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Small airway obstruction markers are stable over time and have potential as outcome measures in clinical trials http://ow.ly/tCzp2

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Bronchial obstruction and reversibility in children: inspiratory or expiratory resistance?

To the Editor:

Assessing bronchial obstruction and reversibility is of help in diagnosing asthma. The forced oscillation technique (FOT) has gained popularity in children since minimal cooperation is required. Owing to the fact

TABLE 1 Subject characteristics, baseline lung function and response to salbutamol

	Control	Asthma	p-value#
Subjects n	23	55	
Age years	7.8±1.8	8.1±1.5	NS
Height cm	130±14	129±9	NS
FEV1 z-score	0.6±1.1	0.3±1.0	NS
***R*rs,i hPa·s·L^{-1}**	6.3±1.7	8.8±3.1	<0.001
***R*rs,e hPa·s·L^{-1}**	6.8±2.0¶	10.0±3.9¶	<0.001
***R*rs,e-i hPa·s·L^{-1}**	0.6±0.8	1.2±1.5	0.07
Subjects n	20	53	
Δ*R*rs,i %	-18±11	-28±15	0.006
Δ*R*rs,e %	-10±15+	-23±16+	0.003

Data are presented as mean± SD, unless otherwise stated. FEV1: forced expiratory volume in 1 s; *R*rs,i: respiratory resistance during inspiration; *R*rs,e: respiratory resistance during expiration; *R*rs,e-i: difference between *R*rs,e and *R*rs,i; Δ*R*rs,i: change in respiratory resistance during inspiration after salbutamol; Δ*R*rs,e: change in respiratory resistance during expiration after salbutamol; NS: nonsignificant. #: control *versus* asthma; ¶: p<0.0001 *versus* inspiration; +: p⩽0.002 *versus* inspiration.

that measurements are performed during tidal breathing, the upper airway may significantly impact on the respiratory resistance (*R*rs) [1, 2]. The glottic aperture narrows during tidal expiration [3], contributing to *R*rs being larger than in inspiration [2, 4, 5]. Acute bronchial obstruction promotes further laryngeal narrowing [6–8], which is expected to impact the *R*rs measured during expiration. It is not known to what extent the mechanism is present in children with stable asthma, or whether the ability of *R*rs to diagnose bronchial obstruction and reversibility is impeded in expiration. With a single excitation frequency, *R*rs may be described along the respiratory cycle and computed in expiration (*R*rs,e) and inspiration (*R*rs,i). The aim of this study was to compare *R*rs,i and *R*rs,e, their response to salbutamol and respective ability to separate asthmatics from controls. The hypothesis was that the diagnostic value of *R*rs,e and its response to bronchodilator inhalation is impeded compared with *R*rs,i.

Patients with asthma were diagnosed in the local paediatric pulmonology clinic (Hôpital d'enfants, CHU de Nancy, Nancy, France). All had discontinued their bronchodilator therapy ⩾12 h prior to the study. Age-matched healthy children served as controls. Written informed consent was obtained and the study was approved by the Ethics Committee (Comité de Protection des Personnes EST III, CHU de Nancy, Nancy, France). Pressure was oscillated at 8 Hz around the child's head to minimise upper airway wall motion (Pulmosfor; SEFAM, Villers-lès-Nancy, France). The measured signals were displayed and quality-controlled at the end of the acquisition, and *R*rs,i and *R*rs,e were averaged separately. Subsequently, forced spirometry was performed (Masterscope; Erich Jaeger GmbH, Wuertzburg, Germany). Measurements were repeated 10 min after inhalation of 200 μg salbutamol (Ventoline; GlaxoSmithKline, Marly Le Roi, France). Data were compared using ANOVA and Fisher's t-test as needed. The ability of *R*rs,i, *R*rs,e and the percentage change in these values induced by salbutamol (Δ*R*rs,i and Δ*R*rs,e) to separate asthmatics and controls was tested by calculating, at relevant thresholds, the Youden index, which is the simple sum of sensitivity and specificity minus one. It ranges from -1 for a nondiagnostic test to +1 for the ideal test. Maximal values (Ymax), corresponding sensitivity, specificity and threshold are reported.

55 asthmatics (36 males) and 23 controls (10 males) entered the study. 27 were taking inhaled steroids. Age, height and forced expiratory volume in 1 s (FEV1) z-score [9] were similar between groups (table 1). Asthmatics showed significantly larger *R*rs,i and *R*rs,e (p⩽0.001) compared with controls. *R*rs,e was larger than *R*rs,i in both groups (p<0.001), but the difference between expiration and inspiration tended to be larger in asthmatics than controls (p=0.07) (table 1) and was negatively correlated with FEV1 z-score (r= -0.35, p<0.01). Ymax was larger for *R*rs,e than *R*rs,i (0.49 *versus* 0.46 at respective thresholds of 8.6 hPa·s·L^{-1} and 7.0 hPa·s·L^{-1}). The corresponding specificity was larger for *R*rs,e (0.87) than *R*rs,i (0.70), but sensitivity was lower (0.62 *versus* 0.76). Asthmatic children presented a larger response to salbutamol than controls by both *R*rs,i and *R*rs,e (p<0.007) (table 1). While the response was larger in inspiration than expiration (p<0.0001), Δ*R*rs,e showed a larger Ymax than Δ*R*rs,i (0.49 *versus* 0.37) at respective thresholds of -15% and -19%, with a corresponding better specificity (0.75 *versus* 0.65) and sensitivity (0.74 *versus* 0.72).

Altogether, the hypothesis that the ability of *R*rs to identify asthma would be less in expiration than inspiration was not verified. Larger *R*rs,e than *R*rs,i at baseline are in keeping with prior reports from the

literature [2, 4, 5]. Lung volume, a major determinant of airway resistance, would be unlikely to play a significant role, provided the time-triggered signal sampling did not bias the computation of tidal volume, due to asymmetry of breathing flow between inspiration and expiration. The fact that the difference between $R_{rs,e}$ and $R_{rs,i}$, obtained with similar digitisation protocols, is not regularly found during artificial ventilation through an endotracheal tube in adults [10] or infants [11] gives indirect support to a role for the upper airways.

Glottis narrowing during expiration [3, 5] increases the upper airway resistance, particularly the nonlinear component [2]. Similar glottis responses in patients and controls would tend to blunt the difference related to the bronchoconstriction. In fact, a trend for a larger difference between expiration and inspiration was observed in asthma *versus* controls, a difference that related to the degree of airway obstruction. An interpretation of these findings could be that glottis adduction occurred in such a manner that the R_{rs} difference relative to control was reinforced during expiration. In other words, the laryngeal constriction would relate to the airway obstruction in children with stable asthma, as previously reported in adults during acute spontaneous or induced asthma [6–8].

Y_{max} was larger for $R_{rs,e}$ than $R_{rs,i}$, suggesting the ability of FOT to separate controls from stable asthmatics was enhanced during expiration. Furthermore, the higher specificity of $R_{rs,e}$ suggests a better identification of patients, *i.e.* fewer false positive responses, than that of $R_{rs,i}$. Threshold values disclosed for $R_{rs,e}$ and $R_{rs,i}$ with the current set-up may not be extrapolated to other FOT variants, since varying pressure around the head has been shown to provide larger R_{rs} than for standard input impedance. In addition, minimising the upper airway artefact was probably helpful in sharpening the R_{rs} difference between expiration and inspiration.

Compared with $\Delta R_{rs,i}$, $\Delta R_{rs,e}$ provided better discrimination between patients and controls, improving specificity and sensitivity, suggesting the reflex relaxation of laryngeal adductors associated with the bronchodilation potentiated the magnitude of the overall response in asthma. Different decision levels have been previously reported for ΔR_{rs} [12]. The current 15% decrease with $R_{rs,e}$ is somewhat lower than the -30% R_{rs} cut-off reported by CALOGERO *et al.* [13], who used a standard input impedance device and estimated the threshold from the 95% confidence interval of healthy subjects in a large two-centre study, rather than from sensitivity–specificity analysis.

Finally, the potential of measuring $R_{rs,e}$ by varying pressure around the head and its response to 200 μg inhaled salbutamol in this cohort of children with stable asthma may not generalise to other conditions. In about half of the patients, inhaled steroids possibly had an indirect effect as a result of improving baseline obstruction, and a different picture might, thus, be observed in children with more severe bronchoconstriction or in response to a larger salbutamol dosage. In a completely different context, $R_{rs,i}$, rather than $R_{rs,e}$, was recommended in patients with chronic obstructive pulmonary disease, because expiratory flow limitation during tidal breathing is responsible for large R_{rs} swings [14] that result from the increase in airway impedance at the choke point [15].

We conclude that the ability of R_{rs} to separate asthmatic from healthy children is enhanced during expiration compared with inspiration, based on both measurement at baseline and assessment of response to bronchodilator. A likely mechanism relates to more pronounced expiratory glottis adduction in children with stable asthma compared with controls, reinforcing the group difference in $R_{rs,e}$ at baseline and in response to salbutamol. The expiration-related measurement improves specificity and appears to ease the identification of patients while decreasing the rate of false negative responses.

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Respiratory resistance assessment of bronchial obstruction: better asthma diagnosis in expiration than in inspiration http://ow.ly/uaMxS

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Job strain and COPD exacerbations: an individual-participant meta-analysis

To the Editor:

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and disability worldwide [1]. The clinical course of COPD is characterised by exacerbations, which can be minor and manageable at home or in primary care, or severe, leading to hospitalisation or even death. Known causes of exacerbations include tobacco smoke, air pollution, dusts and fumes, and respiratory infections [1, 2]. One less well understood risk factor is stress, which could plausibly lead to COPD exacerbations as it can trigger inflammation [3, 4] and is associated with increased smoking [5], which are both implicated in COPD pathology [2]. Work is an important source of stress in the age groups in which COPD is typically diagnosed [1, 6]. However, we are not aware of previous investigations of work-related stress and the risk of COPD exacerbations.

In this study, we examined the associations between job strain (the most widely studied conceptualisation of work-related stress) and severe COPD exacerbations using individual-level data from 10 prospective cohort studies from the Individual Participant Data Meta-analysis in Working Populations (IPD-Work) Consortium [7]. Job strain is defined as a combination of high demands (excessive amounts of work) and low control (having little influence on what tasks to do and how to carry them out) at work.

We ascertained job strain from the participants' responses to questions on demands and control aspects of their work at study baseline. The responses were scored and for each participant, and mean scores were calculated for job-demand items and job-control items. Based on these, participants' job demands and job control were defined as high or low. A combination of high demands (a job demand score above the study-specific median) and low control (job control score below the study-specific median) was defined as high