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

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Funding information
This study was sponsored by the Swedish Heart Lung Foundation (grant number 20110179), the Signhild Engqvist Foundation, the Bror Hjerpstedt Foundation, and the Gillbergska Foundation.

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 (FEV1)≥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 FEV1 fall. 45 of 97 EID subjects responded neither by FEV1 nor FOT to exercise. 19 and 18 subjects responded only by FEV1 (onlyFEV1 responders) or FOT (onlyFOT responders), respectively. Only a lower baseline forced vital capacity (FVC)%predicted and a higher FEV1/FVC distinguished the onlyFEV1 responders from onlyFOT responders. 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 FEV1 and FOT responses, highlighting the need for objective testing. More research is needed to understand whether onlyFEV1 responders and onlyFOT responders represent different endotypes.

**KEYWORDS**
exercise-induced bronchoconstriction, exercise-induced dyspnea, exercise-induced laryngeal obstruction, forced oscillation technique
1 | INTRODUCTION

Exercise-induced respiratory symptoms, including exercise-induced dyspnea (EID), are common among adolescents and tend to increase with age.\textsuperscript{1–4} The most common objectively identified pathology behind EID is probably exercise-induced bronchoconstriction (EIB).\textsuperscript{2} However, exercise-induced laryngeal obstruction (EILO) should also be recognized as a potential cause of EID as a prevalence of \textapprox5.7% was recently reported in adolescents.\textsuperscript{5} 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.\textsuperscript{5}

EIB is defined as a post-exercise decrease in forced expiratory volume in 1s (FEV\textsubscript{1}) \textgreater10% from baseline.\textsuperscript{5} However, FEV\textsubscript{1} measurement requires good spirometry maneuvers and mainly reflects larger airway caliber.\textsuperscript{6} For the investigation of EILO, a continuous laryngoscopy exercise test (CLE test) performed in specialized diagnostic centers is recommended.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10–15} Furthermore, as the relation between exertional symptoms, EIB, and EILO is not strong,\textsuperscript{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.\textsuperscript{14} The FEV\textsubscript{1} and FOT responses to exercise only partially overlap in adults,\textsuperscript{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.\textsuperscript{15}

In this study, we investigated in an adolescent population: (i) the relationship between reported EID, EIB (FEV\textsubscript{1} fall \textgreater10%), 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.

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\textsuperscript{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

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.

2.1 | 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\textsubscript{2}O <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\textsuperscript{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.\textsuperscript{19} The best FEV\textsubscript{1} of three measurements was documented (CardioPerfect dynamic spirometry; Welch Allyn). Post-exercise, the best FEV\textsubscript{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 ELO according to guidelines and methods previously described.2,7

2.2 | Data and statistical analysis

EIB was defined as a decrease ≥10% in FEV1 from baseline.5 The following FOT parameters were analyzed at 5 Hz: total respiratory resistance (R5), reactance (X5), and impedance modulus (|Z5|) together with their inspiratory (R5,insp, X5,insp, |Z5,insp|) and expiratory components (R5,exp, X5,exp, |Z5,exp|). Moreover, the frequency dependence of the resistance (the difference between R5 and the resistance at 19 Hz (R5-R5×)) was obtained. Z-score for R5 and X5 was computed using reference equations previously reported.20 Maximal post-exercise changes in FOT parameters (ΔR5, ΔX5, Δ|Z5|, ΔR5,insp, ΔX5,insp, Δ|Z5,insp|, ΔR5,exp, ΔX5,exp, Δ|Z5,exp|, Δz score R5, and Δz score X5) 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 |Z5,insp| were considered for defining FOT responders. The threshold for a positive FOT response was defined as the 95th percentile of |Z5,insp| changes in the subset of subjects without EID, EIB, ELO, 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 FEV1 and FOT responders, subjects were also divided into four groups according to their response to the exercise challenge: subjects responding to exercise for both FEV1 and FOT (FEV1 responders), only FEV1 (onlyFEV1 responders), only FOT (onlyFOT responders), and non-responders. Subjects of the subset with CLE tests were divided into nonEID-nonEIB subjects without ELO (nonEID-nonEIB) and ELO subjects. The subgroups ELO-nonEIB and ELO-EIB of the EIB group were compared with nonEID-nonEIB nonELO 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 FEV1. 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 FEV1 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 R5 coefficient of variation for the duplicate baseline measurements was <15% for all but five subjects and always <19%. Baseline R5 and X5 were within the range of normality for all the subjects except 3 EID asthmatic subjects. EID-nonEIB and EIB subjects presented higher R5,insp and |Z5,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 FEV1 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 FEV1 to nonEID-nonEIB subjects, both comparing each time point and maximal changes. Post-exercise, significant expiratory flow limitation (X5,insp > X5,exp > 2.825) 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-maximal |Z5,insp|, R5,insp, and X5,insp, and EID. AUC-ROC for FEV1 fall and EIB was 0.65.

3.2 | FEV1 and FOT response to exercise

AUC-ROC with EIB was higher for Δ|Z5,insp| (0.79), post-exercise maximal |Z5,insp| (0.77), ΔR5,insp (0.76), post-exercise maximal R5,insp (0.76), and ΔX5 (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 Δ|Z5,insp|%, 0.72 for ΔR5,insp%, 0.71 for ΔX5%). Figure 2 shows the relationship between FEV1 fall and Δ|Z5,insp|.

Considering the 17 healthy subjects of our dataset, we identified a threshold of 1.15 cmH2O·s·L for positive |Z5,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 FEV1 nor FOT response in almost half of the EID subjects. 18 and 19 subjects responded only for FOT or FEV1, respectively; no differences in their characteristics were found except a lower baseline forced vital capacity (FVC).
%predicted and a higher FEV1/FVC in the onlyFEV1 responders group (Table 2). FEV1 & FOT responders 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. ΔR5,esp was higher in EILO subjects than nonEID-nonEIB nonEID subjects (Table 3). However, considering EILO-nonEIB (five subjects) and EILO-EIB (four subjects) groups separately, only the EILO-EIB group presented different ΔR5,esp from nonEID-nonEIB nonEID subjects.

### 4 | DISCUSSION

To our knowledge, this is the first study reporting post-exercise changes in FOT parameters in an adolescent population. Previous...
studies performing FOT after exercise included younger children only13,22,23 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) EIO subjects did not present specific patterns in baseline or post-exercise changes in FOT parameters.

EID-nonEIB subjects presented higher baseline $R_{5,\text{insp}}$ and $|Z|_{5,\text{insp}}$ 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 1 Post-exercise changes from baseline in inspiratory resistance ($R_{5,\text{insp}}$), reactance ($X_{5,\text{insp}}$), impedance modulus ($|Z|_{5,\text{insp}}$), and forced expiratory volume in 1s (FEV1). EID, exercise-induced dyspnea; EIB, exercise-induced bronchoconstriction.](image-url)
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, and elite athletes 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. Changes in obstruction at high lung volumes greatly influenced FEV₁. In contrast, FOT parameters reflect alteration at operating lung volumes and are affected by changes in end-expiratory lung volume and breathing pattern. Therefore, FEV₁ 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 onlyFEV₁ responders from onlyFOT responders, except a lower baseline FVC and higher FEV₁/FVC. However, a non-significant trend of increasing FeNO and ECP was seen from non-responders to onlyFEV₁ responders or onlyFOT responders to FEV₁&FOT responders. 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

FIGURE 2 Relationship between forced expiratory volume in 1 s (FEV₁) fall and maximal change after exercise in the inspiratory impedance modulus (Δ|Z₅₀|) 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 according to their response to the exercise challenge: subjects that responded to exercise for both FEV₁ and FOT (FEV₁&FOT responders), only FEV₁ (onlyFEV₁ responders), only FOT (onlyFOT responders), and non-responders. Linear regression (r² = .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.
FEV<sub>1</sub> or FOT parameters after the exercise challenge. Despite the vast knowledge on response in FEV<sub>1</sub> after exercise, the cutoffs are debated<sup>35,36</sup> 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.<sup>33</sup> 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,<sup>34</sup> we did not identify specific oscillatory patterns in EILO subjects. A previous study<sup>15</sup> reported an R<sub>5,exp</sub> higher than R<sub>5,insp</sub> in an EILO patients. Previous studies reported the same pattern also during vocal cord dysfunction (VCD).<sup>35,36</sup> None of our 143

### Table 2: FOT and FEV<sub>1</sub> responders to exercise test

|                      | Non-responders | onlyFOTresponders | onlyFEV<sub>1</sub>responders | FEV<sub>1</sub>&FOTresponders |
|----------------------|----------------|-------------------|-------------------------------|-------------------------------|
| FEV<sub>1</sub> fall<10% |                |                   |                               |                               |
| Δ|Z<sub>5,insp</sub>|<1.15 cmH<sub>2</sub>O | 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)    | 161 (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)                         |
| ERS<sup>a</sup>      | 3 (4)          | 2 (11)            | 1 (5)                         | 3 (11)                        |
| EID                  | 45 (58)        | 11 (61)           | 16 (84)                       | 25 (89)^                      |
| ECP [mg/l]           | 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<sub>1</sub> (%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<sub>1</sub>/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<sub>5</sub> [cmH<sub>2</sub>O 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<sub>5</sub> | 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<sub>5,insp</sub> [cmH<sub>2</sub>O 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<sub>5,exp</sub> [cmH<sub>2</sub>O 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)                |
| Z<sub>5,insp</sub> [cmH<sub>2</sub>O 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 Z<sub>5,insp</sub> | 0.16 (-0.32;0.65)| -0.18 (-0.32;0.18)| 0.25 (-0.28;0.38)             | 0.05 (-0.23;0.82)             |
| Z<sub>5,exp</sub> [cmH<sub>2</sub>O 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<sub>5,insp</sub> [cmH<sub>2</sub>O 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)             |
| X<sub>5,exp</sub> [cmH<sub>2</sub>O 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<sub>5,insp</sub> [cmH<sub>2</sub>O 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)                |
| Z<sub>5,exp</sub> [cmH<sub>2</sub>O 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<sub>5,insp</sub>|, inspiratory |Z<sub>5,insp</sub>|; |Z<sub>5,exp</sub>|, inspiratory |Z<sub>5,exp</sub>|; |Z<sub>5</sub>|, 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<sub>1</sub>, forced expiratory volume in 1s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonists; R<sub>5</sub>, respiratory resistance at 5 Hz; R<sub>5,exp</sub>, expiratory R<sub>5</sub>; R<sub>5,insp</sub>, inspiratory R<sub>5</sub>; X<sub>5,insp</sub>, inspiratory X<sub>5</sub>; X<sub>5,exp</sub>, difference between R<sub>5</sub> and the respiratory resistance at 19 Hz; SABA, short-acting beta agonists; X<sub>5</sub>, respiratory reactance at 5 Hz; X<sub>5,exp</sub>, expiratory X<sub>5</sub>; |Z<sub>5,insp</sub>|, changes in the modulus of the inspiratory impedance after exercise.

*tested only on 123 subjects (67 non-responders, 15 onlyFOTresponders, 15 onlyFEV<sub>1</sub>responders, and 26 FEV1&FOTresponders).

*p < .05 compared to FEV1&FOTresponders; *p < .05 compared to onlyFOTresponders.
### TABLE 3 FOT parameters and EILO

|                | nonEID-nonEIB- | EIDO                                                                 |
|----------------|---------------|----------------------------------------------------------------------|
| 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)                                                   |

FEV₁ (% pred) 95.2 (86.8; 99.2) 96.0 (89.9; 98.6)

FEV₁/FVC 0.89 (0.84; 0.93) 0.90 (0.85; 0.93)

R₅ [cmH₂O·s/L] 3.5 (3.2; 3.7) 3.5 (3.14; 3.3)

z score R₅ 0.006 (−0.255; 0.269) −0.021 (−0.087; 0.141)

R₅,insp [cmH₂O·s/L] 3.0 (2.6; 3.3) 3.0 (2.3; 3.5)

R₅,esp [cmH₂O·s/L] 3.9 (3.6; 4.3) 4.2 (3.7; 4.9)

X₅ [cmH₂O·s/L] −0.9 (−1.2; −0.7) −1.2 (−1.5; −0.8)

z score X₅ 0.12 (−0.27; 0.57) 0.46 (0.13; 0.74)

X₅,insp [cmH₂O·s/L] −1.3 (−1.5; −0.9) −1.4 (−2.1; −0.9)

X₅,esp [cmH₂O·s/L] −0.7 (−1.0; 0.5) −0.7 (−1.1; −0.7)

|Z₅| [cmH₂O·s/L] 3.7 (3.4; 3.9) 3.7 (3.3; 4.6)

|Z₅| [cmH₂O·s/L] 3.3 (2.8; 3.7) 3.2 (3.0; 4.0)

|Z₅| [cmH₂O·s/L] 4.1 (3.8; 4.7) 4.3 (3.9; 5.4)

R₅,insp R₅,esp [cmH₂O·s/L] −0.9 (−1.4; −0.7) −1.0 (−1.5; −0.9)

FEV₁ fall 4.3 (2.2; 6.8) 6.1 (4.1; 15.1)

ΔR₅ [cmH₂O·s/L] 0.7 (0.3; 1.0) 1.3 (0.6; 1.8)

Δz score R₅ 0.4 (0.2; 0.5) 0.7 (0.2; 0.9)

ΔR₅,insp [cmH₂O·s/L] 0.6 (0.3; 0.9)* 1.2 (0.7; 1.3)

ΔR₅,esp [cmH₂O·s/L] 0.8 (0.4; 1.3) 0.8 (0.3; 2.1)

ΔX₅ [cmH₂O·s/L] −0.3 (−0.5; −0.03) −0.5 (−0.7; −0.3)

Δz score X₅ 0.5 (0.06; 0.9) 0.9 (0.5; 1.2)

ΔX₅,insp [cmH₂O·s/L] −0.4 (−0.6; −0.2) −0.7 (−0.9; −0.4)

ΔX₅,esp [cmH₂O·s/L] −0.2 (−0.5; −0.06) −0.5 (−0.7; −0.2)

Δ|Z₅| [cmH₂O·s/L] 0.7 (0.2; 1.0) 1.0 (0.1; 1.6)

Δ|Z₅| [cmH₂O·s/L] 0.7 (0.4; 0.9) 1.3 (0.5; 1.4)

Δ|Z₅| [cmH₂O·s/L] 0.9 (0.4; 1.3) 1.0 (0.5; 2.0)

max R₅,insp R₅,esp [cmH₂O·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, inhaled corticosteroid; LTRA, leukotriene receptor antagonists; max R₅,insp R₅,esp, maximal post-exercise value of R₅,insp R₅,esp R₅, respiratory resistance at 5 Hz; R₅,esp, expiratory R₅; R₅,insp, inspiratory R₅; SABA, short-acting beta agonists; X₅, respiratory reactance at 5 Hz; X₅,insp, expiratory X₅; X₅,esp, inspiratory X₅; Δ|Z₅|, maximal post-exercise change in |Z₅|; ΔX₅, maximal post-exercise change in X₅; Δz score R₅, maximal post-exercise change in z score of R₅; Δz score X₅, maximal post-exercise change in z score of X₅.

### TABLE 3 (Continued)

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; FEV₁, forced expiratory volume in 1s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonists; max R₅,insp R₅,esp, maximal post-exercise value of R₅,insp R₅,esp R₅, respiratory resistance at 5 Hz; R₅,esp, expiratory R₅; R₅,insp, inspiratory R₅; SABA, short-acting beta agonists; X₅, respiratory reactance at 5 Hz; X₅,insp, expiratory X₅; X₅,esp, inspiratory X₅; Δ|Z₅|, maximal post-exercise change in |Z₅|; ΔX₅, maximal post-exercise change in X₅; Δz score R₅, maximal post-exercise change in z score of R₅; Δz score X₅, maximal post-exercise change in z score of X₅.

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 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 EIO. Future studies should evaluate FOT parameters during or immediately after exercise in population-based settings.

ACKNOWLEDGEMENTS
Open Access Funding provided by Politecnico di Milano within the CRUI-CARE Agreement. [Correction added on 12-May-2022, after first online publication: CRUI-CARE funding statement has been added.]

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). Chiarter 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 (supporting); Methodology (equal); 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).

PEER REVIEW
The peer review history for this article is available at https://pubons.com/publon/10.1111/pai.13702.

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SUPPORTING INFORMATION

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

How to cite this article: Veneroni C, Pompilio PP, Alving K, et al. Self-reported exercise-induced dyspnea and airways obstruction assessed by oscillometry and spirometry in adolescents. Pediatr Allergy Immunol. 2022;33:e13702. doi:10.1111/pai.13702