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Original Research

Forced oscillatory technique R5-19 values correlate with spirometry FEV1/FVC in severe eosinophilic asthma. An observational, prospective, cohort study

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ABSTRACT

Introduction: Severe asthma affects 3–10 % of asthmatic patients. Biologic therapies can act as disease modifying agents in severe asthma. The prevalence of small airways dysfunction (SAD) increases with asthma severity. Forced Oscillatory Technique (FOT) is a reliable method for studying small airways. The aim of the study was to analyze FOT parameters in a cohort of eosinophilic severe asthma patients naïve of biologic therapy, and to describe the presence of correlation with spirometry data. Variations of FOT parameters after 6 and 12 months from the start of biologic therapy were also prospectively recorded and analyzed.

Methods: 47 severe eosinophilic asthma patients were consecutively enrolled. FOT, spirometry data, levels of asthma biomarkers, number of exacerbations, Asthma Control Test (ACT) were determined at baseline (T0: patients naïve of biologic treatment) and after 6 and 12 months.

Results: at T0, a significant linear correlation was found between R5-19 and FEV1/FVC (Forced expiratory volume in 1 s/Forced Vital Capacity) values ($p = 0.0008$). At T0, FOT R5-19 values were more elevated in obstructed patients. The cut-off value of R5-19 that best discriminates the presence of obstruction (FEV1/FVC <0.70) was determined at 0.81 $cmH_2O/(L/s)$ (sensitivity 0.58, specificity 0.76, ROC-AUC 0.67). A significant relationship was found between FEV1/FVC and FOT R5-19 also after 6 ($p = 0.007$) and 12 months ($p = 0.027$) of biologic therapy. No significant correlations were found between any other FOT parameter and blood eosinophils count, FeNO, number of exacerbations or ACT.

Conclusions: FOT R5-19 values correlate with FEV1/FVC and are significantly higher in obstruction. This correlation could be explained by the higher resistances of small airways in obstructed patients.

1. Introduction

Asthma is a global health problem, affecting 300 million people in the world, with a high prevalence in the economically developing countries. The disease is characterized by airway inflammation and hyper-responsiveness [1]. Severe asthma occurs when patients manifest persistent symptoms, frequent exacerbations and airway obstruction, which remains uncontrolled despite high-dose inhaled corticosteroids (ICS) and bronchodilators, or which require such therapy to prevent loss of control [2]. This condition significantly impacts patients' quality of life and morbidity, leading to chronic functional impairment and frequent hospital admissions. Unfortunately, severe asthma still affects a significant portion of asthmatic patients, ranging from 3 % to 10 %. The challenge in managing severe asthma lies in its clinical heterogeneity, with different phenotypes and underlying endotypes contributing to its complexity [2]. Growing evidence emphasizes the crucial role of the small airways in the pathophysiology of asthma as they are often involved in the inflammatory and remodeling processes of the disease and their dysfunction can contribute significantly to disease severity [3]. This is true not only for asthma but also in COPD, and research on small

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airways in obstructive diseases is growing [4]. The term "small airways" typically refers to the smaller bronchioles in the lungs, generally those with diameters less than 2 mm [5,6]. Small airway disease (SAD) in patients with asthma is the effect of chronic airway inflammation [7]. The contribution of SAD in determining the severity of asthma has been demonstrated in the ATLANTIS study, which concluded that 91 % of asthmatic patients exhibited involvement of the small airways [8]. The involvement of small airways in asthma is characterized by inflammatory processes, specifically an increased infiltration of eosinophils and lymphocytes. This inflammation contributes to remodeling in the airways, which manifests as thickening of the adventitial, submucosal, and muscular layers, along with alterations in the reticular basal membrane [9,10]. These structural changes can lead to significant airflow limitation and hyperresponsiveness, increasing airflow resistance, especially in severe asthma patients [8]. Several studies have identified the following factors as independent predictors of SAD in asthmatic patients: exercise-induced symptoms, overweight/obesity, nocturnal asthma symptoms, older age, smoking, and type-2 inflammation [11]. Despite their importance, small airways involvement is often under-recognized in routine clinical practice, as traditional pulmonary function tests, such as simple and global spirometry, primarily assess larger airways [6]. Given the limitations of conventional spirometry in detecting SAD, alternative diagnostic methods have been explored. Forced Oscillatory Technique (FOT) is a non-invasive tool that measures respiratory impedance and provides valuable information about airway resistance and reactance across different airway regions [12]. FOT has proven particularly useful in identifying SAD, especially in severe asthma, where early detection of changes in small airway function could inform treatment decisions and improve outcomes [13,14]. Among FOT parameters, the R5-19 parameter has been considered a good detector of small airways involvement, earlier than conventional spirometry can do [13]. R5-19 represents the difference between the resistance measured at lower frequencies (R5, 5 Hz), indicating total airway resistance, and the resistance measured at higher frequencies (R19, 19 Hz), reflecting the resistance of the central airways [15,16]. Therefore, it is a good predictor of the resistance associated with the small airways [17]. In the context of severe asthma, where patients often exhibit a poor response to standard therapies, the introduction of biologic drugs has revolutionized treatment strategies. However, not all patients respond equally to biologic treatments, and there is a growing need for biomarkers and diagnostic tools that can predict and monitor the response to treatment. Among the predictors of response to biological therapies, SAD has been highlighted as a significant factor [18]. The ability to assess small airways and their function through techniques like FOT could provide clinicians with early indicators of whether a patient is likely to benefit from biologic therapy. This is particularly valuable in tailoring treatments to individual patients, allowing for more personalized and effective management strategies, as demonstrated in prospective studies [18,19](18) [18]. Several investigations have explored the utility of FOT in monitoring the effects of biologic therapy. Chan et al. reported that the presence of abnormal peripheral airway resistance expressed as R5-R20 on FOT, was associated with a clinical response to biologic therapy [20]. Improvements in FOT parameters, particularly R5 and R20, have been observed earlier than spirometry following the initiation of Benralizumab in patients with severe eosinophilic asthma in some reports [21]. This suggests that FOT could be a more sensitive tool for detecting early improvements in airway function, providing clinicians with a valuable method for tracking the effectiveness of biologic therapies over time. Nonetheless, other reports stated that in real life setting of severe asthma patients, eosinophil depletion induced by Benralizumab, although improved spirometry and asthma control, did not reach the goal to improve SAD in terms both of oscillometry and spirometry measures [22]. Similarly, it has been demonstrated that FOT can be used to monitor the efficacy of Mepolizumab, correlating changes in FOT parameters with both eosinophil counts and asthma control scores [16]. Real-life effects of biologic therapies on FOT parameters have been investigated. Studies have shown that Dupilumab leads to significant improvements in small airway function in patients with severe asthma [23], as evidenced by FOT parameters such as R5-20 [24]. Particularly, Chan et al. demonstrated a superior efficacy of Dupilumab compared to Benralizumab on peripheral airway resistance and compliance using Oscillometry [25]. Furthermore, the repeatability of FOT measurements in patients receiving Benralizumab has been confirmed, establishing the reliability of this technique in assessing small airway function over time [21]. Recent reports supported the role on SAD exerted by the newly released biologic drug Tezepelumab. Menzella et al. reported that after 6 months of treatment with Tezepelumab, spirometry and FOT measures, improved only in patients with SAD [26]. Greig et al. conducted a real-life study on 15 asthmatic patients with SAD who exhibited significant improvements in R5-20 and compliance after treatment with Tezepelumab [27]. These studies highlight the potential of FOT not only as a diagnostic tool but also as a means of monitoring the long-term effects of biologic therapies in severe asthma. Despite the growing body of evidence supporting the use of FOT in asthma management, there is still a need for further research to validate its clinical significance in larger, more diverse patient populations. While FOT seems promising in detecting SAD and monitoring treatment response, its integration into routine clinical practice requires additional validation [13]. Moreover, the correlation between FOT parameters and traditional markers of obstruction at spirometry and other traditional asthma biomarkers, such as blood eosinophil counts and the fraction of exhaled nitric oxide (FeNO), needs further exploration. Blood eosinophils are a well-established biomarker of eosinophilic inflammation, while FeNO reflects airway inflammation associated with nitric oxide synthase activity [28]. Both markers have been linked to asthma severity and response to biologic therapy [29,30]. The integration of FOT with spirometry and biomarkers could provide a comprehensive view of treatment response and offer an effective method for long-term monitoring [31].

The aim of the study was to analyze FOT parameters in a cohort of eosinophilic severe asthma patients naïve of biologic therapy, and to describe the presence of any correlation with spirometry data. Moreover, any correlation between R5-19 values and other traditional asthma biomarkers have been evaluated. Variations of FOT parameters after 6 and 12 months from the start of biologic therapy were also prospectively recorded and analyzed.

2. Materials and methods

2.1. Population of the study

Severe eosinophilic asthmatic patients, naïve of biologic therapy, were consecutively enrolled from November 2021 to May 2024 in the Severe Asthma Outpatient Clinic of the ASST Santi Paolo e Carlo University Hospital in Milan – Italy (a tertiary referring hospital for severe asthma) as part of the Registry Severe Asthma Network in Italy, approved by the Local Institutional Review Board (IRB) with the number 2017/ST/246. All the patients signed an informed consent form approved by the Local IRB, compliant with the Italian legislation (Codex on Privacy, D.Lgs 30 giugno 2003, n.196). The data were prospectively stored in a dedicated Institutional database.

2.2. Variables collected and statistical analysis

After collection, the data were analyzed in this prospective, single-center, observational study. Demographic data, asthma biomarkers levels (peripheral blood eosinophils count, FeNO, serum total IgE), standard and biologic therapy together with FOT and spirometry values were recorded for all the enrolled patients. FOT were performed for all the patients by a dedicated Forced Oscillometer (Resmon Pro Full, Restech Srl, Milan – Italy). Pulmonary Function Tests including spirometry and body plethysmography were recorded with a dedicated

spirometer and body cabin plethysmography (Quark PFT and Q-Box, Cosmed, Rome – Italy). All the data were registered according to the manufacturer's instructions. The statistical tests used to verify the differences between R5-19 values at different time points are: 1) paired *t*-test for two repeated measures; 2) repeated measures ANOVA test for multiple repeated measures. These two types of statistical tests evaluate whether there are statistically significant differences in two (*t*-test) or more (ANOVA test) dependent samples, when variables are measured at different time points. To quantify the linear correlation between FOT R5-19 and the traditional obstructive-related parameter FEV1/FVC values at the different time points, the Pearson's correlation coefficient was computed. The Wilcoxon rank-sum test was used to compare the distributions of R5-19 values between patients with and without obstruction at each time point. Statistical significance was considered for each test in case p-values <0.05. Finally, the ROC-curve analysis and Youden's index was applied to identify cut-off values for R5-19 discriminating the presence of obstruction.

3. Results

3.1. Descriptive characteristics of the population

Forty-seven severe asthmatic patients naïve of biologic therapy were enrolled, of whom 23 males (48.9 %). Forty-four (93.6 %) patients were Caucasian, 2 were Hispanic and 1 was of African descent. The mean age at enrollment was 59.3 (±14.59) years. The youngest enrolled patient was 15 years old, while the oldest was 84 years old. The mean BMI of the population was 26.58. The majority of the patients (30; 63.9 %) had never smoked, 16 (34 %) were former smokers and only 1 (2 %) was an active smoker. Among current and former smokers, the mean of packs smoked per year was 16.47.

Mean blood eosinophils count at baseline was 476.33 (±603.89) cells/mm3, ranging from 20 to 2600 cells/mm3. Moreover, at enrollment, mean serum total IgE level was 276.73 (±248.27) UI/mL, while mean FeNO was 19.35 (±18.03) ppb. As for lung function, the baseline mean FEV1/FVC was 66.47 (±11.94).

As for asthma related comorbidities, 29 (61.7 %) patients showed hypersensitivity and allergy towards common inhalants, 24 (51.0 %) patients suffered from Gastro-esophageal reflux disease, 24 (51.0 %) had nasal polyposis, 16 (34.0 %) allergic rhinitis and 5 (10.6 %) chronic rhino-sinusitis without nasal polyposis (CRSsNP).

As for asthma medication, at enrollment 91.5 % of patients were treated with high doses of Inhaled Corticosteroids/Long Acting Beta 2 Agonists (ICS/LABA) (i.e. Beclometasone/Formoterol 200/6 mcg 2 inhalations twice a day or equivalent), while the remaining with medium doses ICS/LABA (i.e. Beclometasone/Formoterol 100/6 mcg 2 inhalations twice a day or equivalent). 65.9 % of patients were also treated with Long Acting Muscarinic Antagonists (LAMA) (i.e. Tiotropium 2.5 mcg 2 inhalations/day) and 29 (61.7 %) used chronically Leukotriene Receptor Antagonists (LTRA) (i.e. Montelukast 10 mg/die or equivalent). Interestingly, 80.1 % of patients (38) were free from oral corticosteroids (OCS), while 3 patients received 25 mg/day oral prednisone, the remaining 6 patients received low dose oral prednisone (5 mg/day). Noteworthy, the mean duration of OCS therapy during the 12 months before the enrollment was 31.77 days.

Despite at enrollment maximal inhaled therapy was active in all the patients, and in about 20 % of cases, oral corticosteroids too were part of the baseline asthma treatment, mean ACT at enrollment was 16.46 (±4.82), in accordance with a not enough controlled asthma.

Demographic characteristics are summarized in Table 1.

Table 1
Demographic and clinical characteristics of the cohort at baseline.

Clinical and demographic characteristics at baseline	
Enrolled patients	47
Mean (SD) Age, years	59.3 (14.59)
Female, n (%)	24 (51.1)
Ethnicity, n (%)	
* Caucasian	44 (93.6)
* Hispanic	2 (4.3)
* African	1 (2.1)
Mean (SD) BMI, kg/m2	26.58 (4.37)
Smoking history, n (%)	
* Never Smoker	30 (63.9)
* Former Smoker	16 (34)
* Current Smoker	1 (2.1)
Mean (SD) pack-years	16.47 (12.05)
Asthma related Comorbidities, n (%)	
* Allergy towards common inhalants	29 (61.7)
* Gastro-esophageal reflux disease	24 (51.0)
* Nasal polyposis	24 (51.0)
* Allergic rhinitis	16 (34.0)
* Chronic rhino-sinusitis without nasal polyposis	5 (10.6)
Mean (SD) Blood eosinophils count, cells/mm3	476.33 (603.89)
Mean (SD) serum total IgE level, UI/mL	276.73 (248.27)
Mean (SD) FeNO, ppb	19.35 (18.03)
Mean (SD) FEV1/FVC, %	66.47 (11.94)
Mean (SD) ACT, n	16.46 (4.82)
Inhaled Asthma therapy, n (%)	
* ICS/LABA high dosage	43 (91.5)
* ICS/LABA medium dosage	4 (8.5)
* LAMA	31 (65.9)
LTRA, n (%)	29 (61.7)
OCS, n (%)	9 (19.9)

3.2. Correlation analysis at baseline between FOT R5-19 and FEV1/FVC

The primary end point of the study was to evaluate if a linear correlation could be demonstrated between FOT R5-19 values at baseline and the values of FEV1/FVC (Forced expiratory volume in 1 s/Forced Vital Capacity) in the analyzed cohort. Pearson's correlation coefficient and the related p-values were computed. At T0 a significant linear correlation was found between R5-19 and FEV1/FVC values: $R^2 = -0.473$, CI 95 % (−0.669, −0.215); $p = 0.0008$ (Table 2).

3.3. Correlation analysis at baseline between FOT R5-19 and levels of asthma biomarkers and score

Further analyses were performed to test the presence of a correlation between FOT R5-19 and other asthma biomarkers (total IgE level, blood Eosinophils count, FeNO level). No linear correlation could be demonstrated neither between FOT R5-19 and other asthma biomarkers nor with one of the main scores adopted for the evaluation of Asthma control (namely the ACT – Asthma Control Test score) as described in Table 2.

3.4. Other correlation analysis at baseline

Finally, the correlation analysis was performed also for other two important FOT parameters (Expiratory X5 and Expiratory R5) and FEV1/FVC, total IgE level, blood Eosinophils count, FeNO level and ACT score, but no correlation could be demonstrated (Table 2).

Thus, considering as significant p-values <0.05, from the obtained results it is possible to state that there was a significant linear correlation only between R5-19 and FEV1/FVC values at baseline (Fig. 1).

3.5. FOT R5-19 distribution in presence or absence of obstruction

Patients were divided in two groups, according to the presence or absence of obstruction (defined as FEV1/FVC <0.70 at post-bronchodilator PFT) at baseline T0. Twenty-six (55.32 %) patients were obstructed at baseline. The comparison between FOT R5-19 in the two groups of patients with [26] and without [21] obstruction performed through the Wilcoxon rank-sum test showed a statistically significant difference in the two groups ($p = 0.048$), with a Median R5-19 of 0.87 $cmH_2O/(L/s)$ in patients with obstruction and a Median R5-19 of 0.33 $cmH_2O/(L/s)$ in patients without obstruction, and a median

Table 2
Correlation analysis at baseline: FOT R5-19. Expiratory X5 and Expiratory R5 were tested for correlation with FEV1/FVC, total IgE level, blood Eosinophils count, FeNO level and ACT score at baseline. There was a significant linear correlation only between R5-19 and FEV1/FVC values at baseline (p = 0.0008).

	Variable	Number of patients	Coefficient (95 % CI)	p-value
R5-19	ACT	47	−0.146 (−0.416, 0.148)	0.328
	FEV1/FVC	47	−0.473 (−0.669, −0.215)	**0.0008**
	IgE level	34	−0.147 (−0.462, 0.201)	0.408
	Eosinophils	44	−0.047 (−0.339, 0.253)	0.762
	FeNO	48	0.0003 (−0.287, 0.287)	0.998
expiratory X5	ACT	48	0.081 (−0.208, 0.357)	0.585
	FEV1/FVC	48	−0.037 (−0.317, 0.250)	0.805
	IgE level	34	0.168 (−0.180, 0.479)	0.342
	Eosinophils	44	0.027 (−0.272, 0.321)	0.864
	FeNO	48	0.173 (−0.117, 0.436)	0.239
expiratory R5	ACT	48	−0.060 (−0.339, 0.228)	0.684
	FEV1/FVC	48	−0.158 (−0.423, 0.132)	0.284
	IgE level	34	−0.165 (−0.476, 0.184)	0.352
	Eosinophils	44	0.125 (−0.179, 0.407)	0.419
	FeNO	48	−0.020 (−0.303, 0.265)	0.890

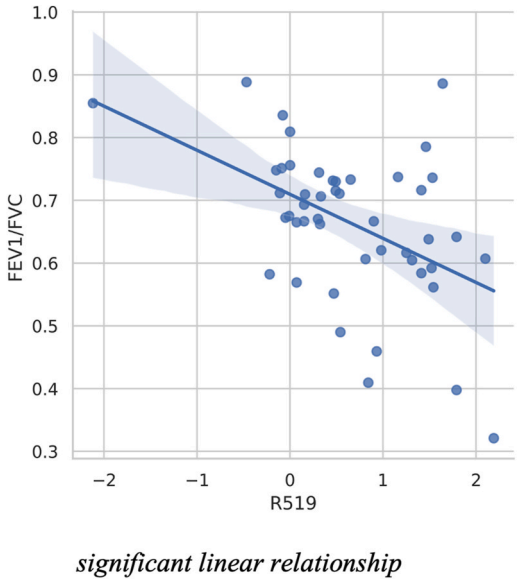


Fig. 1. Scatter Plot demonstrating the significant linear correlation between R5-19 and FEV1/FVC values at baseline at T0: coefficient of determination R^2 = −0.473, CI 95 % (−0.669, −0.215); p = 0.0008.

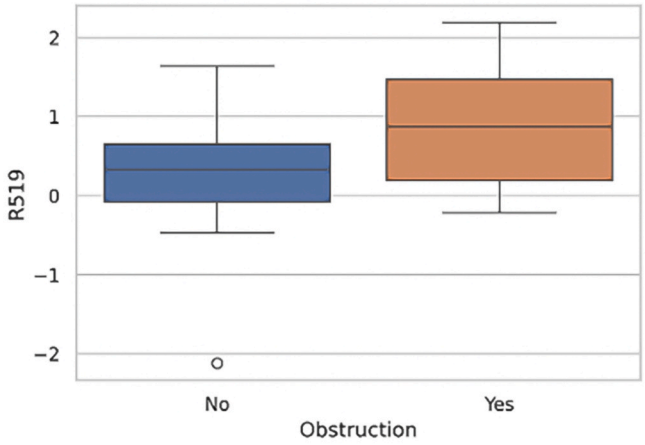


Fig. 2. Boxplot graphic of the median R5-19 values in the two groups of obstructed and not-obstructed patients at baseline. R5-19 values are expressed as $cmH_2O/(L/s)$.

difference of 0.54 $cmH_2O/(L/s)$ (Fig. 2).

The same test was applied for the comparison of expiratory X5 and R5 values in the two groups of obstructed and not-obstructed patients, without reaching a statistically significant difference.

The results of the analysis were summarized in Table 3.

3.6. ROC-curve and Youden's index analysis

Considering the significant linear correlation between FOT R5-19 and FEV1/FVC at baseline, though in the presence of a limited and preliminary number of observations, it was possible to identify the value of R5-19 that best discriminates the presence or absence of obstruction (defined as FEV1/FVC <0.70). For this purpose, a ROC-curve analysis was performed and Youden's index was computed.

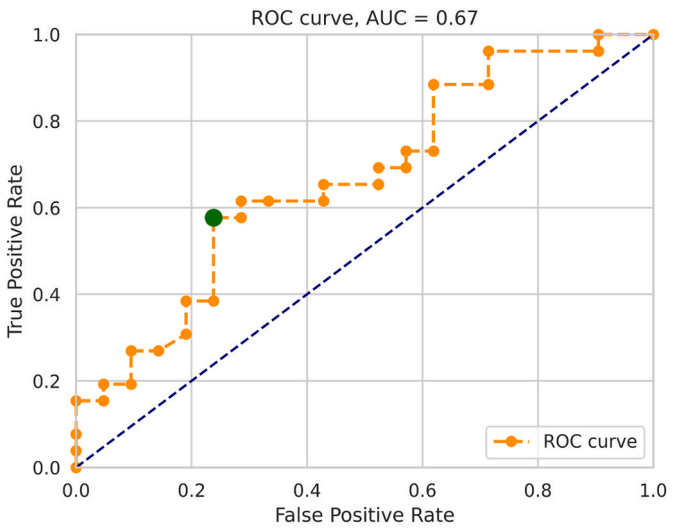
The cut-off value of R5-19 that best discriminated the presence of obstruction was determined at 0.81 $cmH_2O/(L/s)$ (sensitivity at cut-point 0.58, specificity at cut-point 0.76, ROC-AUC 0.67, positive likelihood ratio LR+ 2.42) (Fig. 3).

3.7. Correlation between FOT R5-19 and FEV1/FVC after 6 and 12 months of biologic therapy

The objective of this analysis was to quantify the correlation between FOT R5-19 and the traditional obstructive-related parameter FEV1/FVC values at the different time points after the start of biologic therapy: 6 months (T1) and 12 months (T2). To this end, the Pearson's correlation coefficient was computed between the R5-19 parameter and FEV1/FVC values at the corresponding time points. The obtained p-values indicate that the coefficient could be considered statistically significant both at 6 months T1 (p-value 0.007) and 12 months T2 (p-value 0.027) from the

Table 3
Statistical comparison (Wilcoxon rank-sum test) between FOT R5-19, expiratory X5 and expiratory R5 values in the two groups of patients with and without obstruction (defined as FEV1/FVC <70 %) at baseline. A significant difference was demonstrated in the two groups for FOT R5-19 only.

Parameter	N. of patients with obstruction over the total number	Median FOT parameter in patients with obstruction	Median FOT parameter in patients without obstruction	p-value
FOT R5-19	26/47 (55.32 %)	0.87	0.33	**0.048**
expiratory X5	26/47 (55.32 %)	−1.57	−0.96	0.071
expiratory R5	26/47 (55.32 %)	4.66	3.41	0.170



ROC-curve

Fig. 3. ROC-curve for the FOT R5-19 parameter: the cut-off value of R5-19 that best discriminated between obstructed and not-obstructed patients is 0.81 $cmH_2O/(L/s)$.

start of biologic drugs, independently from the administered biologic therapy, as shown in Fig. 4.

The same correlation analysis was performed for expiratory X5 and expiratory R5 without achieving statistically significant results. Table 4 includes the results of the correlation analysis for R5-19, expiratory X5 and expiratory R5.

4. Discussion

Severe asthma still affects a significant portion of asthmatic patients (3–10 %) and can be considered a health problem with a noteworthy social and economic impact [32]. In this sense, a thorough functional characterization of asthmatic patients is key in order to improve their management [33]. Today, t efforts for developing therapeutic strategies that could modify the history of the disease are of great relevance, with the hopeful aim of obtaining clinical remission [34].

In parallel, the development of efficient and easy to perform diagnostic tools represents a scientific challenge, with some potential goals

Table 4
Correlation analysis between FOT parameters and FEV1/FVC at 6 (T1) and 12 months (T2) from the start of biologic therapy: a significant relationship was found between FEV1/FVC and FOT R5-19 after 6 (T0 vs T1, p = 0.007) and 12 months (T0 vs T2, p = 0.027) of biologic therapy.

Parameter	Time point	Number of patients	Coefficient (95 % CI)	p-value
R5-19	T1	19	−0.598 (−0.828, −0.198)	**0.007**
	T2	14	−0.589 (−0.853, −0.085)	**0.027**
expiratory X5	T1	19	0.430 (−0.030, 0.740)	0.066
	T2	14	0.386 (−0.182, 0.761)	0.173
expiratory R5	T1	19	−0.223 (−0.615, 0.257)	0.358
	T2	14	−0.073 (−0.581, 0.476)	0.804

to be reached in the next future. To this end, FOT is a relatively recent technique with high potentiality among the respiratory function tests.

In this study, we have presented the original data derived from a prospective observational cohort study that was conducted in a tertiary care outpatient clinic for the diagnosis and treatment of severe asthma. Particularly, we focused on the possible correlation of FOT data with conventional spirometry data. For this purpose, we analyzed FOT parameters in a cohort of eosinophilic severe asthmatic patients naïve of biologic therapy, and we analyzed any correlation with spirometry data. Variations of FOT parameters after 6 and 12 months from the start of biologic therapy were also prospectively recorded and any significant variation was described.

We prospectively enrolled 47 patients, with a well-balanced proportion of the male/female ratio and a mean age of 59.3 years. The majority of the patients were never smokers or former smokers. This observation is in line with many other reports in the literature, including the ATLANTIS study, which was conducted on a significantly wider population (773 participants) [35]. This data could be interpreted considering the young age when respiratory symptoms appear in the asthmatic population, with the consequent reduced tendency to expose to inhalant toxics. Asthma is frequently associated with atopy and rhinitis, this can be observed in our cohort too, with most patients presenting comorbidities as allergic rhinitis or nasal polyposis.

FOT is a noninvasive method that allows to measure respiratory mechanics. The technique is based on the adoption of small-amplitude pressure oscillations which are superimposed on the tidal breathing. With respect to the conventional lung function techniques, FOT has the advantage that it does not require the performance of efforts dependent respiratory maneuvers [36].

In the literature, few studies focusing on the role of small airway

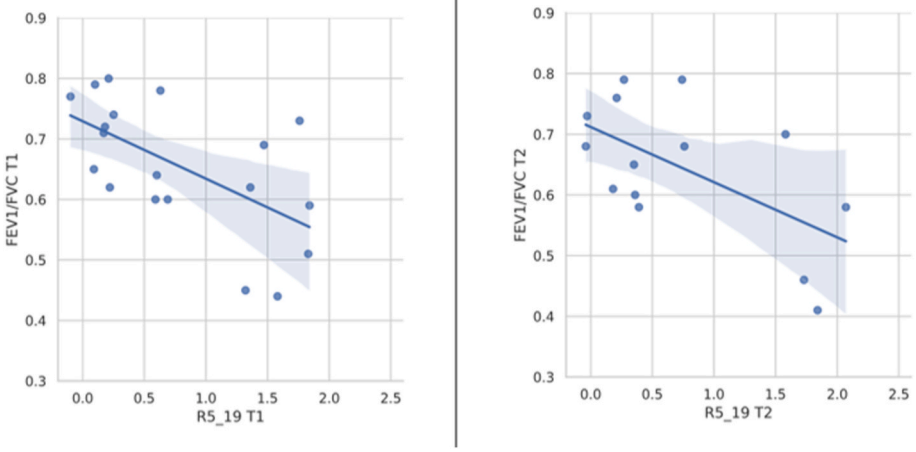


Fig. 4. Scatter Plot demonstrating the significant linear correlation between R5-19 and FEV1/FVC values at 6 months (T1) and 12 months (T2) from the start of biologic therapy. At T1, coefficient of determination $R^2 = -0.598$, CI 95 % (−0.828, −0.198), p = 0.007. At T2, coefficient of determination $R^2 = -0.589$, CI 95 % (−0.853, −0.085), p = 0.027.

disease in asthma had been performed and the majority of them was conducted on subgroups without complete physiological measurements or with a limited sample size. The widest study in the literature that tried to clarify the role of small airways disease in asthma was a large cross-sectional study with a longitudinal follow-up of the cohort for 1 year, namely the already cited ATLANTIS study [35]. The authors found a significant correlation between many FOT parameters and asthma exacerbations. Quite surprisingly, this correlation was not found in our cohort, probably because of the limited number of exacerbations occurred among the enrolled patients. Anyway, to the best of our knowledge, our study is the first specifically aimed at evaluating any significant correlation between FOT parameters and spirometry data in a cohort of severe eosinophilic asthmatic patients naïve of biologic therapy (cross-sectional phase of the study). Moreover, this is also the first report that considers the longitudinal variations of the FOT parameters after 6 and 12 months from the start of biologic therapy.

More in details, our study demonstrated that in univariate analysis a significant linear correlation can be found between FOT R5-19 parameter and the FEV1/FVC. FOT R5-19 values linearly increased for decreasing FEV1/FVC values. This finding can be interpreted considering that FEV1/FVC decreases in presence of obstruction, which is strictly related to the increase in airways resistance. Since the resistance parameters detected by FOT reflect airways resistance, the correlation we found could be thus justified.

Moreover, since the variation of resistances registered at 5 Hz and 19 Hz can give a reasonable estimate of the resistances determined by the small airways (namely, the terminal airways whose caliber is < 2 mm), our findings might help in unravelling the potential use of R5-19 in the evaluation of SAD. Indeed, R5-19 well correlated with the classic spirometry index of obstruction. Of notice, when stratified according to the presence or absence of obstruction (FEV1/FVC <0.70), a statistically significant difference in median R5-19 can be found. Obstructed patients showed median values of FOT R5-19 which were 0.54 $cmH_2O/(L/s)$ higher than not-obstructed patients. This result confirmed that FOT R5-19 is a good measure of airways resistances. Indeed, in presence of obstruction, which is characterized by elevated airways resistances, FOT can well detect higher values of resistance R5-19.

The linear correlation between FOT R5-19 and the FEV1/FVC ratio was confirmed when the maneuvers were repeated after 6 and 12 months from the start of a biologic therapy. This is a further confirmation that FOT could be a useful tool to prospectively monitor any modification of airway resistances, also after the initiation of a biologic therapy.

Although based on a limited number of patients and considering the single-center nature of the study, this work seems to demonstrate that FOT could be a useful instrument to integrate information on lung function obtained by classic spirometry. This study might trace the basis for future longitudinal multicentric studies aimed at determining if FOT could not only integrate spirometry, but even be considered a valid alternative to spirometry for evaluating airways resistances and the presence of SAD in selected cases when the patient is not able to adequately perform the classic spirometry maneuver.

Nonetheless, it would be advisable to conduct wide population studies to determine valid reference values to let FOT be routinely applied in clinic activity.

Finally, it could be of interest to evaluate if the results of this study could be reproducible also in the more general context of mild and moderate asthma.

5. Conclusions

FOT R5-19 values correlate with the FEV1/FVC ratio. Median values of R5-19 are significantly higher in presence of spirometry detected obstruction. This correlation could be explained by the higher resistances of small airways in obstructed patients.

CRediT authorship contribution statement

Claudio Tirelli: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Elena Maria Parazzini:** Writing – original draft, Supervision, Investigation, Data curation, Conceptualization. **Lucia Sacchi:** Methodology, Formal analysis. **Giulia Carone:** Writing – original draft, Investigation. **Francesca Pescol:** Formal analysis. **Sara Maggioni:** Investigation. **Luca Alessandro Belmonte:** Investigation. **Cristina Albrici:** Investigation. **Simone Contino:** Investigation. **Beatrice Re:** Investigation. **Benedetta Mosole:** Data curation. **Michele Mondoni:** Writing – review & editing, Supervision. **Stefano Centanni:** Writing – review & editing, Supervision, Investigation.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Local Institutional Review Board (or Ethics Commit-tee): number 2017/ST/246.

Data availability statement

Data are available by request to the corresponding author.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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