

Resonant frequency as a predictor of phase 3 slope of nitrogen single-breath washout in asthma



Clinical application of the forced oscillation technique (FOT) has recently progressed worldwide with the spread of commercially available broadband frequency FOT devices. Forced oscillations are superimposed on tidal breathing, avoiding the need for any special breathing maneuver or noticeable interference with respiration. FOT provides more information on the lung than that obtained by forced expiration via spirometry. Of the oscillatory parameters, the difference between resistance at 5 Hz and 20 Hz (R5–R20) is interpreted as an indicator of peripheral or small airway function in asthma.^{1,2} The nitrogen (N₂) single-breath washout (SBW) test is a measure of ventilation distribution inhomogeneity and also small airway function that offers complementary information to spirometry.³ The closing volume was previously considered a sensitive index of peripheral airway obstruction, but the phase 3 slope of nitrogen (ΔN_2) is now the preferred index. However, the association between oscillatory parameters and the SBW test is not fully understood. We hypothesized that spirometry and oscillatory parameters would predict the results of the SBW test independently. In this cross-sectional study, we assessed the association between the ΔN_2 derived from N₂ SBW and the pulmonary function parameters. This analysis was performed in addition to our previous study.⁴

Seventy-four patients with overall controlled asthma on the basis of the Asthma Control Test⁵ (mean score, 23.4) who attended outpatient clinics at Shizuoka General Hospital for routine checkups between June 2010 and October 2011 were enrolled in this study. All patients satisfied the definition of asthma of the Global Initiative for Asthma⁶ 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 more than 10 pack-years, or had quit smoking within 1 year before the study; or (3) had chronic obstructive pulmonary disease. On the examination day, the patients underwent testing for respiratory impedance, spirometry, and N₂ SBW in that order. To avoid any influence of forced breathing, spirometry was performed after FOT. Respiratory impedance was measured with FOT using a commercially available broadband frequency device (MostGraph-01, Chest M.I. Co Ltd, Tokyo, Japan) and standard recommendations.⁷ We used inspiratory R5, R20, R5–R20, reactance at 5 Hz (X5), resonant frequency (Fres), and low-frequency reactance area (ALX) in this study. Spirometry and, in order to assess ventilation inhomogeneity, N₂ SBW tests were performed using computerized equipment (model CHESTAC-33; Chest M.I. Inc) according to the standards of the American Thoracic Society and European Respiratory Society/American Thoracic Society consensus statement.^{3,8} Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and forced expiratory flow between 25% and 75% (FEF_{25%–75%}) were determined and the ΔN_2 was calculated as previously described.⁹ Briefly, the seated patients performed a slow full inspiratory and expiratory slow vital capacity maneuver at a flow rate of approximately 0.5 L/s. The expiratory N₂ concentration was plotted against volume changes between total lung capacity and residual volume, producing the expiratory N₂ washout curve. The ΔN_2 was calculated by drawing the best-fit line through phase 3 of the expiratory volume and concentration curve, ensuring freedom from contamination by phases 2 and 4, by a trained technician who was unaware of the

clinical information. These procedures were performed with acceptability criteria defined by the statement.³ Univariate correlations were performed using the Spearman rank correlation coefficient. Multiple regression analyses were performed to determine the predictors of ΔN_2 . Model selection was made by the best subset selection procedure using the Akaike information criterion. StatView statistical software, version 5.0 (SAS Institute Inc, Cary, North Carolina) and R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical calculations. $P < .05$ was considered statistically significant.

The characteristics of the patients were as follows (median values): age, 56 years; male sex, 37; female sex, 37; body mass index (measure of weight in kilograms divided by height in meters squared), 22.2; ex-smokers, 40; never smokers, 34; duration of asthma, 17 years; FVC, 96.8% predicted; FEV₁, 82.9% predicted; FEF_{25%–75%}, 48.7% predicted; ΔN_2 , 1.30 %N₂/L; R5, 3.80 cm H₂O/L/s; R20, 3.22 cm H₂O/L/s; R5–R20, 0.60 cm H₂O/L/s; X5, –0.57 cm H₂O/L/s; Fres, 8.29 Hz; and ALX, 2.00 cm H₂O/L/s $\times$ Hz. As indicated in Table 1, univariate analyses revealed that ΔN_2 correlated positively with age, R5, R5–R20, Fres, and ALX and negatively with body mass index, FVC, FEV₁, FEF_{25%–75%}, and X5. In multiple regression analyses (Table 2), ΔN_2 was independently predicted by body mass index, FEV₁, and Fres ($R^2 = 0.502$, $P < .0001$). R5–R20 was not selected according to the Akaike information criterion and was not significant even when adding in a model.

R5–R20 is an indicator of the frequency dependence of respiratory system resistance (Rrs), which is supposed to reflect inhomogeneous ventilatory mechanics.¹⁰ In the interpretation of data measured with impulse oscillometry, R5, R20, and R5–R20 represent the resistance of the total airway, central airways, and peripheral airways, respectively.^{1,2} Although a number of studies on this have been published, this issue is controversial. There is no statement in the official guidelines that supports this interpretation. R5–R20 values are sometimes zero or negative, which are unlikely in themselves. Furthermore, the interpretation usually refers to asthma but hardly to chronic obstructive pulmonary disease. In this cross-sectional study, we found that Fres, but not R5–R20, was a predictor of the degree of ventilation inhomogeneity, a small airway function, derived from N₂ SBW in asthma. We have found in univariate analyses that R5–R20 significantly correlated with not only

Table 1
Univariate correlations between ΔN_2 and predictor variables^a

Variable	ρ^b	P Value
Age	0.342	.004
Body mass index	–0.251	.03
FVC	–0.319	.006
FEV ₁	–0.603	<.001
FEF _{25%–75%}	–0.648	<.001
R5	0.251	.03
R20	0.141	.23
R5–R20	0.367	.002
X5	–0.301	.01
Fres	0.343	.003
ALX	0.306	.009

Abbreviations: ΔN_2 , phase 3 slope of nitrogen; ALX, low-frequency reactance area; FEF_{25%–75%}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 second; Fres, resonant frequency; FVC, forced vital capacity; Rrs, respiratory system resistance; R5, Rrs at 5 Hz; R20, Rrs at 20 Hz; R5–R20, the difference between R5 and R20; X5, respiratory system reactance at 5 Hz.

^aForced oscillatory parameters are expressed as the mean values during inspiratory phase.

^bValues are the Spearman rank correlation coefficient.

Disclosures: Authors have nothing to disclose.

Table 2
Multiple regression analysis for predictors of ΔN_2^a

Variable	β Coefficient, Mean (SE)	P Value	Cumulative R^2
Body mass index	−0.333 (0.017)	<.001	0.502
FEV ₁	−0.459 (0.041)	<.001	
Fres	0.307 (0.008)	.004	

Abbreviations: ΔN_2 , phase 3 slope of nitrogen; FEV₁, forced expiratory volume in 1 second; Fres, resonant frequency.

^aForced oscillatory parameters are expressed as the mean values during inspiratory phase.

FEV₁ but also ΔN_2 (correlation coefficients: −0.575 vs 0.367), indicating that the correlation was stronger with central airway obstruction than with peripheral ventilation inhomogeneity.⁴ These findings suggest that R5-R20 is not a parameter specific to peripheral airways but one to central airways instead. Further studies are needed to clarify the meaning of R5-R20 and to establish the interpretation of forced oscillatory parameters in asthma.

Toshihiro Shirai, MD, PhD*
Kazutaka Mori, MD†

Tomoyoshi Tsuchiya, MD, PhD‡
Takafumi Suda, MD, PhD†

*Department of Respiratory Medicine
Shizuoka General Hospital
Shizuoka, Japan

†Second Department of Internal Medicine
Hamamatsu University School of Medicine
Hamamatsu, Japan

[‡]Department of Respiratory Medicine
Shizuoka City Shimizu Hospital
Shizuoka, Japan
toshihiro-shirai@i.shizuoka-pho.jp

References

- [1] Shi Y, Aledia AS, Galant SP, George SC. Peripheral airway impairment measured by oscillometry predicts loss of asthma control in children. *J Allergy Clin Immunol*. 2013;131:718–723.
- [2] Bickel S, Popler J, Lesnick B, Eid N. Impulse oscillometry: interpretation and practical applications. *Chest*. 2014;146:841–847.
- [3] Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple and single breath tests. *Eur Respir J*. 2013;41:507–522.
- [4] Shirai T, Mori K, Mikamo M, et al. Respiratory mechanics and peripheral airway inflammation and dysfunction in asthma. *Clin Exp Allergy*. 2013;43:521–526.
- [5] Nathan RA, Sorkness CA, Kosinski M, et al. Development of the Asthma Control Test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113:59–65.
- [6] Global Initiative for Asthma. Global strategy for asthma management and prevention 2011 (update). www.ginasthma.org. Accessed February 24 2012.
- [7] Oostveen E, Macleod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J*. 2003;22:1026–1041.
- [8] American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med*. 1995;152:1107–1136.
- [9] Kanazawa H, Tochino Y, Kyoh S, et al. Potential roles of pentoside in age-related impairment of pulmonary functions in patients with asthma. *J Allergy Clin Immunol*. 2011;127:899–904.
- [10] Dellacà RL, Pompilio PP, Walker PP, et al. Effect of bronchodilation on expiratory flow limitation and resting lung mechanics in COPD. *Eur Respir J*. 2009;33:1329–1337.

Anaphylaxis after application of topical bacitracin-neomycin powder



Bacitracin is a peptide antibiotic, produced by *Bacillus subtilis*, that can inhibit the synthesis of various gram-positive bacteria on the cell wall.

Bacitracin was discovered in 1943 and has increasingly become a popular reagent in different topical products, such as cosmetics, cutaneous ointments, and powders, as a standalone drug or in combination with other antibiotics.

Although this drug was supposed to carry a low sensitization profile, this could not be confirmed by the increasing evidence of allergic delayed contact reactions. For this reason, in the early 1990s, the North American Contact Dermatitis Group listed bacitracin among the top 10 allergens (8–9% positive patch test results).^{1,2} IgE-mediated reactions, such as contact urticaria and anaphylaxis, also were reported, which are potentially life-threatening events, albeit rare.

We report a case of anaphylaxis after the application of powder containing bacitracin on the skin.

A 54-year-old man with a history of rhinitis and allergic asthma was referred to our allergy outpatient clinic for a supposed episode of drug-induced anaphylaxis. Six months previously, he had a mild traumatic skin laceration and he applied to his right first toe an antibiotic powder containing bacitracin, neomycin glycine, cysteine, and threonine (Cicatrene powder; Johnson & Johnson SpA, Rome, Italy). After 5 minutes, he developed local itching that rapidly spread to the rest of his body. This was followed by a sensation of throat constriction, dyspnea, and generalized malaise without loss of consciousness. He was promptly transported to the emergency department of the nearest hospital, where he was found to be slow and unable to respond to commands promptly.

Disclosure: Authors have nothing to disclose.

The patient previously used the same powder on many other occasions without developing any immediate or delayed reaction. On physical examination, the skin was diffusely erythematous, with bilateral eyelid edema and conjunctival redness, and diffuse wheezing was found at chest examination. Blood pressure was 70/50 mmHg, heart rate was 130 rpm, and pulse oximetry was 88% on room air.

He was placed on an oxygen mask and given intravenous saline, epinephrine, chlorphenamine, and methylprednisolone, resulting in complete resolution within 90 minutes. The patient showed no signs of a late reaction and was discharged 12 hours after admission.

During the acute phase of the reaction, tryptase levels were not measured. Skin prick test reactions with common inhalants were positive for house dust mites, birch, ragweed, and *Parietaria* pollen. His basal tryptase level was 5.7 $\mu\text{g/L}$.

We performed an open patch test using the discrete components of the powder. Neomycin (20% in petrolatum; Almirall SA, Barcelona, Spain), bacitracin (15% in petrolatum; FIRMA, Florence, Italy), and a panel of other aminoglycoside antibiotics, including streptomycin sulfate (2%; FIRMA), dihydrostreptomycin sulfate (2%; FIRMA), amikacin sulfate (20%; FIRMA), kanamycin sulfate (25% in petrolatum; Almirall), gentamicin sulfate (25%; FIRMA), amikacin (20%; FIRMA), spectinomycin chlorohydrate (20%; FIRMA), netilmicin sulfate (20%; FIRMA), and the polypeptide polymyxin B sulfate (3% in petrolatum; Almirall) were applied to intact skin on the back. After 15 minutes, the patient developed pruritus on the back and at 20 minutes positive results were observed for bacitracin (wheal 10 × 10 mm and erythema 50 mm; Fig 1) and polymyxin B (wheal 7 × 6 mm). We also performed an additional skin prick test with neomycin, which yielded a negative reaction.