway eosinophilic inflammation in asthma [8]; however, its value for asthma diagnosis remains controversial [7, 9, 10]. Studies have suggested that FeNO has diagnostic value for asthma in school-age children with symptoms suggestive of asthma, predominantly for ruling in asthma, particularly in children with atopy [8, 11]. As demonstrated by Shen et al. [4], six adults with CTVA exhibited eosinophilic infiltration on airway biopsy specimens. FeNO can be considered an effective diagnostic tool for CTVA in children. Consequently, this study aimed to determine the effectiveness of ECT and FeNO as diagnostic tools for CTVA in children.

Materials and Methods

Study Subjects

This study was conducted at the outpatient clinic of the Pediatric Pulmonary Department of Shengjing Hospital of China Medical University from April to September 2021. Consecutive children aged 6–13 years with chest tightness as the sole symptom for >4 weeks, without current wheezing or wheezing on auscultation, cough, or breathlessness, were prospectively enrolled. Children with cardiac disease or a forced expiratory volume in 1 s (FEV₁) <75% of the predicted value were excluded. The present study was approved by the local Ethics Committee, and written informed consent was obtained from the parents or guardians.

Study Methods

All subjects were referred to a pediatric cardiologist for evaluation and underwent myocardial enzyme tests and electrocardiography to exclude cardiac causes. Demographic and clinical characteristics were obtained from parent-completed questionnaires. Peripheral blood was collected to measure eosinophil counts, *Mycoplasma pneumoniae* IgM and IgG antibodies, total IgE, and allergen (a panel of aeroallergens and food allergens)-specific IgE. Allergen-specific

IgE concentrations exceeding 0.35 IU/mL were considered indicative of sensitization. Chest radiography was performed to exclude pneumonia and pleura effusion, among others. Children's anxiety and depression symptoms were assessed using the Chinese version of the Screen for Child Anxiety Related Emotional Disorders (SCARED) [12, 13] and the Children's Depression Inventory (CDI) [14].

FeNO Measurement

Before spirometry, FeNO was measured with an online collection apparatus using an electrochemical device (NIOX MINO; Aerocrine, Stockholm, Sweden) and expressed in parts per billion (ppb), according to American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations [8, 15].

Spirometry Measurement

Prior to ECT, reliable baseline spirometry was performed using a bidirectional digital turbine flowmeter (Pony FX; Cosmed, Rome, Italy), according to the ATS and ERS standards adapted for children [16, 17]. The 2012 Global Lung Function Initiative reference equations for Northeast Asians [18] were used to calculate the predicted values and z-scores for the FEV₁, forced vital capacity (FVC), FEV₁ to FVC (FEV₁/FVC) ratio, mean forced expiratory flow between 25% and 75% of FVC (FEF_{25%–75%}), and instantaneous forced expiratory flow at 75% of FVC (FEF_{75%}).

ECT Measurement

ECT was performed by a skilled technician who was blinded to clinical information in a room with an ambient temperature of 21°C and relative humidity of 45%. Children were instructed to run on a motorized treadmill (T540C; Decathlon, Suzhou, China), with their noses clipped for 8 min. During the first 2 min of exercise, the treadmill's speed and slope were progressively accelerated until a target heart rate of >85% of the predicted maximum (calculated as follows: 220 minus age in years) was achieved. During the last 6 min, the incline was maintained at 10% and speed was adjusted to maintain the target heart rate. The heart rate was continuously monitored using a fitness monitor placed around the forearm (OH1; Polar Electro Oy, Kempele, Finland). Post-exercise spirometry was conducted at 1, 5, 10, 15, and 30 min after the ECT [6, 19, 20]. At each testing interval, at least two acceptable tests within 0.15 L were obtained, unless FEV₁ or FVC was <1 L, in which case two acceptable tests were within 0.10 L. The best FEV₁ at each interval was selected for comparison with the basal values. The greatest FEV₁ decrease from baseline was calculated as FEV₁ fall (%). Subjects who experienced severe symptoms or whose FEV₁ fall was greater than 10% were expected to inhale 200 µg salbutamol, and spirometry was performed 15 min later to ensure an FEV₁ recovery within 10% of baseline.

Follow-Up, Diagnostic Criteria, and Study Groups

All subjects received budesonide/formoterol dry powder inhaler (AstraZeneca AB, Södertälje, Sweden) at a dosage of 80 µg/4.5 µg, twice a day, for 4 weeks. Thereafter, they were interviewed by either outpatient clinic examination or telephone. Subjects who failed to inhale budesonide/formoterol regularly for 4 weeks were excluded. According to previous studies by Shen et al. [4] and Yan et al. [5], CTVA was diagnosed provided a marked clinical improvement in response to budesonide/formoterol was observed. At final diagnosis, the pulmonologist was blinded to the ECT and FeNO results. The subjects were divided into two groups: non-CTVA and CTVA.

Table 1. Demographic and clinical characteristics of the study subjects

Characteristics	Non-CTVA group	CTVA group	<i>p</i> value
<i>N</i>	86	12	–
Age, median (IQR), years	8.7 (7.3–11.2)	8.7 (8.1–11.6)	0.704
Male sex, <i>n</i> (%)	41 (47.7)	9 (75.0)	0.076
Weight, median (IQR), kg	33.0 (25.9–44.0)	28.8 (25.3–43.2)	0.866
Height, median (IQR), cm	136.5 (129.8–153.5)	136.5 (133.0–155.8)	0.766
BMI, median (IQR), kg/m ²	16.5 (15.1–19.7)	16.3 (15.2–19.9)	0.782
Chest tightness duration before enrolment, median (IQR), months	2.0 (1.0–9.0)	1.0 (1.0–9.8)	0.325
Pharyngitis, <i>n</i> (%)	8 (9.3)	3 (25.0)	0.132
Allergic rhinitis, <i>n</i> (%)	27 (31.4)	6 (50.0)	0.211
Adenoidal or tonsillar hypertrophy, <i>n</i> (%)	16 (18.6)	1 (8.3)	0.686
Eczema, <i>n</i> (%)	43 (50)	8 (66.7)	0.361
History of wheezing, <i>n</i> (%)	7 (8.1)	3 (25.0)	0.103
Parental atopy, <i>n</i> (%)	27 (31.4)	5 (41.7)	0.520
SCARED score, median (IQR)	13.0 (10.0–18.3)	13.0 (5.00–17.0)	0.405
CDI score, median (IQR)	26.5 (19.0–32.3)	19.0 (16.0–25.0)	0.077
White blood cell count, median (IQR), 10 ⁹ /L	6.79 (5.52–8.20)	7.12 (4.53–8.16)	0.876
Eosinophil, median (IQR), 10 ⁹ /L	0.14 (0.06–0.22)	0.14 (0.10–0.41)	0.258
<i>Mycoplasma pneumoniae</i> IgM, <i>n</i> (%)	47 (55.6)	5 (41.7)	0.539
<i>Mycoplasma pneumoniae</i> IgG, median (IQR), RU/mL	26.08 (11.14–71.79)	75.31 (39.64–102.68)	0.025
Creatine kinase-myocardial band, mean±SD, U/L	19.28±4.69	20.11±2.98	0.610
Categories, <i>n</i> (%)			
Mites	24 (27.9)	7 (58.3)	0.047
Foods	32 (37.2)	6 (50.0)	0.529
Molds	20 (23.3)	4 (33.3)	0.418
Pets	4 (4.7)	3 (25.0)	0.038
Plants	20 (23.3)	4 (33.3)	0.481
Roaches	0	0	–
Sensitization to any allergen	42 (48.8)	10 (83.3)	0.025
Total IgE level, median (IQR), IU/mL	53.6 (20.8–118.0)	201.1 (69.6–316.3)	0.001

IQR, interquartile range, represented by 25–75% quartile; SD, standard deviation; CTVA, chest tightness variant asthma; BMI, body mass index, determined as the weight in kilograms divided by the square of the height in meters; SCARED, Screen for Anxiety Related Emotional Disorders; CDI, Children's Depression Inventory.

Statistical Analysis

Normally distributed variables are expressed as the mean ± SD, and they were compared between groups using the independent *t* test. Non-normally distributed variables are presented as medians (IQR), and they were compared using the Mann-Whitney U test. Categorical variables are expressed as percentages, and they were compared using the χ^2 test (or Fisher's exact test in cases of expected frequencies <5). Independent variables with significant between-group differences or with clinical significance, related to allergen sensitization, total IgE, FeNO, and FEV₁ fall were included in the logistic regression model to evaluate functional risk factors for CTVA in children. The relationships between FEV₁ fall and FeNO were explored using Spearman's correlations. Receiver operating characteristic (ROC) curves and areas under the curve (AUCs) were used to assess the diagnostic value of different parameters for CTVA in children. The DeLong test was used to compare the AUCs [21]. Two-tailed *p* values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). ROC curves were constructed using MedCalc statistical software version 20.014 (MedCalc Software Ltd., Acaciaaan, Ostend, Belgium).

Results

Demographic and Clinical Characteristics

Ninety-eight children who completed ECT and FeNO examinations met the inclusion and exclusion criteria. On final evaluation, 12 patients (9 boys and 3 girls) were diagnosed with CTVA and 86 (41 boys and 45 girls) were not diagnosed with CTVA. Table 1 displays the demographic and clinical characteristics of these patients. The demographic characteristics were similar in both groups. No differences in chest tightness duration, pharyngitis, allergic rhinitis, adenoidal or tonsillar hypertrophy, eczema, history of wheeze, parental atopy, SCARED score, CDI score, white blood cell count, eosinophil count, *M. pneumoniae* IgM, and sensitization to foods, molds, plants, and roaches were observed between the two groups. However, the *M. pneumoniae* IgG and total IgE

Table 2. Functional characteristics of the study subjects

Characteristics	Non-CTVA group	CTVA group	p value
N	86	12	
FeNO, median (IQR), ppb	11.0 (9.0–16.0)	19.0 (13.0–40.3)	0.002
Spirometry			
FEV ₁			
Predicted, mean ± SD, %	106.2±15.0	101.4±17.7	0.309
z-score, mean ±SD	0.55±1.35	0.10±1.62	0.288
FVC			
Predicted, mean ± SD, %	107.9±16.0	107.3±12.7	0.906
z-score, mean ± SD	0.88±1.83	0.85±1.66	0.096
FEV ₁ /FVC, mean ± SD, %			
Ratio	88.0±5.57	83.9±9.8	0.186
Predicted	98.9±5.9	95.1±10.0	0.228
z-score	−0.12±1.07	−0.69±1.62	0.110
FEF _{25%–75%}			
Predicted, mean ± SD, %	102.4±20.4	91.2±26.0	0.088
z-score, mean ± SD	0.07±0.93	−0.55±1.39	0.156
FEF _{75%}			
Predicted, median (IQR), %	110.8 (92.7–125.3)	98.0 (74.0–133.9)	0.448
z-score, median (IQR)	0.37 (−0.27–0.83)	−0.07 (−1.05–1.11)	0.445
ECT, median (IQR), %			
FEV ₁ fall	4.72 (2.77–6.77)	11.82 (4.75–20.62)	0.001

ECT, exercise challenge testing; IQR, interquartile range, represented by 25–75% quartile; SD, standard deviation; CTVA, chest tightness variant asthma; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF_{25%–75%}, mean forced expiratory flow between 25% and 75% of FVC; FEF_{75%}, instantaneous forced expiratory flow at 75% of FVC; FEV₁ fall, post-exercise fall of FEV₁ as percentage from baseline.

levels were significantly higher in the CTVA group than in the non-CTVA group. Furthermore, patients in the CTVA group exhibited significantly greater sensitization to mites, pets, and any allergen.

FeNO, Spirometry, and ECT Analysis

The functional characteristics are summarized in Table 2. The median FeNO value of the patients with CTVA was 19.0 ppb, which was significantly higher than that of the patients without CTVA (11.0 ppb, $p = 0.002$). No differences in predicted values and z-scores for FEV₁, FVC, FEV₁/FVC, FEF_{25%–75%}, and FEF_{75%} were observed between the groups. The patients with CTVA exhibited a greater post-ECT FEV₁ fall (11.82% vs. 4.72%; $p = 0.001$). Further logistic regression revealed that higher FEV₁ fall and FeNO values were risk factors associated with CTVA. Allergen sensitization and total IgE did not contribute significantly to the model. Every 1 unit increase in FEV₁ fall increased the odds of CTVA (OR, 1.71; 95% CI: 1.20–2.43; $p = 0.003$) and every 1 unit increase in FeNO increased the odds of CTVA (OR, 1.07; 95% CI: 1.00–1.14; $p = 0.04$). Ten chil-

dren with FEV₁ fall >10% inhaled 200 µg salbutamol, and 15 min later, their FEV₁ recovered within 10% of baseline.

Diagnostic Utility of ECT and FeNO for CTVA in Children

The diagnostic values of FEV₁ fall, FeNO, and their combination were assessed using ROC curves. The AUCs of these ROC curves and optimal cutoff values are shown in Figure 1. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR), and negative LR of each optimal cutoff value are displayed in Table 3. AUC comparisons are shown in Table 4. FEV₁ fall and FeNO had similar AUCs (0.79 vs. 0.78; $p = 0.924$). The optimal cutoff value of FEV₁ fall for predicting CTVA was 9.9%, with a high specificity (0.98), PPV (0.80), NPV (0.95), and positive LR (28.67) but relatively low sensitivity (0.67). The optimal cutoff value of FeNO for predicting CTVA was 15.0 ppb, with a high sensitivity (0.75) and NPV (0.96) but relatively low specificity (0.74), PPV (0.29) and positive LR (2.93). No correlation was observed between FEV₁ fall and FeNO ($r = 0.025$, $p =$

Table 3. Diagnostic utility of ECT and FeNO for CTVA in children

Items	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)
FEV ₁ -fall 9.9%	0.67 (0.35–0.90)	0.98 (0.92–1.00)	0.80 (0.49–0.94)	0.95 (0.90–0.98)	28.67 (6.9–119.4)	0.34 (0.2–0.8)
FeNO 15 ppb	0.75 (0.43–0.95)	0.74 (0.64–0.83)	0.29 (0.20–0.40)	0.96 (0.89–0.98)	2.93 (1.8–4.8)	0.34 (0.1–0.9)
FEV ₁ fall 9.9% + FeNO 15 ppb	0.75 (0.43–0.95)	0.93 (0.85–0.97)	0.60 (0.39–0.78)	0.96 (0.91–0.99)	10.75 (4.7–24.9)	0.27 (0.1–0.7)

ECT, exercise challenge testing; CTVA, chest tightness variant asthma; CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FeNO, fractional exhaled nitric oxide; FEV₁ fall, post-exercise fall of FEV₁ as percentage from baseline; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

Table 4. Comparison of the AUCs for the detection of CTVA in children

Items	Difference	95% CI (lower-upper)	p value
FeNO versus FEV ₁ fall	0.013	–0.246 to 0.271	0.924
FeNO versus FeNO + FEV ₁ fall	0.089	–0.113 to 0.290	0.389
FEV ₁ fall versus FeNO + FEV ₁ fall	0.076	–0.045 to 0.197	0.217

AUC, area under the curve; CTVA, chest tightness variant asthma; CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FeNO, fractional exhaled nitric oxide; FEV₁ fall, post-exercise fall of FEV₁ as percentage from baseline.

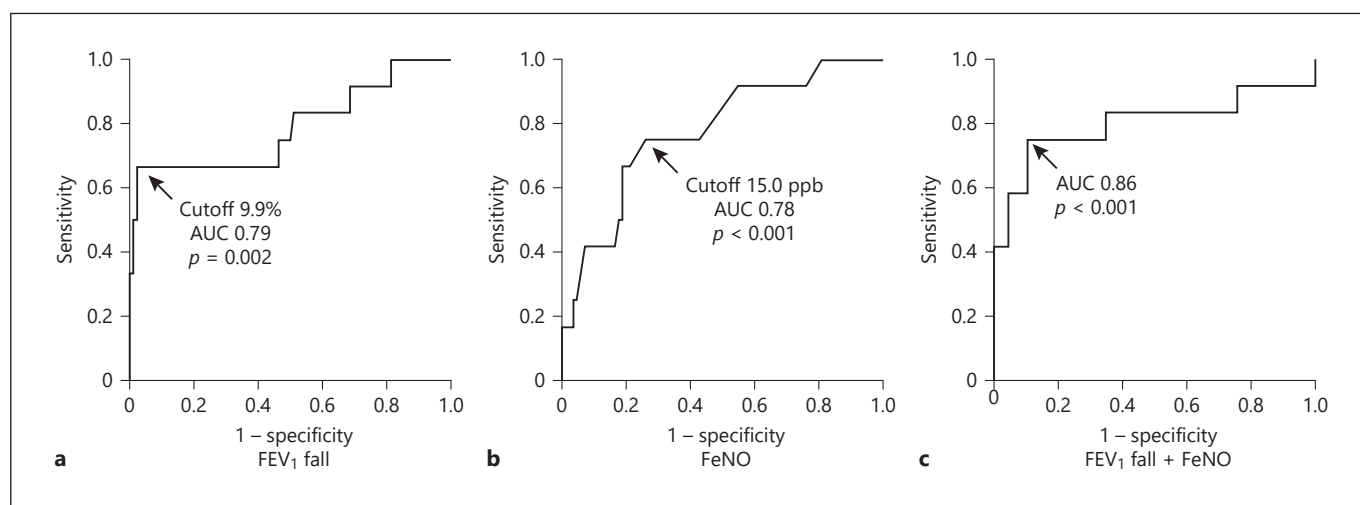


Fig. 1. ROC curves for diagnosis of CTVA in children with unexplained chest tightness. The sensitivity and specificity of FEV₁ fall (a), FeNO (b), and their combination (c) are shown. CTVA, chest tightness variant asthma; FEV₁, forced expiratory volume in 1 s; FEV₁ fall, post-exercise fall of FEV₁ as percentage from baseline; FeNO, fractional exhaled nitric oxide; AUC, area under the curve.

0.804) in our study subjects; subsequently, we further assessed the diagnostic utility of the combination of FEV₁ fall and FeNO. The combination's AUC was higher at 0.86 (95% CI: 0.78–0.93); however, no difference was observed using the single test. The combination had relatively higher sensitivity than that of FEV₁ fall alone (0.75 vs. 0.67), higher PPV than that of FeNO alone (0.60 vs. 0.29), and higher positive LR than that of FeNO alone (10.75 vs. 2.93).

Discussion/Conclusion

The most important finding of the present study was that FEV₁ fall after ECT and FeNO were diagnostically valuable for CTVA in children with unexplained recurrent chest tightness. Notwithstanding, FEV₁ fall had a relatively low diagnostic sensitivity, and FeNO had a relatively low diagnostic specificity. These drawbacks could

be partially overcome by combining FEV₁ fall with FeNO, resulting in increased sensitivity with a minor sacrifice of specificity. Therefore, our findings revealed that combining ECT and FeNO is potentially useful in confirming CTVA diagnosis in children with unexplained recurrent chest tightness.

CTVA is a cause of unexplained recurrent chest tightness in children. In the present study, 12.24% (12/98) children with unexplained chest tightness were diagnosed with CTVA based on their improvement in response to inhaled corticosteroid and long-acting beta₂-agonist. CTVA has been reported in children [2, 3]; however, its prevalence remains unclear. Consistent with the present findings, Evangelista et al. [22] reported on 50 children with the chief complaint of chest pain, of which 12% was due to exercise-induced asthma. Although chest pain does not entirely resemble chest tightness, similarities do exist between them, especially when some children fail to describe their symptoms accurately. The causes of chest tightness in the non-CTVA group were complicated and unclear. Cardiac causes were excluded in the present study, which have been considered the main causes by parents and pediatricians. Chen et al. [23] reported on 7,251 children with chest pain and only 8.0% was of cardiac origin. Possible respiratory-system problems were also excluded, such as pharyngitis, allergic rhinitis, adenoidal or tonsillar hypertrophy, pneumonia, pleura effusion, and bronchiolitis obliterans. Our results revealed that the CDI score tended to be higher in the non-CTVA group than in the CTVA group. Khairandish et al. [24] reported on 194 children with chest pain, of which 45.9% had depression. The association between depression and chest tightness in children should be further studied.

ECT is an indirect bronchoprovocation test for airway hyperresponsiveness, EIB, and asthma diagnosis and can also be used to elucidate the underlying pathophysiology and guide the treatment of asthma [6]. The present study demonstrated that patients with CTVA had a greater FEV₁ fall after exercise, with further logistic regression confirming FEV₁ fall as a risk factor for CTVA. ROC curve analysis revealed that the optimal FEV₁ fall cutoff value for predicting CTVA was 9.9%, with high specificity, NPV, and positive LR but relatively low sensitivity. The ERS guideline recommends an FEV₁ fall $\geq 10\%$ as the criterion for a positive ECT; nonetheless, the specificity is higher with that of 15% [6]. According to the ERS guideline's criterion [6] and cutoff value in the present study, the incidence of EIB in CTVA was 66.67%, thus indicating that EIB partially accounted for the pathophysiology of CTVA in children. Studies by Lin et al. [19] and Lam-

mers et al. [25] reported that 52.3% (78/149) and 55.0% (11/20) of children with classic asthma had EIB, respectively. EIB is a heterogeneous condition, and its mechanisms include the so-called osmolar [26] and vascular [27] hypotheses. Both processes potentially result in epithelial injury and release of inflammatory mediators from mast cells, eosinophils, neutrophils, and other inflammatory cells, thus leading to smooth muscle constriction. Hence, these findings imply that ECT has important diagnostic value for CTVA in children with unexplained recurrent chest tightness; however, negative results cannot exclude a positive diagnosis.

Consistent with classic asthma, CTVA is also associated with atopy and eosinophilic airway inflammation [4, 5, 28]. In the present study, the patients in CTVA group exhibited a higher total IgE level, greater frequency of sensitization to mites and pets, and higher FeNO level; however, no difference in blood eosinophil count was observed between the groups. Consistent with these findings, Cao et al. [28] reported that adults with CTVA had higher FeNO and total IgE levels than healthy controls, which levels were similar among patients with CTVA, classic asthma, and cough variant asthma, indicating a similar pathogenesis among the three phenotypes.

FeNO was a predictor of CTVA in children, in contrast to sensitization or total IgE. The optimal cutoff value of FeNO was 15.0 ppb, which is less than the negative cutoff value (20 ppb) suggested by the ERS guideline [8]. A real-life retrospective study [29] of 3,612 children defined 15.8 ppb as the asthma-predicting FeNO level, consistent with the present study. The cutoff values found in different studies ranged from 15.6 to 28 ppb, and the variance may be due to differences in demographic and biologic features [30]. As a diagnostic tool for CTVA in children, FeNO exhibited relatively low specificity, PPV, and positive LR. The NICE guideline recommends measuring FeNO in combination with other diagnostic parameters as a diagnostic tool for asthma in children [10]. In the present study, FeNO and ECT were combined for the diagnosis of CTVA in children, resulting in increased diagnostic sensitivity (0.75) compared with that of ECT alone (0.67) and increased diagnostic specificity (0.93) compared with that of FeNO alone (0.74) with good PPV (0.60), NPV (0.96), positive LR (10.75), and negative LR (0.27). The AUC of this combination was higher, although no difference was observed with a single index. Collectively, the findings suggest that combining FeNO and ECT potentially contributes to greater diagnostic accuracy for CTVA in children.

There are several limitations to this study. First, although CTVA was diagnosed based on improved response to inhaled corticosteroid and long-acting beta₂-agonist over 4 weeks, concerns regarding underdiagnosis may arise. To date, no diagnostic criteria for CTVA in children have been established. The GINA guideline recommends that symptom improvement, spontaneously or with treatment, supports asthma diagnosis [7]. Shen et al. [4] reported that adult patients with CTVA exhibited a favorable response to inhaled corticosteroids alone or inhaled corticosteroids and long-acting beta₂-agonists treatment, and Yan et al. [5] demonstrated that 4 weeks of treatment significantly decreased the Asthma Control Questionnaire scores of patients with CTVA. The second limitation is the relatively small sample of patients in the CTVA group, which may be partially attributable to the relatively low prevalence of CTVA in children. In a study by Yan et al. [5], only 160 patients from 16 centers were diagnosed with CTVA over 3 years. Third, we did not include classic asthma and cough variant asthma control groups, a process that might have facilitated enhanced analysis of the underlying mechanisms of CTVA in children. Therefore, large-sample studies with long-term follow-up periods are required to further explore the pathogenesis of CTVA in children.

In summary, our findings suggest that CTVA is a cause of unexplained recurrent chest tightness in children. Our results also suggest that both FeNO ≥ 15.0 ppb and FEV₁ fall $\geq 9.9\%$ after ECT are diagnostically valuable for CTVA in children, and their combination could potentially contribute to greater diagnostic accuracy.

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Statement of Ethics

This study was approved by the Ethics Committee of Shengjing Hospital of China Medical University (ethical examination approval number: 2021 PS008J). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

Y.F. and N.C. conceived and designed the study. Y.F. and S.Z. were responsible for the collection and analysis of the experimental data. Y.F. and Y.S. interpreted the data and drafted the manuscript, which was revised by all authors. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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