Bronchodilator response in FOT parameters in middle-aged adults from SCAPIS: normal values and relationship to asthma and wheezing

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To the Editor:

Forced oscillation technique (FOT) is a measure of respiratory impedance first described by DuBois more than 60 years ago [1]. Respiratory impedance (Z_{rs}) can be calculated by superimposing sound waves on normal tidal breathing without special breathing manoeuvres.

Response to bronchodilator in lung function parameters is clinically used to demonstrate exaggerated response to bronchodilators as part of the diagnostic workup of asthma, and to establish an underlying chronic airflow limitation. A recent European Respiratory Society (ERS) technical standards publication [2] recommended following thresholds for defining a positive bronchodilator response: −40% decrease in resistance at 5 Hz (R_5) and +50% increase in reactance at 5 Hz (X_5). However, as highlighted in the guidelines [2], more data on bronchodilator response in healthy subjects is needed, as only few studies have been performed in healthy adults [3–5].

The aim of our study was to define normal response to bronchodilator in R_5 and X_5 in healthy, never-smoking, Swedish individuals aged 50–64 years. A secondary aim was to compare thresholds for abnormal bronchodilator response in the present study with the ones proposed by the ERS technical standards and study these in relation to physician-diagnosed asthma and current wheeze.

In Uppsala, 5030 subjects participated (47% of all invited participants) in the population-based Swedish CArdioPulmonary bioImage Study (SCAPIS) [6] between October 2015 and June 2018. The present analysis is based on 3764 participants who additionally performed FOT measurements. The participants completed a questionnaire, including questions on smoking habits, respiratory disease and respiratory symptoms, described elsewhere [7]. This group is referred to as the "total population".

Reference values for bronchodilator response were generated in a subgroup of 1495 never-smoking participants that did not report physician-diagnosed asthma, physician-diagnosed COPD or emphysema, chronic bronchitis or any respiratory symptoms. This group is referred to as the "reference population".

Impulse oscillometry (IOS) is a modified oscillometric technique where an impulse, which can be mathematically decomposed into different frequencies, is transmitted [6].

The participants were instructed to withhold any inhalation medication prior to bronchodilation test, according to current clinical routines. The IOS (Jaeger MasterScreen IOS system; Jaeger, Würzburg, Germany) was performed before spirometry and both IOS and spirometry were repeated 15 min after four puffs of 100 µg salbutamol administered *via* spacer. Two 30 s interval recordings were performed during stable tidal breathing with the participant sitting, using a nose clip and with their cheeks supported to decrease the shunt compliance of the cheeks. The average values of R_5 and X_5 were recorded. Spirometry was performed according to the American Thoracic Society/ERS recommendations [8] using the Master Screen PFT (Hoechberg, Germany).

Shareable abstract (@ERSpublications)
New estimated useful thresholds for the bronchodilator response in oscillometry parameters in healthy adults. These thresholds are lower than those proposed by recent guidelines.
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STATA 14.2 (StataCorp, College Station, TX, USA) was used. Abnormal bronchodilator response was defined in the reference population as values above the 95th percentile, the upper limit of normal (ULN), for response in R_5, or by values below the 5th percentile, the lower limit of normal (LLN), for response in X_5.

A logistic regression model adjusted for forced expiratory volume in 1 s (FEV_1), age, sex, smoking status (never-, former-, current smoker) and body mass index groups (underweight, overweight and obese) was used to study the association between bronchodilator response above ULN for R_5 and below LLN for X_5 response, and the probability of presence of asthma and current wheeze in the total population. $p<0.05$ was considered significant.

SCAPIS has been approved as a multicentre study by the ethics committee, Umeå University (Dnr 2010-228-31M). The present analyses have been approved by the Swedish Ethical Review Authority (Dnr 2019-03416).

The total population comprised 3764 participants (52% females, mean age 57.6 years). The reference group comprised 1495 participants (46% females) of mean±SD age 57±4.4 years, mean height 173.9±9.9 cm, mean weight 79.4±15.1 kg mean baseline FEV_1 106.8±13.6% pred. A total of 4.2% of the participants in the reference group had a FEV_1/forced vital capacity ratio ⩽0.7.

The reference group mean (ULN) percent bronchodilatory reduction in R_5 was 10.2% (28.9%) and the mean (LLN) percent bronchodilatory change in X_5 was 14.9% (44.9%).

Participants with a percentage bronchodilatory reduction in R_5 above ULN had an approximately two-fold increase in prevalence of physician-diagnosed asthma and current wheeze compared with participants with normal response (17.4% *versus* 8.2%, 13.6% *versus* 5.3% respectively, both $p<0.001$). Similar increase in asthma and wheeze were seen in participants with a percentage bronchodilatory change below LLN in X_5 (14.9% *versus* 8.1%, 12.8% *versus* 5.8% respectively, both $p<0.001$).

These associations remained significant for bronchodilator reduction in R_5 >ULN after adjusting for confounding factors (OR 1.68, 95% CI 1.2–2.4). The association was significant for males (OR 2.45, 95% CI 1.5–4.0) but not for females (OR 1.14, 95% CI 0.57–1.9) and a significant interaction of the association with sex was found ($p=0.03$).

Comparing the thresholds for bronchodilator response in R_5 and X_5 in the present study with thresholds from ERS technical standards, we found that 82% of subjects with abnormal response in R_5 and 31.7% in X_5 according to our own defined thresholds would have been classified as within normal range. These participants had a higher prevalence of asthma and wheeze compared with participants with a normal response to bronchodilation (all p-values <0.05) (table 1). After adjusting for confounding factors, the association between bronchodilator response in R_5 above ULN and asthma remained significant (OR 1.51, 95% CI 1.01–2.26).

We defined in a large population of healthy, never-smoking, middle-aged adults thresholds for the normal bronchodilator response for resistance and reactance at 5 Hz. Bronchodilator responses above these thresholds were associated with asthma and wheeze in a population-based sample. Our defined thresholds differ from proposed thresholds from guidelines and having bronchodilator response between these thresholds related to a higher asthma prevalence.

TABLE 1 Comparisons of percentage decrease in bronchodilator response of R_5 with regard to study defined ULN and guidelines (28.9% and 40%, respectively) and percentage change in X_5 with regard to study defined LLN and guidelines (44.9% and 50%)

	R_5 decrease less than 28.9%, n=3476	R_5 decrease between 28.9% and 40%, n=237	R_5 decrease more than 40%, n=51	X_5 change above 44.9%, n=3493	X_5 change below 44.9%, but less than 50%, n=86	X_5 change more than 50%, n=185
Asthma	271 (7.8%)	34 (14.3%)	13 (25.5%)	281 (7.6%)	13 (15.1%)	24 (12.9%)
Current wheeze	186 (5.4%)	25 (10.5%)	14 (27.4%)	190 (5.2%)	10 (11.6%)	25 (13.5%)
FEV_1 baseline % pred	104.6±14.9	95.6±14.9	87.6±19.1	104.5±14.7	96.4±16.0	92.8±16.2

Data are presented as n (%) or mean±SD. R_5: resistance at 5 Hz; X_5: reactance at 5 Hz; ULN: upper limit of normal; LLN: lower limit of normal; FEV_1: forced expiratory volume in 1 s.

The current technical standards recommend a threshold for R_5 reduction of 40%, largely based on data from studies in children [2]. Our results suggest that in adults this threshold could be lowered, as the 95th percentile of the reduction for R_5 was 29% in our study and this value is close to the value from Oostveen *et al*. [5], where the FOT technique was used in 368 adults (18–80 years old) and a threshold of 32% was found. The corresponding number for X_5 was 45% in the present study, also in line with Oostveen *et al*. [5], where 44% was reported [5], but lower than the proposed threshold from the current technical standards of 50% [2]. Future studies should further differentiate between children and adults regarding reference threshold values.

In this general population we found an abnormal response in R_5 to be associated with physician diagnosed asthma and current wheeze. This pattern was consistent after adjusting for FEV_1 and confounding variables. Our findings are consistent with previous results as individuals with asthma have demonstrated larger response in resistance and reactance in relation to bronchodilation compared with healthy subjects [9, 10].

Our thresholds for R_5 and X_5 were below the ones suggested by the current guidelines [2]. We could demonstrate that in a relatively large proportion of subjects have responses in-between these cut-offs in the present study and these participants had higher proportion of asthma and current wheeze. This suggests that defining bronchodilator response thresholds has practical consequences with potential clinical implications.

Our study is the largest single study defining normal values for the response to bronchodilator of resistance and reactance in healthy adults. A further strength was the possibility to test the bronchodilator responses above these values in relation to asthma and wheeze in a population-based sample. However, the narrow age range (50–64 years old) limits to some extent the generalisability.

In conclusion, our study estimated useful thresholds for the response in oscillometry parameters to bronchodilators and suggests that the current thresholds used in the literature, mainly based on studies in children, could be adjusted to some extent to lower levels, increasing the number of subjects characterised as having significant response to bronchodilation and potentially having clinical implications.

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Conflict of interest: H. Johansson has nothing to disclose. P. Wollmer reports personal fees from Chiesi Pharma, outside the submitted work; and has a patent Device and method for pulmonary function measurement issued. J. Sundström reports ownership in companies providing services to Itrim, Amgen, Janssen, Novo Nordisk, Eli Lilly, Boehringer, Bayer, Pfizer and AstraZeneca, outside the submitted work. C. Janson has nothing to disclose. A. Malinovschi has nothing to disclose.

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