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Self-reported exercise-induced dyspnea and airways obstruction assessed by oscillometry and spirometry in adolescents

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Abstract

Background: Self-reported exercise-induced dyspnea (EID) is common among adolescents. Possible underlying pathologies are exercise-induced bronchoconstriction (EIB) and laryngeal obstruction (EILO). The forced oscillation technique (FOT) may evaluate exercise-induced changes in airway caliber.

Aim: To investigate in adolescents the relationship between EID, EIB (post-exercise fall in forced expiratory volume in 1s (FEV_1)≥10%), EILO, and post-exercise challenge changes in FOT parameters.

Methods: One hundred and forty-three subjects (97 with EID) of 13–15 years old underwent a standardized exercise challenge with FOT measurement and spirometry repeatedly performed between 2 and 30 min post-exercise. EILO was studied in a subset of 123 adolescents. Subjects showing greater changes than the healthy subgroup in the modulus of the inspiratory impedance were considered FOT responders.

Results: EID-nonEIB subjects presented similar post-exercise changes in all FOT parameters to nonEID-nonEIB adolescents. Changes in all FOT parameters correlated with FEV_1 fall. 45 of 97 EID subjects responded neither by FEV_1 nor FOT to exercise. 19 and 18 subjects responded only by FEV_1 (onlyFEV_1responders) or FOT (onlyFOTresponders), respectively. Only a lower baseline forced vital capacity (FVC)%predicted and a higher FEV_1/FVC distinguished the onlyFEV_1responders from onlyFOTresponders. FOT parameters did not present specific post-exercise patterns in EILO subjects.

Conclusion: FOT can be used to identify post-exercise changes in lower airway function. However, EID has a modest relation with both FEV_1 and FOT responses, highlighting the need for objective testing. More research is needed to understand whether onlyFEV_1responders and onlyFOTresponders represent different endotypes.

KEYWORDS
exercise-induced bronchoconstriction, exercise-induced dyspnea, exercise-induced laryngeal obstruction, forced oscillation technique

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1 | INTRODUCTION

Exercise-induced respiratory symptoms, including exercise-induced dyspnea (EID), are common among adolescents and tend to increase with age.[1–4] The most common objectively identified pathology behind EID is probably exercise-induced bronchoconstriction (EIB).[2] However, exercise-induced laryngeal obstruction (EILO) should also be recognized as a potential cause of EID as a prevalence of ~5.7% was recently reported in adolescents.[2] As the relation between symptoms and objective findings is weak, the diagnosis of EIB and EILO should be made with an objective exercise or surrogate challenge.[5]

EIB is defined as a post-exercise decrease in forced expiratory volume in 1s (FEV_1) ≥10% from baseline.[5] However, FEV_1 measurement requires good spirometry maneuvers and mainly reflects larger airway caliber.[6] For the investigation of EILO, a continuous laryngoscopy exercise test (CLE test) performed in specialized diagnostic centers is recommended.[7]

The forced oscillation technique (FOT), also called oscillometry, allows monitoring of the resistance (Rrs) and reactance (Xrs) of the respiratory system during tidal breathing and is sensitive to changes in the upper and lower airways.[8,9] As FOT can detect airway obstruction with minimal patient co-operation, it might be used instead of, or together with, spirometry and CLE test to evaluate post-exercise changes.[10–15] Furthermore, as the relation between exertional symptoms, EIB, and EILO is not strong,[2,16] changes in lung mechanics during quiet breathing may correlate better and could explain additional symptoms.

To the best of our knowledge, the relationship between changes in FOT parameters and EID has only been studied in adult athletes, including only a limited selection of FOT parameters and only measured immediately post-exercise.[14] The FEV_1 and FOT responses to exercise only partially overlap in adults,[10,12,14] and no data are available in children or adolescents. To date, only one case study has addressed the possibility to identify EILO by FOT.[15]

In this study, we investigated in an adolescent population: (i) the relationship between reported EID, EIB (FEV_1 fall ≥10%), and the post-exercise challenge changes in FOT parameters; and (ii) the overlap between abnormal FOT response and EIB in relation to inflammatory characteristics and EID; and (iii) baseline and exercise-induced changes in FOT parameters in relation to EILO.

Key Messages

This is the first study reporting post-exercise changes in oscillometry parameters in a large adolescent population (143 subjects). 45 of 97 subjects with reported exercise-induced dyspnea did not have objective abnormal responses to exercise challenge by spirometry nor oscillometry. This result suggests the need for objective testing. Oscillometry and spirometry detected a similar proportion of subjects with abnormal responses to exercise, but the groups were only partially overlapped. Whether subjects responding to exercise only by oscillometry or spirometry represent different endotypes is still to be understood with future studies. Our results suggest a limited value of oscillometry measurements after exercise to identify exercise-induced laryngeal obstruction. However, as the measurements were performed 2 min after exercise, further studies are needed to evaluate the oscillometry parameters during or immediately after exercise to identify this pathology.

2 | MATERIALS AND METHODS

The subjects enrolled in this study are the same as in a previously reported study evaluating the prevalence of EIB and EILO[2] (see Appendix). Subjects were classified as having EID (EID group) or not (nonEID group) according to their response to the question: "Have you had an attack of shortness of breath that happened after strenuous activity at any time during the last 12 months?"

At a first visit, height, weight, rhinitis, physician-diagnosed asthma, and use of asthma medication were recorded. The fraction of exhaled nitric oxide (FeNO) was measured according to ATS/ERS recommendations[17] using a chemiluminescence NO analyzer (NIOX Flex, Aerocrine AB, Solna, Sweden). Blood samples were collected for measurement of immunoglobulin E (IgE) antibodies against a mix of aeroallergens (Phadiatop) and serum eosinophil cationic protein (ECP) (ImmunoCAP, Thermo Fisher Scientific, Uppsala, Sweden). Subjects were instructed to cease long-acting β2-agonists (24 h before the EIB test), short-acting β2-agonists (8h before the EIB test), and inhaled steroids (on the test day). On average, the subjects underwent the EIB test 12 days after the first visit.

2.1 | Exercise challenge tests

Subjects performed a treadmill exercise wearing a nose clip and breathing dry air through a tube connected to a central gas container (H_2O <5 mg/L, 18–22°C). Heart rate was monitored (CASE Exercise Testing System; GE Medical Systems). Within the first 1.5 min, the cardiac frequency was increased to 90% of the predicted maximum[18] and then maintained for 6 min. FOT and spirometry, in this order, were performed before (baseline) and at 5, 10, 15, and 30 min post-exercise. FOT was performed also at 2 min post-exercise.

Baseline spirometry was performed according to ATS/ERS guidelines.[19] The best FEV_1 of three measurements was documented (CardioPerfect dynamic spirometry; Welch Allyn). Post-exercise, the best FEV_1 of two measurements was recorded at each time point. FOT was performed with the subject in a seated position using a nose clip and supported cheeks to decrease the shunt compliance. A multifrequency signal comprising 5, 11, and 19 Hz was used (Resmon ProFULL, Restech Srl). To reduce the

number of measurements performed by a subject, duplicate FOT measurements were performed at baseline and only single measurements afterward.

On average 38 days later, the subjects underwent the CLE test to detect EILO according to guidelines and methods previously described.[2,7]

2.2 | Data and statistical analysis

EIB was defined as a decrease ≥10% in FEV_1 from baseline.[5] The following FOT parameters were analyzed at 5 Hz: total respiratory resistance (R_5), reactance (X_5), and impedance modulus ($|Z_5|$) together with their inspiratory ($R_{5,insp}$, $X_{5,insp,}$ $|Z_{5,insp}|$) and expiratory components ($R_{5,esp}$, $X_{5,esp}$, $|Z_{5,esp}|$). Moreover, the frequency dependence of the resistance (the difference between R_5 and the resistance at 19 Hz (R_5-R_{19})) was obtained. Z_score for R_5 and X_5 was computed using reference equations previously reported.[20] Maximal post-exercise changes in FOT parameters (ΔR_5, ΔX_5, $\Delta|Z_5|$, $\Delta R_{5,insp}$, $\Delta X_{5,insp,}$ $\Delta|Z_{5,insp}|$, $\Delta R_{5,esp}$, $\Delta X_{5,esp}$, $\Delta|Z_{5,esp}|$, Δz_score R_5, and Δz_score X_5) were calculated as absolute values and percentage of baseline.

The areas below the receiver operator characteristic (AUC-ROC) of all FOT parameters for determining EID and EIB were computed. To account for both changes in Rrs and Xrs and to avoid the confounding effect of the expiratory flow limitation (see Appendix), changes in $|Z_{5,insp}|$ were considered for defining FOT responders. The threshold for a positive FOT response was defined as the 95th percentile of $|Z_{5,insp}|$ changes in the subset of subjects without EID, EIB, EILO, asthma, rhinitis, or atopy ("healthy" subjects).

Subjects were classified as nonEID-nonEIB, EID-nonEIB, and EIB according to the self-reported EID and EIB detection by exercise challenge. To investigate the relationship between FEV_1 and FOT responders, subjects were also divided into four groups according to their response to the exercise challenge: subjects responding to exercise for both FEV_1 and FOT (FEV_1&FOTresponders), only FEV_1 (onlyFEV_1responders), only FOT (onlyFOTresponders), and non-responders. Subjects of the subset with CLE tests were divided into nonEID-nonEIB subjects without EILO (nonEID-nonEIB-nonEILO) and EILO subjects. The subgroups EILO-nonEIB and EILO-EIB of the EILO group were compared with nonEID-nonEIB-nonEILO subjects.

Data were tested for normality by Shapiro-Wilk test. According to data distribution, differences in continuous variables among two and more groups were tested by rank-sum test or Kruskal-Wallis one-way ANOVA on ranks, respectively. Post hoc analysis after ANOVA was performed by Dunn's method. Differences in categorical variables among groups were tested by Fisher test. Two-way analysis of variance (ANOVA) for repeated measurements tested post-exercise changes vs time in breathing pattern, FOT parameters, and FEV_1. Spearman's correlation tested the correlation between changes in breathing patterns and FOT parameters.

Data were analyzed using MATLAB R2020b (MathWorks), SigmaPlot v11 (Systat Software, Inc.), and R version 4.0.4 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | EID and post-exercise changes in FEV_1 and FOT parameters

FOT measurements in relation to spirometry were analyzed in 143 subjects (97 with and 46 without EID). EIB was detected in six out of the 46 nonEID subjects and in 41 out of 97 EID subjects. The R_5 coefficient of variation for the duplicate baseline measurements was <15% for all but five subjects and always <19%. Baseline R_5 and X_5 were within the range of normality for all the subjects except 3 EID asthmatic subjects. EID-nonEIB and EIB subjects presented higher $R_{5,insp}$ and $|Z|_{5,insp}$ at baseline than nonEID-nonEIB subjects (Table 1). EIB subjects presented higher FeNO levels than EID-nonEIB (Table 1). More subjects with asthma were in the EID-nonEIB and EIB groups than nonEID-nonEIB group (Table 1).

Changes in breathing pattern parameters post-exercise were similar in all groups at all time points. Minute ventilation was significantly increased from baseline to 5 min after exercise in all groups. No association was found between percentage changes in tidal volume, respiratory rate or minute ventilation, and changes in impedance. At all post-exercise timepoints, the EIB subjects presented greater changes in FEV_1 and inspiratory oscillometry parameters than nonEID-nonEIB and EID-nonEIB subjects (Figure 1). Moreover, EIB subjects presented higher maximal absolute and percentual post-exercise changes in all FOT parameters than EID-nonEIB and nonEID-nonEIB subjects. Conversely, EID-nonEIB subjects present similar post-exercise changes in oscillometry parameter and FEV_1 to nonEID-nonEIB subjects, both comparing each time point and maximal changes. Post-exercise, significant expiratory flow limitation ($X_{5,insp}$ - $X_{5,exp}$ >2.8[21]) developed in only one subject, with previously diagnosed asthma. AUC-ROC was lower than 0.60 for maximal changes in all the oscillometry parameters and EID. The highest AUC-ROC (0.66) was for post-exercise maximal $|Z_5|$, $|Z_{5,insp}|$, R_5 or $R_{5,insp}$ and EID. AUC-ROC for FEV_1 fall and EID was 0.65.

3.2 | FEV_1 and FOT response to exercise

AUC-ROC with EIB was higher for $\Delta|Z_{5,insp}|$ (0.79), post-exercise maximal $|Z_{5,insp}|$ (0.77), $\Delta R_{5,insp}$ (0.76), post-exercise maximal $R_{5,insp}$ (0.76), and ΔX_5 (0.76). Lowest AUC-ROC (≤ 0.71) was with expiratory parameters. Expressing the changes as %baseline lowered the AUC-ROC with all the parameters (eg, 0.75 for $\Delta|Z_{5,insp}|$%, 0.72 for $\Delta R_{5,insp}$%, 0.71 for ΔX_5%). Figure 2 shows the relationship between FEV_1 fall and $\Delta|Z_{5,insp}|$. Considering the 17 healthy subjects of our dataset, we identified a threshold of 1.15 cmH_2O^*s/L for positive $|Z_{5,insp}|$ response to exercise. Figure 3 shows the association between EID, EIB, and FOT responders. Among the 97 subjects with EID, additional 11 subjects with objective findings of bronchial hyper-responsiveness were identified by the FOT response. However, we found neither an abnormal FEV_1 nor FOT response in almost half of the EID subjects. 18 and 19 subjects responded only for FOT or FEV_1, respectively; no differences in their characteristics were found except a lower baseline forced vital capacity (FVC)

TABLE 1 Studied population

	nonEID-nonEIB	EID-nonEIB	EIB	All
n	40	56	47	143
Age [y]	14 (14; 15)	14 (14; 15)	14 (14; 15)	14 (14;15)
Girls	22 (55)	29 (52)	35 (74)	86 (60)
Height [cm]	171 (163; 177)	167 (162; 173)	166 (162; 173)	168 (163; 175)
Weight [kg]	57 (52; 69)	57 (51; 66)	58 (55; 64)	58 (53; 67)
Atopy (IgE≥0.35 kU/L)	17 (42)	27 (59)	19 (40)	63 (44)
Rhinitis	11 (27)	30 (54)	17 (36)	58 (41)
Ever asthma	2 (5)	19 (34)*	21(45)*	42 (29)
ICS	3 (7)	8 (14)	12 (25)	23 (16)
SABA	2 (5)	22 (39)*	18 (38)*	42 (29)
LTRA	0 (0)	3 (5)	2 (4)	5 (3)
EILO[a]	2 (5)	3 (5)	4 (10)	9 (7)
ECP [mgl]	8.7 (5.7; 13.9)	10.9 (7.0; 16.9)	14.9 (8.9; 23.3)*	11.6 (7.1; 17.0)
FeNO [ppb]	13.2 (9.5; 18.9)	11.2 (8.5; 17.0)	14.4 (10.7; 30.8)^	13.1 (9.5; 19.1)
FVC (%pred)	97.0 (89.6; 104.3)	93.6 (88.5; 105.8)	92.8 (84.1; 98.8)	93.7 (86.2;103.2)
FEV_1 (% pred)	95.6 (87.4; 98.9)	96.1 (85.9; 99.0)	90.4 (83.6; 95.5)	93.6 (85.9; 98.3)
FEV_1/FVC	0.88 (0.84; 0.92)	0.89 (0.84; 0.92)	0.86 (0.82; 0.94)	0.88 (0.83; 0.93)
R_5 [cmH_2O*s/L]	3.5 (3.2; 3.7)	3.6 (3.4; 4.4)	3.8 (3.3; 4.3)	3.6 (3.3; 4.3)
z_score R_5	−0.07 (−0.25; 0.16)	0.04 (−0.10; 0.26)	0.09 (−0.14;0.30)	0.02 (−0.14;0.27)
$R_{5,insp}$ [cmH_2O*s/L]	2.9 (2.6; 3.3)	3.2 (2.8; 3.7)*	3.3 (2.9; 3.6)*	3.1 (2.8;3.5)
$R_{5,esp}$ [cmH_2O*s/L]	3.8 (3.5; 4.3)	4.1 (3.7; 5.1)	4.1 (3.6; 4.9)	4.0 (3.6; 4.8)
X_5 [cmH_2O*s/L]	−0.9 (−1.2; −0.7)	−1.1 (−1.4; −0.8)	−1.0 (−1.4; −0.8)	−1.0 (−1.4; −0.75)
z_score X_5	0.02 (−0.30;0.50)	0.16 (−0.33;0.56)	0.15 (−0.24;0.50)	0.11 (−0.30;0.51)
$X_{5,insp}$ [cmH_2O*s/L]	−1.2 (−1.5; −0.9)	−1.4 (−1.7; −1.0)	−1.4 (−1.8; −1.0)	−1.4 (−1.6; −1.0)
$X_{5,esp}$ [cmH_2O*s/L]	−0.7 (−0.9; −0.5)	−0.9 (−1.2; −0.6)	−0.8 (−1.1; −0.6)	−0.8 (−1.1; −0.6)
$\|Z_5\|$ [cmH_2O*s/L]	3.6 (3.3; 3.9)	3.8 (3.5; 4.6)	3.9 (3.5; 4.5)	3.8 (3.4; 4.5)
$\|Z_{5,insp}\|$ [cmH_2O*s/L]	3.2 (2.7; 3.7)	3.5 (3.0; 4.0) *	3.7 (3.1; 4.0) *	3.4 (3.1;3.8)
$\|Z_{5,esp}\|$ [cmH_2O*s/L]	4.0 (3.8; 4.7)	4.3 (3.9; 5.4)	4.4 (3.9; 5.2)	4.2 (3.8; 5.2)
R_5-R_{19} [cmH_2O*s/L]	0.03 (−0.16; 0.27)	0.11 (−0.05;0.30)	0.20 (−0.02;0.35)	0.12 (−0.06;0.31)

Note: Data are reported as median (IQR) or number (percentage). ICS, SABA, and LTRA usage in the previous 3 months was self-reported.

Abbreviations: $|Z_{5,esp}|$, expiratory $|Z_5|$; $|Z_{5,insp}|$, inspiratory $|Z_5|$; $|Z_5|$, impedance modulus at 5 Hz; ECP, eosinophil cationic protein; EIB, exercise-induced bronchoconstriction; EID, exercise-induced dyspnea; EILO, exercise-induced laryngeal obstruction; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonists; R_5, respiratory resistance at 5 Hz; $R_{5,esp}$, expiratory R_5; $R_{5,insp}$, inspiratory R_5; R_5-R_{19}, difference between R_5 and the respiratory resistance at 19 Hz; SABA, short-acting beta agonists; X_5, respiratory reactance at 5 Hz; $X_{5,esp}$, expiratory X_5; $X_{5,insp}$, inspiratory X_5.

[a]tested only on 123 subjects (37 nonEID-nonEIB, 45 EID-nonEIB, and 41 EIB).

*$p<0.05$ compared to nonEID-nonEIB; ^ $p<0.05$ compared to EID-nonEIB.

%predicted and a higher FEV_1/FVC in the onlyFEV_1responders group (Table 2). FEV_1&FOTresponders presented higher ECP, FeNO levels, and asthma and EID prevalence than non-responders (Table 2).

3.3 | EILO and FOT parameters

FOT measurements in relation to EILO were analyzed in 123 subjects (82 with and 41 without EID). EILO was detected in two nonEID subjects, three EID-nonEIB subjects and four EIB subjects. Baseline and post-exercise changes in FOT parameters did not present specific patterns in subjects with EILO. $\Delta R_{5,insp}$ was higher in EILO subjects than nonEID-nonEIB-nonEILO subjects (Table 3). However, considering EILO-nonEIB (five subjects) and EILO-EIB (four subjects) groups separately, only the EILO-EIB group presented different $\Delta R_{5,insp}$ from nonEID-nonEIB-nonEILO subjects.

4 | DISCUSSION

To our knowledge, this is the first study reporting post-exercise changes in FOT parameters in an adolescent population. Previous

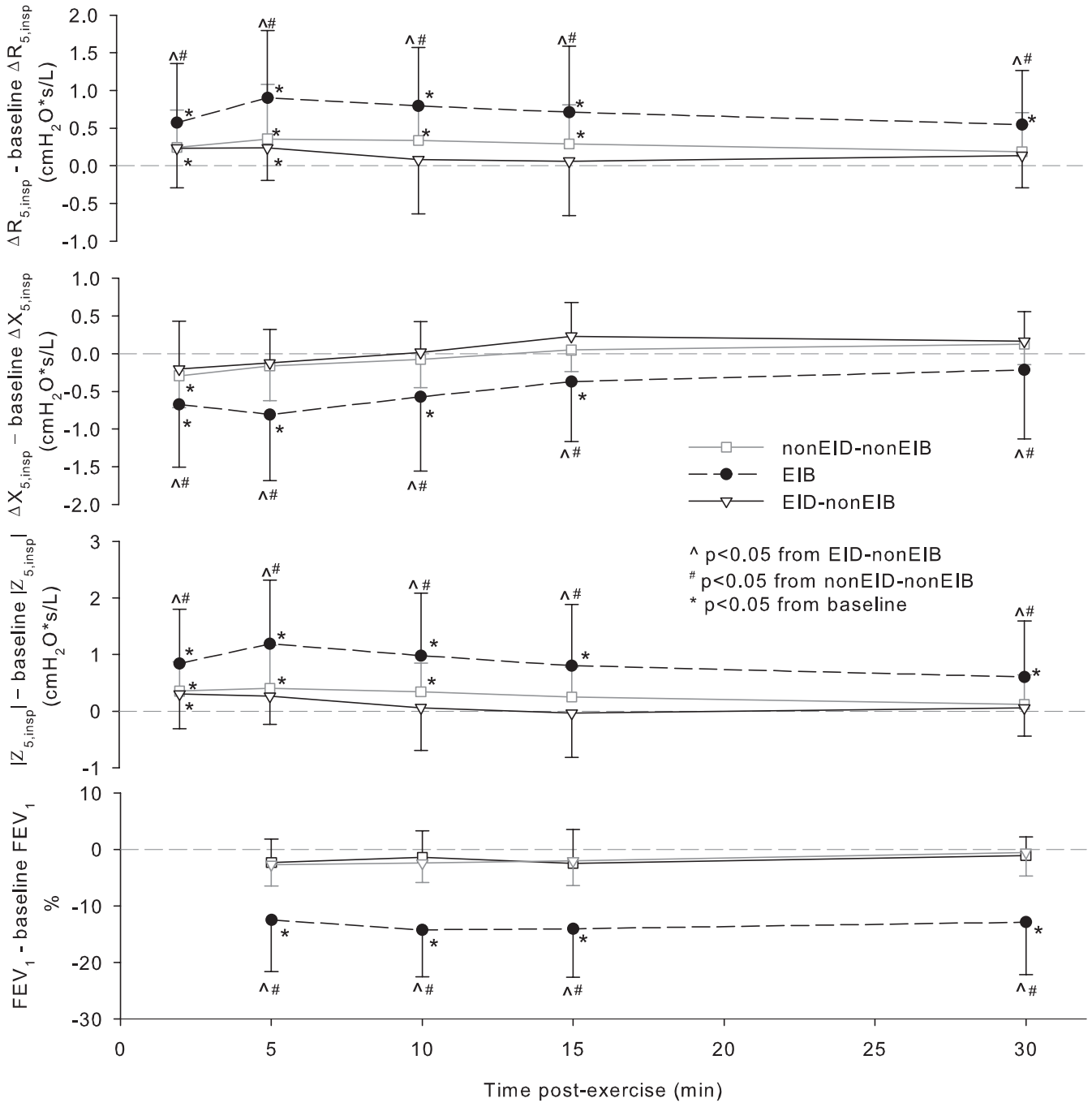

FIGURE 1 Post-exercise changes from baseline in inspiratory resistance ($R_{5,insp}$), reactance ($X_{5,insp}$), impedance modulus ($|Z_{5,insp}|$), and forced expiratory volume in 1s (FEV_1). EID, exercise-induced dyspnea; EIB, exercise-induced bronchoconstriction

studies performing FOT after exercise included younger children only[13,22,23] or together with a few adolescents with suspected asthma.[24–26] Our main findings were as follows: (i) Changes in oscillometry parameters after exercise were greater for the EIB group and similar for EID-nonEIB and nonEID-nonEIB subjects. Approximately half of the EID subjects did not have objective measures of abnormal response to exercise challenge by FOT nor spirometry; (ii) FOT and spirometry detected a similar proportion of subjects with abnormal response to exercise, but the groups only partially overlapped and no specific characteristics (except baseline FVC) differentiated onlyFOTresponders and onlyFEV1responders; and (iii) EILO subjects did not present specific patterns in baseline or post-exercise changes in FOT parameters.

EID-nonEIB subjects presented higher baseline $R_{5,insp}$ and $|Z|_{5,insp}$ compared with nonEID-nonEIB but similar post-exercise changes in all FOT parameters. Absolute maximal post-exercise values correlated better with EID than changes in parameters. We could not find different breathing patterns in these individuals (ie, higher tidal volumes, breathing frequency, or different inspiration/expiration phase ratio). However, dysfunctional breathing cannot

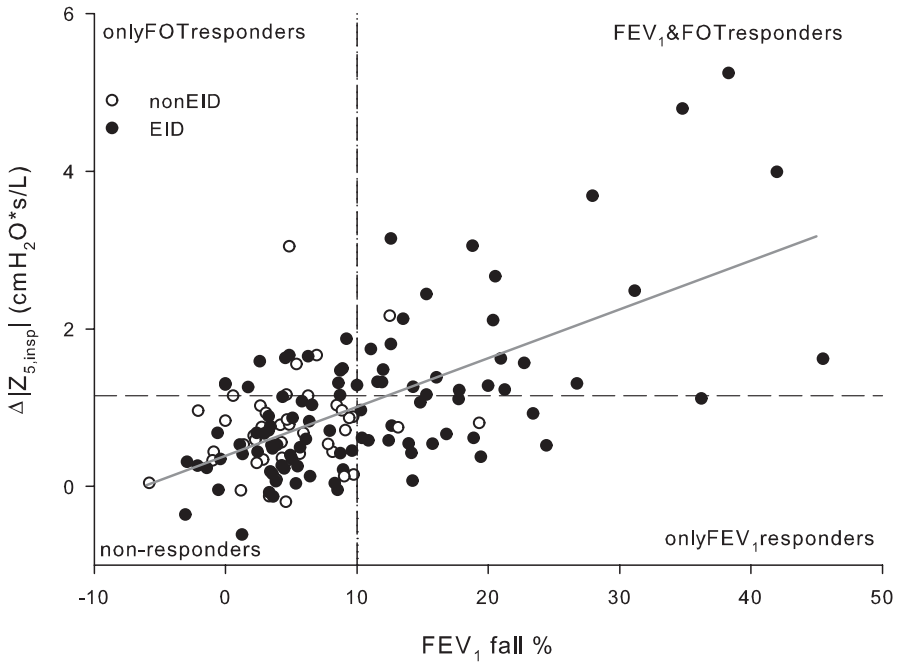

FIGURE 2 Relationship between forced expiratory volume in 1 s (FEV_1) fall and maximal change after exercise in the inspiratory impedance modulus ($\Delta|Z_{5,insp}|$) in subjects with (EID, close circles) and without (nonEID, open circles) exercise-induced dyspnea. Dashed lines represent the thresholds for positive responses to exercise. Four groups are identified groups according to their response to the exercise challenge: subjects that responded to exercise for both FEV_1 and FOT (FEV_1&FOTresponders), only FEV_1 (onlyFEV_1responders), only FOT (onlyFOTresponders), and non-responders. Linear regression ($r^2 = .38$, $p < .001$) is also shown (dark gray line)

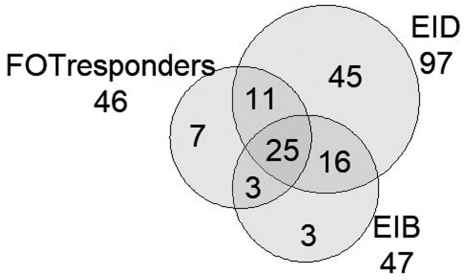

FIGURE 3 Venn diagram depicting the association between exercise-induced dyspnea (EID), exercise-induced bronchoconstriction (EIB), and exercise-induced changes in oscillometry (FOT responders) in adolescents

be excluded.[27] Moreover, a higher proportion of EID-nonEIB than nonEID-nonEIB subjects reported asthma diagnosis and use of short-acting β2-agonists, suggesting that at some point they received medical evaluation of their symptoms and medications even if no EIB nor altered inflammatory findings could be proven in this study. Only approximately half of the EID subjects exhibited post-exercise bronchial hyper-responsiveness by either spirometry or FOT. This finding is in good agreement with previous studies, suggesting that self-reported symptoms in high-school, college students,[28,29] and elite athletes[30] are not predictive of a positive EIB test with spirometry. Furthermore, in recreational adult athletes after eucapnic hyperventilation test, no clear relationship was found between respiratory symptoms and airway dysfunction detected by either spirometry or FOT.[14]

Only two previous studies performed both FOT and spirometry in children.[13,26] FOT appeared better in identifying asthmatic children upon exercise test,[13] and a significant but weak correlation was reported between absolute FEV_1 and FOT parameters before and after exercise in asthmatic children.[26] However, changes in FOT parameters and FEV_1 were never directly compared. In adults, only one study (including only 5 asthmatics subjects with EIB) reported high agreement between FEV_1 and FOT parameters.[11] Even if there is a correlation between FEV_1 and FOT responses to exercise, a dissociation is present in several subjects of previous studies including adults with probable EIB,[10] asthma,[12] and athletes.[14] For example, the largest study[14] published so far, including 101 recreational adult athletes, classified 17% of subjects as FEV_1 responders (EIB) and 18% as FOT responders. Still, only 10% of the participants met both the diagnostic thresholds.

Similarly, although our EIB subjects presented greater changes in all the FOT parameters (both expressed as absolute and percentage of baseline) than nonEID-nonEIB and EID-nonEIB groups, we found 37 adolescents with an exclusive FEV_1 (19 subjects) or FOT response (18 subjects) to exercise. Despite being both affected by airway obstruction, FEV_1 and FOT are different measures reflecting different airway obstruction characteristics.[31] Changes in obstruction at high lung volumes greatly influenced FEV_1. In contrast, FOT parameters reflect alteration at operating lung volumes and are affected by changes in end-expiratory lung volume and breathing pattern. Therefore, FEV_1 may be more sensitive to rigid airways less distensible by deep inhalation, while FOT parameters are more sensitive to instabilities around functional residual capacity. We could not identify any characteristics that differentiated onlyFEV_1responders from onlyFOTresponders, except a lower baseline FVC and higher FEV_1/FVC. However, a non-significant trend of increasing FeNO and ECP was seen from non-responders to onlyFEV_1responders or onlyFOTresponders to FEV_1&FOTresponders. Thus, further investigations are needed to understand whether the two methods can identify different endotypes or if their combination can increase the overall sensitivity of exercise challenges. Moreover, additional considerations are required, especially for individuals with borderline changes in

TABLE 2 FOT and FEV_1 responders to exercise test

	Non-responders	onlyFOTresponders	onlyFEV_1responders	FEV_1&FOTresponders
	FEV_1 fall<10% $\Delta|Z_{5,insp}|$ <1.15 cmH_2O	FEV_1 fall <10% $\Delta|Z_{5,insp}|$>1.15 cmH_2O	FEV_1 fall >10% $\Delta|Z_{5,insp}|$<1.15 cmH_2O	FEV_1 fall >10% $\Delta|Z_{5,insp}|$>1.15 cmH_2O
n	78	18	19	28
Age [y]	14 (14; 15)	14 (14; 15)	14 (14; 15)	14 (14; 15)
Girls	46 (59)	5 (28)	15 (79)^	20 (71)^
Height [cm]	170 (163; 176)	168 (160; 173)	167 (161; 174)	166 (163; 171)
Weight [kg]	57 (52; 67)	58 (51; 69)	62 (53; 65)	57 (55; 61)
Atopy(IgE≥0.35kU/L)	36 (46)	8 (44)	5 (26)	14 (50)
Rhinitis	33 (42)	8 (44)	4 (21)	13 (46)
Ever asthma	18 (23)	3 (17)	5 (26)	16 (57)*
ICS	10 (13)	1 (6)	3 (16)	9 (32)
SABA	19 (24)	5 (28)	7 (37)	11 (39)
LTRA	1 (1)	0 (0)	1 (5)	2 (7)
EILO[a]	3 (4)	2 (11)	1 (5)	3 (11)
EID	45 (58)	11 (61)	16 (84)	25 (89)*
ECP [mgl]	9.8 (6.1; 15.9)	12.2 (5.5; 15.9)	11.6 (7.5; 17.5)	15.8 (11.1; 28.7)*
FeNO [ppb]	11.4 (8.7; 17.3)	15.2 (10.2; 22.3)	12.8 (9.2; 16.3)	19.9 (12.8; 38.4)*
FVC (%pred)	93.8 (86.4; 102.3)	102.1 (93.7; 109.4)	89.9 (83.3; 99.0)^	93.3 (85.1; 98.3)
FEV_1 (%pred)	96.0 (85.9; 99.1)	95.9 (92.2; 98.5)	93.3 (84.3; 97.0)	89.5 (82.1; 94.6)
FEV_1/FVC	0.89 (0.85; 0.93)	0.85 (0.78; 0.89)	0.92 (0.84; 0.98)^	0.84 (0.82; 0.92)
R_5 [cmH_2O*s/L]	3.6 (3.3; 4.3)	3.6 (3.3; 4.3)	3.8 (3.4; 4.1)	3.8 (3.2; 4.4)
z_score R_5	0.02 (−0.14;0.29)	−0.03 (−0.09;0.13)	0.11 (−0.12;0.34)	0.06 (−0.16;0.29)
$R_{5,insp}$ [cmH_2O*s/L]	3.0 (2.7; 3.5)	3.2 (2.8; 3.5)	3.3 (3.0;3.5)	3.3 (2.9; 3.8)
$R_{5,esp}$ [cmH_2O*s/L]	3.9 (3.6;4.6)	4.0 (3.6;5.1)	4.1 (3.8; 4.6)	4.1 (3.5; 5.0)
X_5 [cmH_2O*s/L]	−1.1 (−1.4; −0.7)	−0.9 (−1.1; −0.8)	−1.0 (−1.4; −0.8)	−1.1 (−1.4; −0.8)
z_score X_5	0.16 (−0.32;0.65)	−0.18 (−0.32;0.18)	0.25 (−0.28;0.38)	0.05 (−0.23;0.82)
$X_{5,insp}$ [cmH_2O*s/L]	−1.3 (−1.7; −0.9)	−1.3 (−1.5; −1.1)	−1.5 (−1.8; −1.0)	−1.4 (−1.6; −1.0)
$X_{5,esp}$ [cmH_2O*s/L]	−0.8 (−1.1; −0.5)	−0.7 (−0.9; −0.6)	−0.8 (−1.0; −0.4)	−0.8 (−1.2; −0.6)
$|Z_5|$ [cmH_2O*s/L]	3.7 (3.4; 4.5)	3.7 (3.4; 4.4)	4.0 (3.5; 4.3)	3.8 (3.4; 4.6)
$|Z_{5,insp}|$ [cmH_2O*s/L]	3.4 (2.9; 3.8)	3.5 (2.9; 3.9)	3.7 (3.2; 3.8)	3.6 (3.1; 4.1)
$|Z_{5,esp}|$ [cmH_2O*s/L]	4.2 (3.8; 5.0)	4.1 (3.8; 5.5)	4.5 (4.0; 5.0)	4.3 (3.8; 5.3)
R_5-R_{19} [cmH_2O*s/L]	0.12 (−0.07;0.30)	0.02 (−0.17;0.17)	0.14 (−0.02;0.36)	0.21(−0.02;0.33)

Note: Data are reported as median (IQR) or number (percentage). ICS, SABA, and LTRA usage in the previous 3 months was self-reported.

Abbreviations: $|Z_{5,esp}|$, expiratory $|Z_5|$; $|Z_{5,insp}|$, inspiratory $|Z_5|$; $|Z_5|$, impedance modulus at 5 Hz; ECP, eosinophil cationic protein; EID, exercise-induced dyspnea; EILO, exercise-induced laryngeal obstruction; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonists; R_5, respiratory resistance at 5 Hz; $R_{5,esp}$, expiratory R_5; $R_{5,insp}$, inspiratory R_5; $X_{5,insp}$, inspiratory X_5; R_5-R_{19}, difference between R_5 and the respiratory resistance at 19 Hz; SABA, short-acting beta agonists; X_5, respiratory reactance at 5 Hz; $X_{5,esp}$, expiratory X_5; $\Delta|Z_{5,insp}|$, changes in the modulus of the inspiratory impedance after exercise.

[a]tested only on 123 subjects (67 non-responders, 15 onlyFOTresponders, 15 onlyFEV_1responders, and 26 FEV1&FOTresponders).

*$p < .05$ compared to FEV1&FOTresponders; ^$p < .05$ compared to onlyFOTresponders.

FEV_1 or FOT parameters after the exercise challenge. Despite the vast knowledge on response in FEV_1 after exercise, the cutoffs are debated[32] and a range 10%–15% is suggested in ATS clinical guidelines to interpret EIB. Moreover, the reproducibility of bronchial response to the exercise challenge test is not high in mild EIB.[33] The knowledge is much more limited regarding FOT cutoffs. Therefore, exercise-induced changes in spirometry and FOT should be evaluated within the clinical picture in relation to respiratory symptoms for clinical decision making.

Despite the reported high FOT sensitivity to changes in the upper airways,[34] we did not identify specific oscillatory patterns in EILO subjects. A previous study[15] reported an $R_{5,insp}$ higher than $R_{5,exp}$ in an EILO patients. Previous studies reported the same pattern also during vocal cord dysfunction (VCD).[35,36] None of our 143

TABLE 3 FOT parameters and EILO

	nonEID-nonEIB-nonEILO	EILO
n	35	9
Age [y]	14 (14; 15)	14 (14;15)
Girls	20 (57)	7 (78)
Height [cm]	171 (163; 177)	167 (163; 174)
Weight [kg]	57 (51; 68)	57 (53; 76)
Atopy (IgE≥0.35kU/L)	15 (43)	2 (22)
Rhinitis	11 (32)	1 (11)
Ever asthma	2 (6)	3 (33)
ICS	3 (9)	1 (11)
SABA	2 (6)	2 (22)
LTRA	0 (0)	1 (11)
ECP [mgl]	9.2 (5.6; 14.0)	7.9 (4.0; 34.3)
FeNO [ppb]	13.2 (9.6; 18.8)	14.4 (8.2; 19.9)
FVC (%pred)	94.9 (86.9; 104.4)	98.4 (89.7; 102.6)
FEV_1 (% pred)	95.2 (86.8; 99.2)	96.0 (89.9; 98.6)
FEV_1/FVC	0.89 (0.84; 0.93)	0.90 (0.85; 0.93)
R_5 [cmH_2O*s/L]	3.5 (3.2;3.7)	3.5 (3.1;4.3)
z_score R_5	0.006 (−0.259; 0.269)	−0.021 (−0.087; 0.141)
$R_{5,insp}$ [cmH_2O*s/L]	3.0 (2.6;3.3)	3.0 (2.8;3.5)
$R_{5,esp}$ [cmH_2O*s/L]	3.9 (3.6;4.3)	4.2 (3.7;4.9)
X_5 [cmH_2O*s/L]	−0.9 (−1.2; −0.7)	−1.2 (−1.5; −0.8)
z_score X_5	0.12 (−0.27; 0.57)	0.46 (0.13; 0.74)
$X_{5,insp}$ [cmH_2O*s/L]	−1.3 (−1.5; −0.9)	−1.4 (−2.1; −0.9)
$X_{5,esp}$ [cmH_2O*s/L]	−0.7 (−1.0; −0.5)	−0.7 (−1.1; −0.7)
$\|Z_5\|$ [cmH_2O*s/L]	3.7 (3.4;3.9)	3.7 (3.3;4.6)
$\|Z_{5,insp}\|$ [cmH_2O*s/L]	3.3 (2.8;3.7)	3.2 (3.0; 4.0)
$\|Z_{5,esp}\|$ [cmH_2O*s/L]	4.1 (3.8;4.7)	4.3 (3.9;5.4)
$R_{5,insp}$- $R_{5,esp}$ [cmH_2O*s/L]	−0.9 (−1.4; −0.7)	−1.0 (−1.5;−0.9)
FEV_1 fall	4.3 (2.2;6.8)	6.1 (4.1;15.1)
ΔR_5 [cmH_2O*s/L]	0.7 (0.3; 1.0)	1.3 (0.6;1.8)
Δz_score R_5	0.4 (0.2;0.5)	0.7 (0.2;0.9)
$\Delta R_{5,insp}$ [cmH_2O*s/L]	0.6 (0.3;0.9)*	1.2 (0.7; 1.3)
$\Delta R_{5,esp}$ [cmH_2O*s/L]	0.8 (0.4;1.3)	0.8 (0.3;2.1)
ΔX_5 [cmH_2O*s/L]	−0.3 (−0.5; −0.03)	−0.5 (−0.7; −0.3)
Δz_score X_5	0.5 (0.06; 0.9)	0.9 (0.5; 1.2)
$\Delta X_{5,insp}$ [cmH_2O*s/L]	−0.4 (−0.6; −0.2)	−0.7 (−0.9; −0.4)
$\Delta X_{5,esp}$ [cmH_2O*s/L]	−0.2 (−0.5; −0.06)	−0.5 (−0.7; −0.2)
$\Delta\|Z_5\|$ [cmH_2O*s/L]	0.7 (0.2;1.0)	1.0 (0.1;1.6)
$\Delta\|Z_{5,insp}\|$ [cmH_2O*s/L]	0.7 (0.4;0.9)	1.3 (0.5;1.4)
$\Delta\|Z_{5,esp}\|$ [cmH_2O*s/L]	0.9 (0.4;1.3)	1.0 (0.5;2.0)
max $R_{5,insp}$-$R_{5,esp}$ [cmH_2O*s/L]	−0.7 (−0.9; −0.3)	−0.7 (−0.9; −0.5)

Note: Data are reported as median (IQR) or number (percentage). ICS, SABA, and LTRA usage in the previous 3 months was self-reported.

Abbreviations: $|Z_{5,insp}|$, inspiratory $|Z_5|$; $|Z_{5,esp}|$, expiratory $|Z_5|$; $|Z_5|$, impedance modulus at 5 Hz; ECP, eosinophil cationic protein; EIB, exercise-induced bronchoconstriction; EID, exercise-induced dyspnea; EILO, exercise-induced laryngeal obstruction; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonists; max $R_{5,insp}$-$R_{5,esp}$, maximal post-exercise value of $R_{5,insp}$-$R_{5,esp}$; R_5, respiratory resistance at 5 Hz; $R_{5,esp}$, expiratory R_5; $R_{5,insp}$, inspiratory R_5; SABA, short-acting beta agonists; X_5, respiratory reactance at 5 Hz; $X_{5,esp}$, expiratory X_5; $X_{5,insp}$, inspiratory X_5; $\Delta|Z_{5,esp}|$, maximal post-exercise change in $|Z_{5,esp}|$; $\Delta|Z_{5,insp}|$, maximal post-exercise change in $|Z_{5,insp}|$; $\Delta|Z_5|$, maximal post-exercise change in $|Z_5|$; ΔR_5, maximal post-exercise change in R_5; $\Delta R_{5,esp}$=maximal post-exercise change in $R_{5,esp}$; $\Delta R_{5,insp}$, maximal post-exercise change in $\Delta R_{5,insp}$; ΔX_5, maximal post-exercise change in X_5; $\Delta X_{5,esp}$, maximal post-exercise change in $X_{5,esp}$; $\Delta X_{5,insp}$, maximal post-exercise change in $X_{5,insp}$; Δz_score R_5, maximal post-exercise change in z_score of R_5; Δz_score X_5= maximal post-exercise change in z_score of X_5.

atested only on 123 subjects (67 non-responders, 15 onlyFOTresponders, 15 onlyFEV_1responders, and 26 FEV1&FOTresponders).

*$p < .05$ compared to FEV1&FOTresponders; ^$p < .05$ compared to onlyFOTresponders.

patients presented this oscillatory pattern. The almost instant fading of the obstruction in EILO, compared to the ongoing obstruction in VCD, together with our first measure being performed 2 min after exercise, may explain this difference.

4.1 | Strengths

We performed standardized EIB and CLE tests on a large population of randomly sampled adolescents where weighting for EID was performed. This makes our findings more generalizable on a population level.

4.2 | Weaknesses

EID was self-reported, and we did not study symptoms reproducibility during the exercise tests performed. As any self-reported symptoms, it was dependent on the subjects' interpretation of the question asked. We did not perform triplicate FOT measurements as recommended by the technical guidelines. However, the measurements were performed by trained personal, and we obtained a high measurement reproducibility at baseline. Moreover, a recent study suggested that a single measurement might suffice.[37] Our protocol included several FVC maneuvers that may impact FOT measurements. However, we performed FOT before spirometry at each timepoint. The threshold for FOT responders was defined on relatively few subjects. CLE tests were performed at a separate visit at a median of 38 days after the FOT measurements. The EILO group was small, and, as EIB is a common comorbidity,[38] it was impossible to study EILO separately as pathology. As the EILO changes are transient,[7] they might have disappeared before the first FOT measurement. Moreover, we assumed FOT, EIB, and CLE test results are

reproducible at the two different challenge tests. This assumption may be invalid[39,40] and may impact our results.

In conclusion, oscillometry can be helpful to evaluate response to exercise in adolescents. The modest relation between EID and objective airway hyper-responsiveness, detected by spirometry and FOT, suggests the need for objective testing. Whether subjects responding to exercise only by FOT or spirometry represent different endotypes is still to be understood. Our results suggest FOT measurements after 2 min from exercise can miss EILO. Future studies should evaluate FOT parameters during or immediately after exercise in population-based settings.

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CONFLICT OF INTERESTS

P.P. and R.D. are co-founders and serve as board members of RESTECH s.r.l., a company that designs, manufactures, and sells devices for lung function testing based on forced oscillation technique (FOT). R. D. also reports grants and others from Restech, personal fees from Philips Healthcare outside the submitted work. In addition, Dellaca' has a patent on the detection of EFL by FOT with royalties paid to Philips Respironics and Restech s.r.l, a patent on monitoring lung volume recruitment by FOT with royalties paid to Vyaire, and a patent on early detection of exacerbations by home monitoring of FOT with royalties paid to Restech s.r.l. The other authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

Chiara Veneroni: Conceptualization (equal); Data curation (lead); Formal analysis (equal); Investigation (supporting); Methodology (equal); Project administration (supporting); Writing – original draft (lead). **Pasquale Pio Pompilio:** Conceptualization (equal); Data curation (supporting); Formal analysis (equal); Methodology (equal); Writing – review & editing (equal). **Kjell Alving:** Conceptualization (equal); Methodology (equal); Writing – review & editing (equal). **Christer Janson:** Conceptualization (equal); Funding acquisition (supporting); Methodology (equal); Project administration (lead); Writing – review & editing (equal). **Leif Nordang:** Conceptualization (equal); Methodology (equal); Writing – review & editing (equal). **Raffaele Lorenzo Dellaca':** Conceptualization (equal); Methodology (equal); Project administration (supporting); Writing – review & editing (equal). **Henrik Johansson:** Conceptualization (equal); Data curation (supporting); Formal analysis (equal); Funding acquisition (lead); Investigation (lead); Methodology (equal); Project administration (lead); Writing – original draft (supporting). **Andrei Malinovschi:** Conceptualization (equal); Data curation (supporting); Formal analysis (equal); Funding acquisition (supporting); Methodology (equal); Project administration (lead); Writing – original draft (supporting).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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