Small airway dysfunction is an independent dimension of wheezing disease in preschool children

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Abstract

Background. Whether small airway dysfunction (SAD), which is prevalent in asthma, helps to characterize wheezing phenotypes is undetermined. The objective was to assess whether SAD parameters obtained from impedance measurement and asthma probability are linked. Methods. One hundred and thirty-nine preschool children (mean age 4.7 years, 68% boys) suffering from recurrent wheeze underwent impulse oscillometry that allowed calculating peripheral resistance and compliance of the respiratory system (markers of SAD) using the extended RIC model (central and peripheral Resistance, Inertance and peripheral Compliance of the respiratory system). Children were classified using the probability-based approach of GINA guidelines (few, some, most having asthma). A principal component analysis (PCA) that determined the dimensions of wheezing disease evaluated the links between SAD and asthma probability. Results. Forty-seven children belonged to the few, 28 to the some and 64 to the most having asthma groups. Whereas their anthropometrics and measured parameters were similar, the most having asthma group exhibited the lowest mean value of airway inertance after bronchodilator probably due to airway inhomogeneities. PCA characterized nine independent dimensions including a peripheral resistance (constituted by baseline peripheral resistance, AX, R5-20Hz, X5Hz), a central resistance (baseline central resistance, R20Hz) and an airway size dimension (post-bronchodilator inertance and central resistance). PCA showed that the SAD markers were independent from clinical dimensions (control and asthma probability were two other dimensions) and did not help to define wheezing phenotypes. Conclusions. Lung function parameters obtained from impulse oscillometry and asthma probability were belonging to independent dimensions of the wheezing disease.

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Running title: Small airway dysfunction in wheezers

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Methods. One hundred and thirty-nine preschool children (mean age 4.7 years, 68% boys) suffering from recurrent wheeze underwent impulse oscillometry that allowed calculating peripheral resistance and compliance of the respiratory system (markers of SAD) using the extended RIC model (central and peripheral Resistance, Inertance and peripheral Compliance of the respiratory system). Children were classified using the probability-based approach of GINA guidelines (few, some, most having asthma). A principal component analysis (PCA) that determined the dimensions of wheezing disease evaluated the links between SAD and asthma probability.

Results. Forty-seven children belonged to the few, 28 to the some and 64 to the most having asthma groups. Whereas their anthropometrics and measured parameters were similar, the most having asthma group exhibited the lowest mean value of airway inertance after bronchodilator probably due to airway inhomogeneities. PCA characterized nine independent dimensions including a peripheral resistance (constituted by baseline peripheral resistance, AX, R5-20Hz, X5Hz), a central resistance (baseline central resistance, R20Hz) and an airway size dimension (post-bronchodilator inertance and central resistance). PCA showed that the SAD markers were independent from clinical dimensions (control and asthma probability were two other dimensions) and did not help to define wheezing phenotypes.

Conclusions. Lung function parameters obtained from impulse oscillometry and asthma probability were belonging to independent dimensions of the wheezing disease.

Key words: airway compliance; airway resistance; asthma; impulse oscillometry; wheezing

Introduction

In a recent systematic review for the European Academy of Allergy and Clinical Immunology, the clinical practice recommendations on diagnostics of preschool wheeze stated that it is difficult to establish guidelines for monitoring asthma in preschool children.(1) Lung function measurement is an essential tool in the differential diagnosis of preschool wheezing, although reliable lung function measurements are challenging in this age group and the diagnosis value of functional tests remains debated.(1) This issue is important given the possible underestimation of asthma prevalence in preschool children.(2) On the other hand, wheeze has been associated with prescriptions of asthma medications in young children, which could lead to inappropriate and too high prescription rate of inhaled corticosteroids.(3)

We recently showed that small airway dysfunction (SAD: increased peripheral resistance and decreased peripheral compliance of the respiratory system) was an almost constant finding in asthmatic children with increased interrupter resistance.(4) One may hypothesize that SAD markers obtained from a more sensitive method than spirometry, namely impulse oscillometry,(5–7) could be linked to asthma probability.

Several wheezing phenotypes coexist at preschool age but not all preschoolers with recurrent wheezing develop asthma at school-age; the asthma diagnosis still needs to be based on clinical predicted models or scores.(8) A probability-based approach, based on the pattern of symptoms during and between viral respiratory infections, is given in GINA guidelines that classifies the wheezing phenotypes of childhood.(9) We thus evaluated the ability of IOS indices to differentiate these wheezing phenotypes.

Methods

This cross-sectional study complied with The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. Consecutive preschool children aged 3 to 6 years referred for the first assessment of their wheezing disease were enrolled. These children were suffering from persistent wheeze (symptoms began before the age of 3 years and continued) or late-onset wheeze (symptoms began after the age of 3 years). The children were belonging to the "few" (<3 episodes per year of symptoms [cough, wheeze, heavy breathing] for < 10 days during upper respiratory tract infections and no symptoms between episodes) or "some" or "most" (>3 episodes per year of symptoms [cough, wheeze, heavy breathing] for > 10 days during upper respiratory tract infections and between episodes symptoms) having asthma patterns described in GINA guidelines.(9) As compared to the group "some", the group "most" having asthma was defined by the presence of allergic sensitization or family history of asthma. Therapeutic steps (1 to 4) and control assessment were those defined in GINA guidelines.(9) Adequate withdrawal of beta-agonist before testing was an additional inclusion criterion. Severe exacerbation definition was defined by the need of at least three days of oral steroid.

This study was approved by our local Ethics Committee (PHENOBS: N° 2018-430). The parents were informed of the collection of the prospective data for research purposes and they could request that their child to be exempted from this study in accordance with French law (non-interventional observational research).

Pulmonary function tests

Interrupter resistance (Rint) was measured using SpiroDyn'R apparatus (Dyn'R Ltd, Toulouse, France), as previously described.(4) Z-scores of Rint were calculated according to Merkus et al.(10)

Impedance of the respiratory system was measured using an impulse oscillatory system (IOS: Master Scope Body, Carefusion Technologies, Yorba Linda, California, USA), as previously described.(4) We used the following IOS variables: impedance at 5, 10, 15, 20, 25, 30 and 35 Hz, resistance and reactance at 5 Hz and 20 Hz, fall in resistance between R5 and R20 (R5-20Hz), area under the reactance curve (AX) and resonance frequency (Fres). Z-scores of IOS variables were calculated according to Gochicoa-Rangel et al.(11)

Rint and IOS measurements were obtained at baseline and after salbutamol (400 µg) administration using an inhaler device.

We used two mechanistic models capable of accounting for significant frequency dependence of the respiratory impedance, which have previously been described.(4) Airway inertance Iaw is included in the RIC model as compared to the simple RC circuit (Resistance of the airways and Compliance of the alveoli). The RIC model with proximal shunting describes the effect of cheeks (proximal compliance) that could affect impedance measurement (measurement bias). In the extended RIC model, eRIC, R is partitioned in central (Rc) and peripheral (Rp) resistance of the respiratory system, while Cp is the peripheral compliance of the respiratory system (including parenchymal and chest wall compliances). Thus, SAD is characterized by Rp and Cp. The model was fitted to the impedance data (5–35 Hz) and the minimization of a performance index allowed the calculation of model parameters, as previously done.(4) To determine the relative appropriateness of the various inverse model topologies, we used the corrected Akaike information criterion, as previously done.(4)

Statistical analyses

Principal component analysis (PCA) is a mathematical procedure that uses an orthogonal transformation to convert a set of observations of possibly correlated variables into a set of values of uncorrelated variables called principal components (dimensions). We performed PCA of 27 variables (the minimal number of subjects providing usable data for the analysis should be five times the number of variables being analysed), using orthogonal varimax rotation. Results were expressed as mean ± SD. Intergroup comparisons were made using t tests (two groups) or ANOVA (three groups), before and after salbutamol conditions were compared using paired t test. A P value < 0.05 was deemed significant. Statistical analyses were performed with StatView 5.0 (SAS institute, Cary, North Carolina, USA) and OpenStat (version 5) softwares. Due to the exploratory design of the study, no correction for multiplicity of testing was done.(12)

Results

One hundred and sixty asthmatic children were enrolled of whom 12 children were excluded because the coherence of impedance measurements was unsatisfactory (coherence 5Hz < 0.60 or 20Hz <0.80) and 9 children were excluded because their impedance spectra were better fitted by the RIC model with proximal (upper airway) shunting. The remaining 139 children who were adequately fitted by the extended RIC model are described in Table 1 (clinical characteristics) and Table 2 (functional characteristics). The Figure 1 shows the impedance spectra obtained by fitting the model. Whereas the results of IOS measurements were similar (almost normal lung function after bronchodilator), some modelled parameters were significantly different after bronchodilation (inertance and peripheral compliance) between the three groups. The most having asthma group exhibited both the highest value of mean peripheral compliance and the lowest mean value of airway inertance after bronchodilator. This group was also characterized by more frequent recent severe exacerbations.

Bronchodilator response based on R5Hz decrease correlated weakly with Rint response (r=0.20, p=0.002) and with Rp response (r=0.15, p=0.019), and mainly with Rc response (r=0.63, p<0.0001). All modelled parameters, with the exception of Iaw, were significantly different after bronchodilator: Rc, p=0.0001; Cp, p=0.0055; Rp, p=0.0096.

Twenty-nine children were premature ([?]36 weeks of gestational age); they were characterized by increased baseline z-score of Rint (2.05 +- 1.61 versus 1.50 +- 1.23, p=0.032), z-score of X5Hz (0.68 +- 2.51 versus -0.28 +- 1.39, p=0.002) and Rp (1.04 +- 0.43 kPa.s/L versus 0.86 +- 0.28 kPa.s/L, p=0.003) as compared to non-premature children. After bronchodilation, the z-score of X5Hz (-0.55 +- 1.44 versus -1.43 +- 1.29, p=0.0008) and Rp (0.95 +- 0.46 kPa.s/L versus 0.77 +- 0.43 kPa.s/L, p=0.042) remained higher in premature children.

The Figure 2 shows the results of PCA using the 27 variables. Communality of all variables was $> 60\%$ (with the exception of post-BD peripheral resistance) and 73.8% of the total variance was explained by the factors (all factors had Eigenvalues > 1). The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.651.

Nine dimensions were found, some groupings of variables were expected such as anthropometrics (age, height: dimension 3), wheezing control (controlled versus uncontrolled and recent severe exacerbation: dimension 7) and asthma probability (wheezing patterns and therapeutic steps: dimension 4). Markers of SAD (peripheral resistance and compliance of the respiratory system) belonged to two different dimensions (dimension 1 and 8, respectively) that were independent from the clinical dimensions (wheezing control and asthma probability). A peripheral resistance (constituted by baseline peripheral resistance, AX, R5-20Hz, X5Hz and Rint, dimension 1), a central resistance (baseline central resistance and R20Hz, dimension 2) and a post-bronchodilator airway characterization (post-bronchodilator inertance, peripheral compliance and central resistance, dimension 5) were evidenced. The dimension 6 describes mainly full term boys, with elevated BMI z-score and early wheezing. The dimension 8 is constituted of children born prematurely of non-Caucasian origin.

Discussion

The main result of our cross-sectional study in preschool wheezers is to show that lung function parameters obtained from impulse oscillometry and asthma probability were belonging to independent dimensions of the wheezing disease.

Previous classifications of wheezing phenotypes (such as episodic wheeze and multiple-trigger wheeze) do not appear to identify stable phenotypes,(13) and their clinical usefulness is uncertain, as stated in GINA 2020 guidelines.(9) These guidelines recommend the use of a probability-based approach.(9)

The studies evaluating the oscillometric technique's ability to classify lung function in wheezing and healthy children have been contradictory. Depending on the patient selection, both significant differences(14) and lack of differences(15,16) have been reported. Subtle changes have been observed in the small airway indexes of IOS among children with mild to moderate recurrent wheezing.(17) Several studies have suggested that IOS parameters could be more sensitive than spirometry to diagnose asthma in children.(5,6) Finally, we recently showed that SAD was almost constant in young asthmatics exhibiting an increased interrupter resistance.(4) Based on this background, one may have supposed that IOS and additional modelling of SAD markers may have differentiated the three groups of wheezers defined on asthma-probability.

Among the three groups of wheezers, the most having asthma group was characterized by more recent severe exacerbations requiring oral steroid, which may seem expected in a group mainly constituted of asthmatic children. This group depicted the lower baseline interrupter resistance, which could be related to the higher proportion of asthmatics, responding to inhaled corticosteroid treatment (high dose for 59/64 children). IOS parameters were similar among the three groups, showing a slight mean basal impairment (for instance, mean z-score of R5Hz value of +1.46 in the whole population, with a mean z-score of post-bronchodilator of +0.12, almost normal). Thus, in contradiction with our hypothesis, conventional IOS parameters were not able to differentiate these three wheezer groups, which may be related to the presence of asthmatic children into the three groups. Malmberg and colleagues showed better results for R5Hz and its bronchodilator response in identifying preschool children with probable asthma, but their groups were different from ours (treated asthma, probable asthma, chronic cough and healthy children).(15) By contrast, some parameters obtained from the eRIC model were significantly different among the three groups. Inertance is proportional to the length and inversely proportional to the cross-sectional area of the airways. The group with the highest probability of asthma had the smaller post-bronchodilator inertance; this result may seem counterintuitive since asthma has been associated with reduced peripheral airway caliber. This observation could be explained by the virtual decrease of inertance due to augmented airway inhomogeneities.(18) This group also had a higher compliance of the peripheral respiratory system that may favor ventilation inhomogeneity, a finding that has previously been evidenced in wheezing children having had a recent exacerbation.(19) This higher respiratory system compliance may have been related to either increased airway(20) or tissue compliance(21) that have been evidenced in asthma.

Reduced lung function in early infancy is predictive of persistent asthma in young adults and a persistent reduction in lung function, suggesting abnormal lung development and growth in utero or very early in life.(22) Preterm birth is associated with increased risks of asthma symptoms in childhood. The underlying mechanism seems to include persistently higher airway resistance.(23) We thus evaluated IOS measurements in premature versus non-premature children, showing that even after bronchodilation, the respiratory reactance and peripheral resistance remained higher in premature children, which further validate the parameters obtained from the eRIC model.

The main findings of our study are evidenced in Figure 2. We first confirm that AX, R5-20Hz and X5Hz are related to SAD since these parameters belonged to the same dimension than peripheral resistance of the respiratory system. Rint belonged to this dimension also, which is consistent with our previous results(4) and the previously reported high sensitivity of Rint in asthmatic children.(24) A proximal resistance dimension was also evidenced that included R20Hz and central resistance. Proximal and distal resistances were independent dimensions of wheezing disease. As previously evidenced in childhood asthma,(25) control, severity (treatment) and lung function were independent dimensions of the wheezing disease also. The ATLANTIS study showed that SAD is present across adult patients with all severities of asthma.(26) In this latter study,

the levels of statistical correlations between IOS parameters and severity or control were mild (maximum r value of 0.25 and 0.23 for the number of exacerbations and GINA score, respectively).(26) Thus, our results in wheezing children are in agreement with those obtained in adult asthmatics. Asthma probability was an independent dimension of wheezing disease, which may explain the difficulty to predict asthma in this population.(8,9) Importantly, SAD markers were not linked to this asthma probability.

One may have hypothesized that an increased airway tone (reduced compliance) would have been associated with reduced airway caliber (increased resistance). Nevertheless, peripheral compliance and resistance belonged to two independent dimensions (dimensions 8 and 1, respectively). Peripheral resistance is related to both airway anatomy and smooth muscle contraction, which may explain the absence of correlation. Reduced peripheral airway caliber in asthmatics is well known.(27) Moreover, both a decrease and an increase in airway distensibility have been described in asthma.(20,28) It has to be highlighted that peripheral compliance of the respiratory system is related to airway but also tissue compliance. Increased pulmonary compliance has recently been described in some asthmatic children that is associated with increased static volumes.(21)

The other dimensions that were evidenced further suggest the validity of the PCA. Gestational age was linked to ethnicity in the ninth dimension, a fact that is well demonstrated.(29) The sixth dimension regrouped sex, z-score of BMI and persistent wheezing that could be in agreement with the "fat happy wheezer" phenotype in boys.(30)

Our study has some limitations. The included children were unable to perform spirometry, whether the children with abnormal Rint or IOS parameters had normal or abnormal spirometry cannot be assessed. Given the absence of follow-up of the children, asthma diagnosis cannot be assessed confidently since bronchodilator reversibility may be observed in other children during their follow-up. Nevertheless, our study was designed to assess the usefulness of the cross-sectional assessment by IOS parameters, which belonged to other dimensions than the clinical ones.

In conclusion, the characterization of SAD by IOS gives parameters independent from clinical dimensions in wheezing preschool children that does not help to define wheezing phenotypes of Global Initiative for Asthma guidelines in a cross-sectional design.

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Impact statement, Key Message

Impulse oscillometry does not help to predict asthma in wheezing preschool children. Lung function is an independent dimension of wheezing disease, as shown in asthma.

Author Contributions

Conceptualization: PB and CD2; Formal analysis: PB, CD2; Investigation: PB, DM; Methodology: PB, FA, VH; Project administration: CD2, FA, VH; Supervision: CD2, FA, VH; Validation: PB, CD2; Roles/Writing - original draft: PB, CD2; Writing - review &editing: DM, FA, VH.

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Table 1. Clinical characteristics of the wheezing children.

Characteristics Whole population Few having asthma Some having asthma Most having asthma P value Intergroup

comparisons

Number of children 139 47 28 64

ethnicity, C / B / A / M 90/37/6/6 32/13/1/1 16/9/1/2 42/15/4/3 0.797

gestational age, weeks 38 +- 3 38 +- 3 38 +- 4 38 +- 2 0.500

sex (male, %) 94 (68) 34 (72) 18 (64) 42 (66) 0.692

age, years 4.7 +- 0.8 4.7 +- 0.8 4.7 +- 0.8 4.7 +- 0.8 0.926

height, cm 108.3 +- 7.4 108.7 +- 8.3 107.7 +- 5.8 108.2 +- 7.4 0.700

weight, kg 19.3 +- 3.9 19.6 +- 4.4 18.7 +- 3.3 19.3 +- 3.9 0.584

BMI z-score 0.40 +- 1.33 0.44 +- 1.42 0.18 +- 1.48 0.47 +- 1.20 0.542

persistent wheeze, n (%) 101 (73) 32 (68) 23 (82) 46 (72) 0.410

personal atopy (positive skin prick test) , (n tested) 53 (120) 13 (33) 0 40 (59) ND

rhinitis, n (n available) 45 (129) 12 (43) 5 (28) 28 (58) 0.011 1,2<3

eczema, n (n available) 49 (124) 17 (40) 4 (28) 28 (56) 0.006 2<1,3

parental asthma, n (n available) 50 (130) 12 (41) 0 38 (61) ND

parental atopy, n (n available) 58 (114) 12 (37) 12 (27) 34 (50) 0.003 1,2<3

Asthma control

GINA score, 0 / 1 / 2 / 3 / 4 (past month) 64/20/24/17/14 22/8/5/6/6 16/4/4/3/1 26/8/15/8/7 0.655

controlled / uncontrolled, n 64/75 22/25 16/12 26/38 0.340

severe exacerbation within last three months, n (%) 39 (28) 10 (21) 4 (14) 25 (39) 0.023

Asthma treatment

beta-agonist on demand only (inhaled treatment), n 48 41 1 0 ND 2=3

low ICS dose, n 2 0 1 1 ND 2=3

medium ICS dose, n 7 0 3 4 ND 2=3

high ICS dose, n 82 0 23 59 ND 2=3

LABA, n 42 0 11 31 ND 2=3

LTRA, n 24 0 10 14 ND 2=3

Therapeutic steps

1 / 2 / 3 / 4 47/6/47/39 47/0/0/0 0/2/17/9 0/4/30/30 ND

BMI denotes body mass index, BD denotes bronchodilator, ICS notes inhaled corticosteroid, LABA denotes long-acting beta-agonist, LTRA denotes leukotriene receptor antagonist

Ethnicity: C denotes Caucasian, B denotes African-American, A denotes Asian and M denotes mixed

Results are provided as mean +- SD or absolute number with percentage (%)

Table 2. Functional characteristics of the wheezing children.

Characteristics Whole population Few having asthma Some having asthma Most having asthma P value Intergroup

comparisons

Number of children 139 47 28 64

Resistance and impedance measurements

Rint, z-score before BD 1.49 +- 1.30 1.83 +- 1.36 1.69 +- 1.36 1.14 +- 1.16 0.033 1,2>3

Rint, z-score after BD 0.06 +- 1.10 0.24 +- 1.15 0.39 +- 1.24 -0.21 +- 0.93 0.054

Coherence 5Hz, before BD 0.76 +- 0.08 0.78 +- 0.09 0.75 +- 0.08 0.75 +- 0.07 0.141

Coherence 20Hz, before BD 0.94 +- 0.04 0.94 +- 0.05 0.94 +- 0.04 0.94 +- 0.04 0.977

Coherence 5Hz, after BD 0.73 +- 0.07 0.74 +- 0.08 0.72 +- 0.08 0.72 +- 0.07 0.444

Coherence 20Hz, after BD 0.92 +- 0.04 0.92 +- 0.04 0.92 +- 0.04 0.92 +- 0.04 0.846

R20Hz, z-score before BD 1.08 +- 1.65 0.92 +- 1.28 1.21 +- 1.91 1.215+- 1.78 0.706

R20Hz, z-score after BD 0.39 +- 1.52 0.20 +- 1.69 0.59 +- 1.61 0.45 +- 1.35 0.517

R5Hz, z-score before BD 1.46 +- 2.13 1.16 +- 1.83 1.93 +- 2.72 1.47 +- 2.04 0.245

R5Hz, z-score after BD 0.12 +- 1.60 -0.07 +- 1.68 0.54 +- 1.72 0.08 +- 1.48 0.269

R5-20Hz, z-score before BD 1.01 +- 2.31 0.75 +- 2.08 1.54 +- 2.85 0.96 +- 2.21 0.261

R5-20Hz, z-score after BD -0.24 +- 1.45 -0.33 +- 1.36 0.17 +- 1.50 -0.37 +- 1.48 0.234

X5Hz, z-score before BD -0.28 +- 1.58 -0.12 +- 1.46 -0.22 +- 1.66 -0.41 +- 1.63 0.838

X5Hz, z-score after BD -1.60 +- 1.29 -1.52 +- 1.55 -1.45 +- 1.22 -1.74 +- 1.10 0.525

AX, z-score before BD 0.78 +- 2.31 0.73 +- 2.54 0.79 +- 1.82 0.81 +- 2.36 0.722

AX, z-score after BD -0.87 +- 1.44 -0.85 +- 1.55 -0.43 +- 1.37 -1.09 +- 1.37 0.136

Fres, z-score before BD 0.10 +- 1.80 -0.12 +- 1.40 -0.06 +- 2.06 0.33 +- 1.94 0.144

Fres, z-score after BD -0.91 +- 1.29 -0.99 +- 1.23 -0.45 +- 1.46 -1.06 +- 1.24 0.102

eRIC model indices

Performance Index before BD 0.045 +- 0.056 0.046 +- 0.062 0.061 +- 0.071 0.037+- 0.042 0.169

corrected AIC before BD -70 +- 11 -70 +- 11 -66 +- 12 -72 +- 11 0.066

Performance Index after BD 0.041 +- 0.054 0.033 +- 0.024 0.042 +- 0.045 0.047 +- 0.071 0.439

corrected AIC after BD -72 +- 12 -72 +- 9 -70 +- 11 -72 +- 14 0.752

Rc, kPa.s/L before BD 0.75 +- 0.16 0.74 +- 0.14 0.76 +- 0.16 0.75 +- 0.17 0.872

Rc, kPa.s/L after BD 0.70 +- 0.16 0.69 +- 0.17 0.70 +- 0.14 0.71 +- 0.16 0.738

Iaw, cPa.s2/L before BD 111 +- 42 110 +- 41 112 +- 46 112 +- 41 0.986

Iaw, cPa.s2/L after BD 116 +- 36 124 +- 32 122 +- 33 108 +- 40 0.044 1,2>3

Cp, mL/kPa before BD 84 +- 135 91 +- 151 87 +- 129 75 +- 113 0.769

Cp, mL/kPa after BD 108 +- 147 74 +- 72 90 +- 156 141 +- 185 0.040 1,2<3

Rp, kPa.s/L before BD 0.93 +- 0.29 0.98 +- 0.29 0.93 +- 0.29 0.90 +- 0.28 0.363

Rp, kPa.s/L after BD 0.81 +- 0.53 0.79 +- 0.45 0.87 +- 0.52 0.80 +- 0.60 0.829

Bronchodilator response, %

R5Hz decrease, % baseline 14 +- 15 14 +- 16 13 +- 13 15 +- 16 0.606

Results are provided as mean +- SD. BD denotes bronchodilator. AIC denotes Akaike Information Criterion

Results in italic are quality criteria of impedance measurement or model fitting

Figure legends

Figure 1. The impedance spectra obtained by fitting the model.

Respiratory system resistance (A) and reactance (B) obtained by fitting the model (thick solid lines) to the prebronchodilator data of the experimental measurements represented by the median values and the 25th and 75th percentiles for each frequency.

Figure 2. Results of the principal component analysis.

PCA shows factors which have very high (red to brown, positive values or blue colors, negative values) or very low (green color) loadings for the original variables and thus simplifies the interpretation of the resulting factors. Each single dimension is characterized by the variables with high loadings (red and blue colors).

The 27 variables were: 1 ethnicity (0 Caucasian), 2 age, 3 sex (0 female), 4 height, 5 z-score of BMI, 6 gestational age, 7 persistent wheezing (0 absent, 1 present), 8 severe exacerbation within previous 3 months (0 absent, 1 present), 9 GINA therapeutic steps (1 to 4), 10 probability (1 few, 2 some, 3 most having asthma), 11 control (0 controlled versus 1 uncontrolled based on GINA score), 12 baseline Rint, 13 baseline Fres, 14 baseline AX, 15 baseline R5Hz, 16 baseline X5Hz, 17 baseline R20Hz, 18 baseline R5-20Hz, 19 baseline Rc, 20 baseline Iaw, 21 baseline Cp, 22 baseline Rp, 23 post-BD Rc, 24 post-BD Iaw, 25 post-BD

Cp, 26 post-BD Rp, 27 BD response based on R5Hz. Raw values of pulmonary function parameters were used in the PCA.

SAD denotes small airway dysfunction, BD denotes bronchodilator.