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Respiratory mechanics and peripheral airway inflammation and dysfunction in asthma

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Summary

Background Clinical application of the forced oscillation technique (FOT) has progressed with the spread of commercially available FOT devices. The correlation between respiratory impedance and spirometry has been reported; however, the association with airway inflammation and pulmonary function, in the lung periphery in particular, is unclear.

Objective To assess whether respiratory impedance is associated with peripheral airway inflammation and dysfunction in asthma.

Methods Subjects included 78 patients with overall controlled asthma. We measured whole-breath or within-breath respiratory system resistance (Rrs) and reactance (Xrs) using a commercially available multi-frequency FOT device (MostGraph-01), and assessed the correlation with the fraction of exhaled nitric oxide (FeNO), alveolar nitric oxide concentration (CANO), maximal NO flux in the conductive airways (J'awNO), and the N₂ phase III slope of single breath N₂ washout (delta N₂).

Results The differences between inspiratory and expiratory phases of Xrs at 5 Hz (X5), resonant frequency (Fres), and a low-frequency reactance area (ALX) were significantly correlated with CANO; however, there was no correlation between respiratory impedance and FeNO or J'awNO. The delta N₂ values were significantly correlated with whole-breath, inspiratory, and expiratory Rrs and Xrs, except for R20.

Conclusions and Clinical Relevance We conclude that respiratory impedance reflects peripheral airway inflammation and ventilation inhomogeneity.

Keywords alveolar nitric oxide, forced oscillation technique, multi-frequency, ventilation inhomogeneity

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Introduction

The forced oscillation technique (FOT) is a non-invasive method with which to measure respiratory impedance, the spectral relationship between pressure and airflow [1]. The real part of impedance is called respiratory system resistance (Rrs), whereas the imaginary part is called respiratory system reactance (Xrs), which is supposed to reflect elastic and inertial properties of the lung. Forced oscillations are superimposed on tidal breathing, avoiding the need for any special breathing manoeuvre or noticeable interference with respiration. Recently, clinical application of the FOT has progressed with the spread of commercially available FOT devices, including the impulse oscillation system [2] and MostGraph [3]. Increasing numbers of reports have examined the usefulness of the FOT in the evaluation or

management of obstructive diseases, including, chronic obstructive pulmonary disease (COPD) or asthma [4–7]. The correlation between respiratory impedance and spirometry in asthma has been reported; however, the association of respiratory impedance with airway inflammation and pulmonary function, in particular, in the lung periphery, is not fully understood [8, 9].

In this cross-sectional study, we examined the association of respiratory impedance with peripheral airway inflammation and function in patients with asthma.

Methods

Subjects

Seventy-eight patients with asthma who attended outpatient clinics at Shizuoka General Hospital for routine

check-ups between June 2010 and October 2011 were enrolled in this study. All patients satisfied the definition of asthma of the Global Initiative for Asthma [10] and had been receiving inhaled corticosteroids with or without other medications, including long-acting β_2 -agonists, leukotriene receptor antagonists, or sustained release theophylline for at least 6 months. Patients were excluded from the study if they [1] had had any acute viral infections within at least 1 month before the study; [2] were current smokers, had a smoking history of > 10 pack-years, or had quit smoking within 1 year prior to the study; and [3] had COPD. In patients with obstructive impairment ($FEV_1/FVC < 70\%$), high-resolution CT or diffusing capacity for carbon monoxide of the lung was performed to exclude COPD (emphysema). Applicable patients underwent a high-resolution CT scan (Aquilion; Toshiba, Tokyo, Japan) and lack of a focal region of low attenuation without visible walls was confirmed. The diffusing capacity of the lung for carbon monoxide was measured using the CHESTAC-33 (CHEST MI) by the single-breath method and the result was divided by the alveolar volume. Values > 80% predicted were considered normal.

Thirty-nine healthy control subjects without pulmonary diseases were recruited from our hospital staff. The protocols were approved by the local ethics committee (approval number: SGH 11-07-13) and informed consent was obtained from all patients prior to the study.

Respiratory impedance

On the examination day, the patients underwent testing for respiratory impedance, FeNO, and pulmonary function tests in that order. Short-acting β_2 agonists were not used for more than 12 hours before these tests in every case.

Respiratory impedance was measured with FOT using a commercially available device (MostGraph-01; Chest M.I., Co. Ltd., Tokyo, Japan) [8, 9] and met standard recommendations [1]. Impulse oscillatory signals generated by a loud speaker at intervals of 0.25 s were applied to the respiratory system through the mouth-piece during tidal breathing at rest. The mouth pressure and flow signals were measured and calculated to obtain Rrs and Xrs properties against oscillatory frequency ranging from 5 to 35 Hz. During measurements, the subjects supported their cheeks firmly to reduce upper airway shunting while sitting with their neck in a comfortable neutral posture. We used Rrs at 5 and 20 Hz (R5 and R20 respectively), and the difference between R5 and R20 (R5–R20) as an indicator of the frequency dependence of Rrs, which is supposed to reflect inhomogeneous ventilatory mechanics [11]. We also used Xrs at 5 Hz (X5), which reflects elastic and inertial properties of the lung, resonant frequency (Fres)

where Xrs crosses zero and the elastic and inertial forces are equal in magnitude and opposite, and a low-frequency reactance area (ALX) which is the integral of Xrs at 5 Hz to the Fres. Each oscillatory index was expressed as the mean values during a respiratory cycle (whole breath), inspiratory and expiratory phases, and the differences between inspiratory and expiratory phases (Δ).

Fraction of exhaled NO

The fraction of exhaled NO levels (FeNO) was measured by an online method at a flow of 50 mL/s using an NO analyzer (Sievers NOA 280i; GE Analytical Instruments, Boulder, CO, USA) according to the American Thoracic Society/European Respiratory Society recommendations [12]. Four exhalation flow rates (100, 150, 200, and 250 mL/s) in addition to 50 mL/s were used and alveolar NO concentration (CANO) and maximal NO flux in the conductive airways (J'awNO) were calculated according to the two-compartment model of Tsoukias and George [13] and the trumpet-shaped airways and axial diffusion model of Condorelli et al. [14].

Pulmonary function tests

Spirometry and, to assess ventilation inhomogeneity, nitrogen single-breath washout tests were performed using computerized equipment (model CHESTAC-33; CHEST MI, Inc., Tokyo, Japan) according to the standards of the American Thoracic Society [15]. FEV₁, FEV₁/FVC, and FEF_{25–75%} were determined. The N₂ phase III slope of single-breath N₂ washout (ΔN_2) was calculated as previously described [16].

Statistical analysis

Categorical data were summarized as counts, and quantitative data were summarized as the mean $\pm$ SD. The Spearman rank correlation coefficient was used to assess pair-wise associations between quantitative outcome variables. Stat View Version 5.0 (SAS Institute, Cary, NC, USA) was used for statistical calculations. A *P*-value of < 0.05 was considered significant, and all tests were two sided.

Results

The clinical characteristics of the subjects are shown in Table 1. The mean Asthma Control Test score of 23.5 indicates that the studied population of this study was overall controlled. The results of whole-breath and within-breath analyses of respiratory impedance are shown in Table 2. Greater values were found in the expiratory than in the inspiratory phases, suggesting respira-

Table 1. Characteristics of the subjects

	Asthma	Controls
Age (years)	52 ± 16	47 ± 10
Gender (male/female)	39/39	20/19
Body mass index (kg/m ²)	24.2 ± 6.8	21.9 ± 3.2
Ex/never smoker	43/35*	13/26
Duration of asthma (years)	20.7 ± 17.7	NA
Coexisting nasal disease	53*	17
Asthma Control Test score	23.5 ± 2.3	NA
FeNO (p.p.b.)	53.2 ± 44.0*	23.8 ± 13.9
CANO (p.p.b.)	6.39 ± 6.32*	3.23 ± 3.51
J'awNO (nL/s)	3.87 ± 4.34*	1.58 ± 1.20
FEV1 (L)	2.31 ± 0.75*	3.26 ± 0.80
FEV1 (% predicted)	82.5 ± 17.5*	99.1 ± 10.2
FEV1/FVC (%)	73.2 ± 12.5*	84.9 ± 5.8
FEF25-75% (% predicted)	52.4 ± 29.5*	80.8 ± 17.7
Delta N ₂ (%N ₂ /L)	1.78 ± 1.30*	0.95 ± 0.34

*P < 0.05 vs. controls.

Values are the means ± SD or numbers.

CANO, alveolar NO concentration; FEF25-75%, forced expiratory flow between 25% and 75% of FVC; FeNO, fraction of exhaled NO; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; J'awNO, maximal NO flux in the conductive airways; NA, not applicable; NO, nitric oxide.

tory cycle dependence. There were significant differences in exhaled NO parameters, pulmonary function, and respiratory impedance between patients with asthma and controls. Correlations between respiratory impedance and exhaled NO associated parameters in patients with asthma are shown in Table 3. The differences between inspiratory and expiratory phases of X5, Fres, and ALX were significantly correlated with CANO. There was also a weak correlation between the difference between inspiratory and expiratory phases of ALX and FeNO; however, there was no other correlation between respiratory impedance- and exhaled NO-associated parameters. If we add normal controls to the patients with asthma and give greater ranges of pulmonary function and inflammatory markers, there is no correlation between CANO and Rrs or Xrs parameters other than the differences between inspiratory and expiratory phases of X5, Fres, and ALX. Correlations between respiratory impedance and pulmonary function tests are shown in Table 4. Overall, the %FEV1, FEV1/FVC, and %FEF25-75% values were significantly correlated with Rrs or Xrs parameters. The delta N₂ values were also significantly correlated with whole-breath, inspiratory, and expiratory R5, R5-R20, X5, Fres, and ALX.

Discussion

We assessed the association of respiratory impedance with peripheral airway inflammation and function in patients with asthma. We demonstrated that the differences between inspiratory and expiratory phases of Xrs

Table 2. Whole-breath and within-breath analyses of respiratory impedance

	Asthma	Controls
R5 (cmH ₂ O/L/s)		
Whole breath	4.37 ± 1.48*	2.90 ± 0.98
Inspiratory	3.89 ± 1.28*	2.50 ± 0.79
Expiratory	4.85 ± 1.79*	3.30 ± 1.26
ΔR5	-0.97 ± 0.91	-0.79 ± 0.75
R20 (cmH ₂ O/L/s)		
Whole breath	3.53 ± 1.02*	2.55 ± 0.63
Inspiratory	3.32 ± 0.97*	2.36 ± 0.57
Expiratory	3.73 ± 1.11*	2.73 ± 0.75
ΔR20	-0.41 ± 0.43	-0.37 ± 0.46
R5-R20 (cmH ₂ O/L/s)		
Whole breath	0.84 ± 0.58*	0.36 ± 0.52
Inspiratory	0.56 ± 0.52*	0.15 ± 0.43
Expiratory	1.12 ± 0.77*	0.57 ± 0.64
Δ(R5-R20)	-0.56 ± 0.61	-0.42 ± 0.33
X5 (cmH ₂ O/L/s)		
Whole breath	-0.83 ± 0.94*	-0.37 ± 0.35
Inspiratory	-0.69 ± 0.63*	-0.39 ± 0.33
Expiratory	-0.97 ± 1.40*	-0.35 ± 0.39
ΔX5	0.28 ± 1.08	-0.04 ± 0.20
Fres (Hz)		
Whole breath	9.39 ± 4.12*	7.17 ± 2.27
Inspiratory	8.89 ± 3.32*	7.06 ± 1.82
Expiratory	9.90 ± 5.28*	7.29 ± 2.90
ΔFres	-1.00 ± 3.16	-0.23 ± 1.70
ALX (cmH ₂ O/L/s x Hz)		
Whole breath	4.85 ± 7.93*	1.51 ± 1.68
Inspiratory	3.31 ± 3.92*	1.47 ± 1.40
Expiratory	6.39 ± 12.92*	1.56 ± 2.08
ΔALX	-3.08 ± 10.64	-0.09 ± 1.13

*P < 0.05 vs. controls.

Values are the means ± SD.

ALX, integrated low-frequency reactance area; Δ, difference between inspiratory and expiratory phases; X5, respiratory system reactance at 5 Hz; R5 and R20, respiratory system resistance at 5 Hz and 20 Hz; Fres, resonant frequency.

were significantly correlated with CANO, but not FeNO or J'awNO, while whole-breath, inspiratory, and expiratory Rrs and Xrs were significantly correlated with ventilation inhomogeneity expressed as delta N₂ values.

The correlation between respiratory impedance and pulmonary function has been reported. Cavalcanti et al. found that more severely obstructed patients with asthma showed elevated values of Rrs and increasing levels of frequency dependence of Rrs [17]. Also, we showed that there were weak or moderate correlations between Rrs and Xrs values and FEV1 and FEV1/FVC [7], which were confirmed in this study again; however, very few investigators have examined the association of respiratory impedance with airway inflammation, especially in peripheral airways. Matsumoto et al. found weak correlations between CANO levels and prebronchodilator R5-R20 ($r = 0.35$), X5 ($r = -0.31$) and ALX

Table 3. Correlations between respiratory impedance and exhaled NO-associated parameters

	FeNO	CANO	J'awNO
R5 (cmH ₂ O/L/s)			
Whole breath	0.032	-0.073	0.006
Inspiratory	0.055	-0.013	0.006
Expiratory	0.034	-0.091	0.017
ΔR5	0.024	0.200	-0.036
R20 (cmH ₂ O/L/s)			
Whole breath	0.021	-0.043	0.003
Inspiratory	0.020	-0.035	-0.011
Expiratory	0.028	-0.069	0.027
ΔR20	0.055	0.136	0.011
R5-R20 (cmH ₂ O/L/s)			
Whole breath	0.058	-0.067	0.012
Inspiratory	0.065	0.013	0.008
Expiratory	0.045	-0.109	0.011
Δ(R5-R20)	-0.011	0.197	-0.077
X5 (cmH ₂ O/L/s)			
Whole breath	0.033	0.056	0.051
Inspiratory	-0.072	-0.076	-0.068
Expiratory	0.073	0.171	0.073
ΔX5	-0.202	-0.410*	-0.100
Fres (Hz)			
Whole breath	-0.022	-0.045	-0.037
Inspiratory	0.053	0.096	0.031
Expiratory	-0.054	-0.135	-0.062
ΔFres	0.146	0.371*	0.053
ALX (cmH ₂ O/L/s x Hz)			
Whole breath	-0.027	-0.059	-0.049
Inspiratory	0.066	0.081	0.058
Expiratory	-0.069	-0.159	-0.072
ΔALX	0.236*	0.421*	0.115

* $P < 0.05$.

Values are Spearman rank correlation coefficients.

ALX, integrated low-frequency reactance area; CANO, alveolar NO concentration; Δ, difference between inspiratory and expiratory phases; FeNO, fraction of exhaled NO; Fres, resonant frequency; J'awNO, maximal NO flux in the conductive airways; NO, nitric oxide; X5, respiratory system reactance at 5 Hz; R5 and R20, respiratory system resistance at 5 Hz and 20 Hz.

($r = 0.35$), and bronchodilator reversibility of X5 ($r = -0.24$) and ALX ($r = -0.31$), but no association with FeNO or J'awNO levels in patients with stable asthma [8]. Williamson et al. also found weak correlations between CANO and R5-R20 ($r = 0.24$), and between FeNO and R5-R20 ($r = 0.24$) and Fres ($r = 0.27$) in patients with asthma or COPD [9]. Both of these studies expressed respiratory impedance only as whole-breath analyses, but not as within-breath analyses.

In this study, within-breath changes, that is, the differences between inspiratory and expiratory phases of X5, Fres, and ALX (ΔX5, ΔFres, and ΔALX respectively) were significantly correlated with CANO ($r = -0.410$, 0.371, and 0.421 respectively). Previous studies have indicated that within-breath changes of Xrs measured

Table 4. Correlations between respiratory impedance and pulmonary function tests

	%FEV1	FEV1/FVC	%FEF25-75%	Delta N ₂
R5 (cmH ₂ O/L/s)				
Whole breath	-0.394*	-0.238*	-0.333*	0.247*
Inspiratory	-0.433*	-0.291*	-0.385*	0.251*
Expiratory	-0.368*	-0.201	-0.299*	0.258*
ΔR5	0.074	0.076	-0.005	-0.205
R20 (cmH ₂ O/L/s)				
Whole breath	-0.268*	-0.115	-0.214	0.159
Inspiratory	-0.290*	-0.135	-0.229*	0.141
Expiratory	-0.240*	-0.083	-0.187	0.193
ΔR20	-0.053	0.139	0.042	-0.205
R5-R20 (cmH ₂ O/L/s)				
Whole breath	-0.515*	-0.386*	-0.442*	0.284*
Inspiratory	-0.575*	-0.512*	-0.555*	0.367*
Expiratory	-0.447*	-0.285*	-0.352*	0.240*
Δ(R5-R20)	0.135	-0.034	0.042	-0.148
X5 (cmH ₂ O/L/s)				
Whole breath	0.420*	0.339*	0.380*	-0.267*
Inspiratory	0.443*	0.355*	0.389*	-0.301*
Expiratory	0.413*	0.358*	0.391*	-0.274*
ΔX5	-0.139	-0.113	-0.106	0.082
Fres (Hz)				
Whole breath	-0.478*	-0.388*	-0.421*	0.301*
Inspiratory	-0.503*	-0.435*	-0.456*	0.343*
Expiratory	-0.448*	-0.379*	-0.412*	0.288*
ΔFres	0.175	0.135	0.144	-0.116
ALX (cmH ₂ O/L/s x Hz)				
Whole breath	-0.423*	-0.345*	-0.383*	0.259*
Inspiratory	-0.452*	-0.362*	-0.395*	0.306*
Expiratory	-0.414*	-0.358*	-0.390*	0.272*
ΔALX	0.088	0.065	0.067	-0.012

* $P < 0.05$.

Values are Spearman rank correlation coefficients.

ALX, integrated low-frequency reactance area; Δ, difference between inspiratory and expiratory phases; FEF25-75%, forced expiratory flow between 25% and 75% of FVC; FEV1, forced expiratory volume in 1 second; Fres, resonant frequency; FVC, forced vital capacity; X5, respiratory system reactance at 5 Hz; R5 and R20, respiratory system resistance at 5 Hz and 20 Hz.

with FOT allowed the detection of expiratory flow limitation (EFL) [11]. EFL during tidal breathing is a major determinant of dynamic hyperinflation and exercise limitation in COPD [18]. EFL is common in patients with COPD and is caused by the loss of lung elastic recoil. It is supposed that normally the reactance reflects the elastic and inertial properties of the respiratory system but with flow limitation, oscillatory signals cannot pass through the choke points and reach the alveoli. During EFL, impedance will reflect the mechanical properties of airways proximal to the choke points, which are much stiffer than the periphery, producing a marked reduction in the apparent compliance and a fall

in reactance. Several investigators have reported that within-breath changes in Xrs could discriminate between patients with COPD and those with asthma [4, 5, 7]; however, loss of lung elastic recoil can occur in patients with acute and chronic moderate to severe persistent asthma, leading to persistent EFL [19]. Thus, ΔX_5 , ΔF_{res} , and ΔALX are thought to reflect EFL also in asthma. The relationship between FeNO and obstructive parameters is two-sided. In general, when airway inflammation improves after treatment with inhaled corticosteroids, airways become enlarged and FeNO levels decrease; however, when bronchoconstriction occurs after methacholine inhalation, for example, FeNO levels can decrease, and increase after inhalation with bronchodilators [20]. Similarly, decreased CANO levels can increase in some asthmatic patients with high FeNO levels after treatment with inhaled corticosteroids [21]. This decrease in FeNO or CANO levels is thought to depend on the bronchoconstriction of peripheral airways and ventilation inhomogeneity. The negative correlation between CANO and ΔX_5 (plus values) indicates that when severe EFL exists, CANO levels decrease and vice versa in this study. There was a positive correlation between CANO and ΔF_{res} and ΔALX (minus values), indicating similar relationships.

If impedance and inflammation really are linked, then presumably one would expect CANO to be linked to absolute values of either resistance or reactance. Why is it only the difference between inspiratory and expiratory Xrs that shows a significant relationship? Answers to this question are as follows. On the basis of previous reports [4, 5, 7, 11, 18], we now consider the differences between inspiratory and expiratory Xrs (ΔX_{rs}) as quite different oscillatory parameters from absolute values of either Rrs or Xrs and even ΔR_{rs} . As stated above, ΔX_{rs} , in particular ΔX_5 , is regarded as a surrogate marker of EFL, a phenomenon observed during tidal breathing. Compared with the correlations of spirometric parameters with whole-breath, inspiratory, and expiratory Rrs and Xrs, no correlation with ΔX_{rs} and ΔR_{rs} was distinct, supporting the idea that ΔX_{rs} and ΔR_{rs} are different oscillatory properties. In contrast to ΔX_{rs} , it was confirmed previously that ΔR_{rs} was not associated with EFL [18]. Also, we added normal controls to our study population to give them greater ranges of lung function and inflammatory markers with which to look for correlations; however, it was found that there was no correlation between CANO and absolute values of either resistance or reactance.

FeNO measurements are considered a surrogate for eosinophilic airway inflammation; however, FeNO is an indirect biomarker and correlations with sputum eosinophils are modest even in the large population study ($r^2 = 0.26$, $P < 0.001$) [22]. This might be an explanation for the somewhat weak correlations between peripheral airway mechanics and inflammation in this study. Despite this limitation, FeNO can serve as an aid to a diagnosis, a measure of asthma control, and a predictor of steroid responsiveness. Also, there are confounding factors that affect FeNO measurements, including age, gender, atopy, and concurrent cigarette smoking [23]. Clinicians should keep these in mind in FeNO measurements. We consider measurements of respiratory impedance useful in research and in clinical practice in future for the following reasons. First, they are performed during tidal breathing and do not require specific manoeuvres or noticeable interference with respiration. Secondly, they provide information that is applicable to resting conditions or daily activities. Thirdly, they can be performed under different breathing conditions and so provide information on the mechanical properties of the respiratory system that can be complementary to spirometry. Recently, an attempt of home monitoring of Rrs by a portable FOT device to diagnose asthma and predict acute deterioration was reported [24]. More studies will clarify the usefulness of FOT in clinical practice.

This study also demonstrated that whole-breath, inspiratory, and expiratory R5, R5–R20, X5, F_{res} , and ALX were significantly but weakly correlated with ventilation inhomogeneity expressed as delta N_2 values. The finding that R5–R20 values correlated better with delta N_2 values than any other FOT parameters suggests the validity of the notion that the frequency dependence of Rrs reflects inhomogeneous ventilatory mechanics. To the best of our knowledge, this is the first study to demonstrate that whole-breath and within-breath analyses of respiratory impedance reflected not only peripheral airway inflammation but dysfunction in patients with asthma.

In conclusion, respiratory impedance reflects peripheral airway inflammation and ventilation inhomogeneity.

Conflict of interests

The authors declare no conflict of interests.

References

- 1 Oostveen E, Macleod D, Lorino H *et al.* On behalf of the ERS Task Force on Respiratory Impedance Measurements. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J* 2003; 22:1026–41.
- 2 Hellinckx J, Cauberghs M, De Boeck K, Demedts M. Evaluation of impulse

- oscillation system: comparison with forced oscillation technique and body plethysmography. *Eur Respir J* 2001; 18:564–70.
- 3 Kurosawa H, Ohishi J, Shimizu Y *et al*. Visualization of frequency and respiratory cycle dependency in the lung evaluated using impulse oscillation. Available at: www.ers-education.org/media/2009/eposters/1118.html. (Date last accessed: 11 April 2012).
- 4 Paredi P, Goldman M, Alamen A *et al*. Comparison of inspiratory and expiratory resistance and reactance in patients with asthma and chronic obstructive pulmonary disease. *Thorax* 2010; 65:263–67.
- 5 Kanda S, Fujimoto K, Komatsu Y, Yasuo M, Hanaoka M, Kubo K. Evaluation of respiratory impedance in asthma and COPD by an impulse oscillation system. *Intern Med* 2010; 49:23–30.
- 6 Yamaguchi M, Niimi A, Ueda T *et al*. Effect of inhaled corticosteroids on small airways in asthma: investigation using impulse oscillometry. *Pulm Pharmacol Ther* 2009; 22:326–32.
- 7 Mori K, Shirai T, Mikamo M *et al*. Colored 3-dimensional analyses of respiratory resistance and reactance in COPD and asthma. *COPD* 2011; 8:456–63.
- 8 Matsumoto H, Niimi A, Jinnai M *et al*. Association of alveolar nitric oxide levels with pulmonary function and its reversibility in stable asthma. *Respiration* 2011; 81:311–7.
- 9 Williamson PA, Clearie K, Menzies D, Vaidyanathan S, Lipworth BJ. Assessment of small-airways disease using alveolar nitric oxide and impulse oscillometry in asthma and COPD. *Lung* 2011; 189:121–9.
- 10 Global strategy for asthma management and prevention 2011 (update). Available at: www.ginasthma.org. (Date last accessed: 24 February 2012).
- 11 Dellacà RL, Pompilio PP, Walker PP, Duffy N, Pedotti A, Calverly PMA. Effect of bronchodilatation on expiratory flow limitation and resting lung mechanics in COPD. *Eur Respir J* 2009; 33:1329–37.
- 12 American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal oxide, 2005. *Am J Respir Crit Care Med* 2005; 171:912–30.
- 13 Tsoukias NM, George S. A two-compartment model of pulmonary nitric oxide exchange dynamics. *J Appl Physiol* 1998; 85:653–66.
- 14 Condorelli P, Shin HW, Aledia AS, Silkoff PE, George SC. A simple technique to characterize proximal and peripheral nitric oxide exchange using constant flow exhalation and an axial diffusion model. *J Appl Physiol* 2007; 102:417–25.
- 15 American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152:1107–36.
- 16 Kanazawa H, Tochino Y, Kyoh S, Ichimaru Y, Asai K, Hirata K. Potential roles of pentoside in age-related impairment of pulmonary functions in patients with asthma. *J Allergy Clin Immunol* 2011; 127:899–904.
- 17 Cavalcanti JV, Lopes AJ, Jansen JM, Melo PL. Detection of changes in respiratory mechanics due to increasing degrees of airway obstruction in asthma by the forced oscillation technique. *Respir Med* 2006; 100:2207–19.
- 18 Dellacà RL, Santus P, Aliverti A *et al*. Detection of expiratory flow limitation in COPD using the forced oscillation technique. *Eur Respir J* 2004; 23:232–40.
- 19 Gelb AF, Zamel N, Krishnan A. Physiologic similarities and differences between asthma and chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2008; 14:24–30.
- 20 Tadaki H, Mochizuki H, Muramatsu R *et al*. Effect of bronchoconstriction on exhaled nitric oxide levels in healthy and asthmatic children. *Ann Allergy Asthma Immunol* 2009; 102:469–74.
- 21 Van Muylem A, Kerckx Y, Michils A. Acinar effect of inhaled steroids evidenced by exhaled nitric oxide. *J Allergy Clin Immunol* 2010; 126:730–35.
- 22 Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005; 35:1175–9.
- 23 Kostikas K, Minas M, Papaioannou AI, Papiris S, Dweik RA. Exhaled nitric oxide in asthma in adults: the end is the beginning? *Curr Med Chem* 2011; 18:1423–31.
- 24 Gulotta C, Suki B, Brusasco V *et al*. Monitoring the temporal changes of respiratory resistance: a novel test for the management of asthma. *Am J Respir Crit Care Med* 2012; 185:1330–1.