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Monitoring of respiratory resistance in the diagnosis of mild-intermittent asthma

Short running title: Variability of respiratory resistance in asthma

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To the Editor

The evidence of significant variability in lung function is required to confirm the clinical diagnosis of asthma [1]. This is commonly obtained in laboratory settings by bronchoreversibility or bronchoprovocation testing. Because the hallmark of asthma is the variability of symptoms, a more clinically relevant method to confirm the diagnosis should be by revealing an increase of spontaneous variability in lung function [1]. Studies using home measurements of peak expiratory flow (PEF) to monitor lung function consistently found a greater variability in asthmatic than healthy subjects, either within or between days, but with significant overlap between groups, which limits diagnostic accuracy [2]. Therefore, even if recommended by expert committees [1], PEF is not commonly used in clinical practice [3].

The forced oscillation technique (FOT) is an alternative lung function test conducted during quiet tidal breathing. In a pioneering study, Que et al. [4] found that the variability of respiratory impedance measured by FOT over 15 minutes was significantly greater in asthmatics than healthy subjects. This finding, however, was not confirmed by other studies using similar short-term FOT monitoring [5]. More recently, Gulotta et al. [6] found the day-to-day variability of inspiratory resistance (CVR_{insp}) self-measured at home by FOT be significantly greater in asthmatic than healthy subjects when calculated over non-overlapped periods ≥ 4 consecutive days and averaged over six months. However, whether CVR_{insp} identifies the presence of asthma in a clinical real-case scenario has not been reported yet. Therefore, we designed this prospective study to evaluate the predictive ability of FOT variability in identifying asthmatic subjects with mild-intermittent asthma in comparison with the recommended assessment of PEF variability.

Subjects with well-controlled mild-intermittent asthma [1] and healthy controls were eligible for this study. The diagnosis of asthma was based on a detailed medical history and confirmed by airway hyperresponsiveness, i.e., a provocative dose of methacholine causing a

20% decrease of $FEV_1 < 1,000 \mu g$. Exclusion criteria were smoking history > 5 pack-years, obesity, diabetes, other respiratory diseases, and current regular treatment with inhaled corticosteroids and/or long-acting beta-agonists. Healthy controls were non-smoker, non-obese subjects, without history of pulmonary disorders. The study was approved by the local Ethical Review Board (no. 50/2010) and all subjects gave written informed consent before the start of study.

At inclusion, subjects had spirometry measured according to ATS-ERS standards and respiratory resistance by a FOT device (Resmon PRO DIARY, Restech Srl, Italy) identical to those used thereafter by each individual for home monitoring [7]. Subjects collected daily FOT data at 5 Hz in the morning for two consecutive weeks, without prior bronchodilator use. For performing FOT measurements, subjects were asked to breathe spontaneously for two minutes while connected to the device by a mouthpiece, seated and with cheeks firmly supported by their hands. The day-to-day variability of inspiratory resistance (CVR_{insp}) was calculated over the fortnight period as previously described [6]. Briefly, for each study day, within-breath respiratory resistance was calculated from the ratio between mouth pressure and airflow tracings using the least-squares method [7] and the mid-inspiratory portions of the breaths without artifacts [8] were retained and averaged to obtain the mean inspiratory resistance (R_{insp}). CVR_{insp} (i.e. the day-to-day coefficient of variation of R_{insp}) was calculated from the resulting daily R_{insp} time-series as the ratio between the standard deviation and the mean of the available R_{insp} data over a prespecified time window (e.g. two weeks). Subjects also collected morning and evening PEF (myPEF, Vitalograph Ltd., UK), with morning measurements always obtained immediately after FOT measurements. The PEF variability ($varPEF$) was the difference between evening and morning measurements divided by their daily mean and averaged over the two weeks [1]. For direct comparison with CVR_{insp} , PEF

variability was also calculated with the same approach used for FOT measurements, i.e. as the coefficient of variation of morning measurements over the same two weeks (CV_{PEF}).

The sample size of the study was estimated by Cohen's d of 0.89, taken for varPEF from Higgins et al. [2]. After allowing for a 10% attrition rate, at least 24 subjects had to be enrolled in each group to ensure a study power of 80% with type-I error of 5%. Between-group differences were tested for significance by Fisher's exact test, t-test, or Mann-Whitney test, as appropriate. The optimal cutoff for CVR_{insp} to separate the two groups was determined in a 5-fold cross-validation procedure as the average of Youden's index maxima while the recommended 10% cutoff was taken as the optimal value for varPEF and CV_{PEF} [1]. Sensitivity, specificity and area under the ROC curve (AUC) were determined to estimate the predictive accuracy of CVR_{insp} , varPEF and CV_{PEF} in separating asthmatic from the healthy subjects. AUC were compared by z-test. Data were analyzed by Prism version 7.0e (GraphPad Software Inc., CA).

A total of 60 subjects were included in the study. Asthmatic ($n=35$) and healthy ($n=25$) groups were matched for anthropometric characteristics, while baseline FEV_1 and FEV_1/FVC were significantly lower, and R_{insp} significantly higher in the former (Table 1). Adherence to FOT and PEF measurements was $>80\%$ in both groups. No participant dropped out and no asthmatic subject experienced exacerbations during the monitoring period.

CVR_{insp} , but not varPEF or CV_{PEF} , was significantly higher in the asthmatic than healthy group (Figure 1A). The mean (95% confidence interval) accuracy (AUC) of CVR_{insp} in identifying asthmatics was 0.91 (0.85-0.97), significantly higher than varPEF (0.57 (0.40-0.75), $p<0.001$) and CV_{PEF} (0.51 (0.34-0.68), $p<0.001$; Figure 1B). At the calculated optimal cutoff of 0.10, CVR_{insp} provided a mean (95% confidence interval) sensitivity of 75 (60-87)% with 97 (84-100)% specificity. In comparison, varPEF and CV_{PEF} provided only 29 (13-51)%

and 18 (8-36)% sensitivity with 79 (54-94)% and 89 (69-98)% specificity, respectively, at the recommended cutoff [1]. Moreover, when calculated over one week only, the accuracy of CVR_{insp} (AUC=0.83 (0.74-0.92)) was still superior to fortnight varPEF or CV_{PEF} ($p=0.006$ and $p<0.001$, respectively), although slightly lower than when calculated over two weeks ($p=0.02$, Figure 1B).

In asthma, the airway caliber is modulated by complex interactions among intrinsic airway smooth muscle contractility, cholinergic tone, external triggers, and the milieu in which the airway smooth muscle operates. Fluctuations of these factors contribute to the variability of lung function and symptoms [9], which have been recognized as distinctive features of the disease. Therefore, it appears logical to use indexes of lung function variability over multiple days as objective tools for confirming the diagnosis of asthma and monitor its severity [10].

In the present study, we confirmed that daily self-administered FOT is feasible and suitable for the clinical assessment of the temporal variability of airway obstruction in mild-intermittent asthma, where objective confirmation is particularly important to confirm clinical diagnosis. When measured in a real-case scenario, CVR_{insp} , measured over one or two weeks, was significantly more sensitive, specific, and accurate than varPEF or CV_{PEF} measured over two weeks in separating asthmatics from healthy subjects. Possible reasons for the poor performance of PEF include limited reproducibility of unattended forced expiratory maneuvers without graphical display, which makes quality control difficult, and the need of a prior deep inspiration, which may have variable effects on airway caliber [11].

Even though further validation studies are warranted, these results support the view that FOT may become an accurate and rapid tool to document day-to-day variability of airway obstruction, thus possibly representing an additional diagnostic tool for asthma.

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Competing Interests

AG and RD own stocks of a spin-off company of the Politecnico di Milano University (Restech SRL) involved in the development and commercialization of FOT devices. The other authors have no conflict of interests to declare in relation to this study.

Authors contribution

A.G. participated in the conception and design of the study, data management, statistical analysis, interpretation of the data and preparation of the manuscript; C.G. participated in the

data collection, data management, and preparation of the manuscript; B.S. participated in the statistical analysis, interpretation of the data and preparation of the manuscript; E.M. Participated in the experimental activity and data analysis; R.P. and V.B. participated in the design of the study, interpretation of the data and in the preparation of the manuscript; R.D. participated in the conception and design of the study, data analysis, interpretation of the data and preparation of the manuscript.

Table 1. Main anthropometric and baseline lung function data.

	Asthma	Healthy	p
Sex (M/F)	17/18	17/8	0.19
Age (yr)	40 (17)	44 (14)	0.28
Weight (kg)	67 (11)	71 (15)	0.23
BMI (kg·m ⁻²)	23 (3)	24 (4)	0.39
FEV ₁ (L)	3.26 (1.04)	3.78 (0.86)	0.04
FEV ₁ (% predicted)	92 (16)	106 (11)	<0.001
FEV ₁ /FVC (% predicted)	95 (9)	104 (13)	<0.01
R _{insp} (cmH ₂ O·s·L ⁻¹)	3.77 (1.06)	2.51 (0.51)	<0.001

Data are mean (SD). BMI: body mass index; FEV₁: forced expiratory volume in 1 sec; FVC: forced vital capacity; R_{insp}: inspiratory resistance at 5Hz measured at enrollment visit.

Figure 1. Comparison between FOT variability (CVR_{insp}) and PEF variability ($varPEF$ and CV_{PEF}) in the asthmatic and healthy groups. (A) distributions of CVR_{insp} , $varPEF$ and CV_{PEF} over two weeks. Boxes and whiskers are the interquartile ranges and the 5th and 95th percentiles, respectively; the bands inside boxes are median values. (B) ROC curves for two-week CVR_{insp} (solid line), one-week CVR_{insp} (interrupted line), two-week $varPEF$ (dotted line) and two-week CV_{PEF} (solid-dotted line) for the identification of asthma. AUC is reported as mean value. Pairs of symbols indicate a statistically significant difference between AUCs. n.s.: not significant; *, \$, §: $p < 0.001$; ¶: $p = 0.006$; #: $p = 0.02$.

