

The nasal provocation test combined with spirometry establishes paradoxical vocal fold motion in allergic subjects

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ABSTRACT

Vocal cord dysfunction (also called paradoxical vocal cord motion) or paradoxical vocal fold motion (PVFM) is an event elicited by specific and nonspecific triggers in which its diagnosis is limited by the restricted number of available functional tests. This study was designed to appreciate the contribution of the spirometric changes elicited by the allergen-specific nasal provocation test (NPT) performed with *Dermatophagoides pteronyssinus* for the diagnosis of PVFM in subjects with known sensitization to this allergen. In total, 63 subjects with allergic rhinitis who had previously been shown to be sensitized to *D. pteronyssinus* and who had experienced one or more episodes of inspiratory shortness of breath underwent two spirometric tests, one before (pre-NPT) and another 15 minutes after the allergen-specific NPT (post-NPT). The forced inspiratory vital capacity (FIVC), forced inspiratory volume in 2 seconds (FIV₂), and the ratio between the FIV in 1 second and FIVC (FIV₁/FIVC) were measured by spirometry. The morphology of the post-NPT inspiratory loop was compared with the pre-NPT inspiratory loop. We found that 18 subjects (28.5%) showed alterations suggestive of PVFM on post-NPT spirometry (e.g., truncation and/or flattening of the inspiratory loop). The mean differences between the pre-NPT and post-NPT values for the whole group were significant using a two-tailed paired *t*-test for the FIVC (4.1; 95% confidence interval [CI_{95%}], 1.4–6.8), FIV₁/FIVC ratio (2.7; CI_{95%}, 0.05–5.3), and FIV₂ (7.2; CI_{95%}, 3.4–11). Allergen-specific NPT combined with spirometry is useful to show allergen-specific laryngeal hyperresponsiveness in allergic subjects with PVFM. Brazilian clinical trial registry platform (Plataforma Brasil, CAAE 07971212.0.0000.5480).

(Allergy Asthma Proc 34:453–458, 2013; doi: 10.2500/aap.2013.34.3681)

Diagnostic differentiation of the organs responsible for respiratory symptoms is essential for a proper therapeutic approach. This differentiation is usually not very difficult for the experienced physician, but sometimes the subjects may present nonspecific symptoms that can mislead the diagnostic approach.¹ In addition, some disorders may remain asymptomatic until the functional reserves are approached, as in the case of asthma, or may manifest on intermittent occasions, as in the case of paradoxical vocal fold motion (PVFM) disorder and, therefore, might not be shown during a single clinical visit when the subject is asymptomatic.^{2,3} Airway hyperresponsiveness may be elicited by a variety of mechanisms, and direct contact with specific antigens is the main trigger in allergic conditions.⁴ Nonspecific airway hyperresponsiveness may be shown by pharmacologic

challenges to contribute to the anatomic diagnosis,⁵ whereas the specific causative agents may be indicated by allergen challenges.⁶ Respiratory challenge with allergens may induce immediate hyperresponsiveness (by stimulating autacoids *via* IgE-mediated hypersensitivity and/or nonspecific neural mechanisms)⁷ as well as late and delayed immunoreactivity.⁸ The nasal provocation test (NPT) may be assessed using symptom scoring systems,⁹ nasal patency measurements (peak nasal inspiratory flow, rhinomanometry, acoustic rhinometry, or optical rhinometry), and cytological/biochemical studies of the nasal fluid.^{10,11} Similarly, the bronchial provocation test provides valuable information about bronchial hyperresponsiveness in asthmatic subjects and may be assessed using spirometry and cytological/biochemical studies of the sputum.¹² Among respiratory disorders, PVFM (also known as vocal cord dysfunction or paradoxical vocal cord motion) is the entity in which its etiologic diagnosis is the most complex because there are no standardized functional challenging tests to show causality between specific triggers and symptoms.¹³ PVFM may present as asthma-like symptoms^{14,15} and may result from an assorted collection of causes in response to a triggering stimulus such as exercise, gastroesophageal reflux disease (pharyngolaryngeal or extraesophageal reflux), vagal neuropathy, psychological problems, la-

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CE Olivier, DGP Argentão, RPS Lima, MD Silva, and RAPG Santos received grant support from Instituto Alergoimuno de Americana

The authors have no conflicts of interest to declare pertaining to this article
Supplemental data available at www.IngentaConnect.com

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ryngeal disorders, neurological disorders, and laryngeal hyperresponsiveness.¹⁶ Diagnosis of PVFM when the subject is symptomatic is suggested by signs of extrathoracic upper airway obstruction on spirometry such as flattening or premature ending (truncation) of the inspiratory limb. It can be confirmed using direct visualization by video laryngoscopy to view the paradoxical adduction of the cords,¹⁷ but because of the intermittent nature of these episodes, the diagnosis can sometimes be challenging.¹⁸ The aim was to study the spirometric changes induced by allergen-specific NPT in allergic subjects with at least one event of inspiratory shortness of breath, in search of signs for the diagnosis of PVFM.

METHODS

Study Design and Subjects

We examined 63 subjects (50 women; overall mean age, 28.1 years; $\pm$ SD, 10.2 years). The subjects were asymptomatic and did not use any medication for at least 2 weeks before the examination. All of the subjects had previous clinical diagnoses of allergic rhinitis according to the Allergic Rhinitis and Its Impact on Asthma criteria,¹⁹ as well evidence of IgE-mediated hypersensitivity to *Dermatophagoides pteronyssinus* by skin prick test and skin scrape test performed as previously described.^{20,21} The study was approved by the Ethical Review Board of the Irmandade de Misericórdia de Campinas, registered at the Brazilian clinical trial registry platform (Plataforma Brasil, CAAE 07971212.0.0000.5480) and conducted according to the principles of the declaration of Helsinki. Informed assent and consent was obtained before enrollment. Subject's information was kept confidential. No investigational drugs were used.

Allergen-Specific NPT

The allergen-specific NPT was performed in subjects who showed an adequate inspiratory loop in the previous spirometry. An isotonic, buffered, neutral pH aqueous solution (100 μ L) with 10% (w/v) *D. pteronyssinus* extract (Immunotech, Rio de Janeiro, Brazil) adapted to room temperature was applied with a pump spray device to both nostrils of a subject. The subject was instructed to inhale before allergen application, hold his/her breath during application, and exhale immediately after application. A symptom score (SS; NPT-SS) ranging from 0 to 12 for immediate reactions was implemented after each NPT as described by Lebel and colleagues.⁹ The NPT-SS punctuates (a) sneezing (3–4 sneezes = 1 point; >5 sneezes = 3 points), (b) rhinorrhea (anterior and moderate = 1 point; posterior = 1 point; both symptoms = 2 points; important anterior and posterior = 3 points); (c) blockade (patient can breathe with difficulty = 1 point; one

nostril is blocked = 2 points; both nostrils blocked = 2 points); and (d) pruritus (nose = 1 point; palate or ear = 1 point; conjunctivitis = 1 point).

Spirometry

The values obtained by spirometry for each subject before the NPT (pre-NPT) and 15 minutes after the NPT (post-NPT) were recorded as spirometric data. The subjects were acclimatized for at least 30 minutes before the pre-NPT. Spirometry was performed under medical supervision with the subject in a sitting position and wearing a nose clip. The subjects were encouraged to use maximum efforts first for the inspiratory and then for expiratory loops. In the final analysis, we used the loops that had the best inspiratory and expiratory curves. The forced inspiratory vital capacity (FIVC), forced inspiratory volume in 2 seconds (FIV₂), and the ratio between the FIV in 1 second and FIVC (FIV₁/FIVC) were measured by flowmeter spirometry (WinspiroPRO 3.6.3 USB spirometer; MIR Medical International Research, Rome, Italy). The FIVC is the volume change of the lung between a maximal expiration to residual volume and a full inspiration to total lung capacity performed during forceful inhalation. The quality of this maneuver may be verified comparing the FIVC volume with the forced vital capacity (FVC). The results must be about the same. If the FIVC maneuver is performed after a forced expiration in a patient with pronounced airway obstruction, the FIVC may be larger than FVC. To avoid this difference, the FIVC maneuver must be performed before the forced expiration. FIV₁ and FIV₂ are the volumes that can be forcefully inhaled, respectively, in the 1st and 2nd seconds during the FIVC maneuver. The ratio between FIV₁ and FIVC represents the initial inspiratory flow that can be affected by the proximal airway permeability obstruction associated with PVFM.¹⁸

The spirometer software also calculated the percent of each predicted result (%pred) for each lung function test in the reference population (Knudson) according to each subject's sex, age, and height (Fig. 1).²² The appearance of the inspiratory loop was inspected in search of abnormalities: absence, truncation (early termination of the curve), or flattening (lack of normal concavity). Each curve was reviewed by all investigators to reach agreement on the differences between the pre-NPT and post-NPT spirometry data. The differences between the %pred pre-NPT and %pred post-NPT spirometric values were also calculated by the software (difference of percent of predicted FIVC [FIVC_{df%}], FIV_{2df%}, and FIV₁/FIVC_{df%}).

Statistical Analyses

Gaussian distribution was proven using d'Agostino and Pearson's omnibus normality test. Group compar-

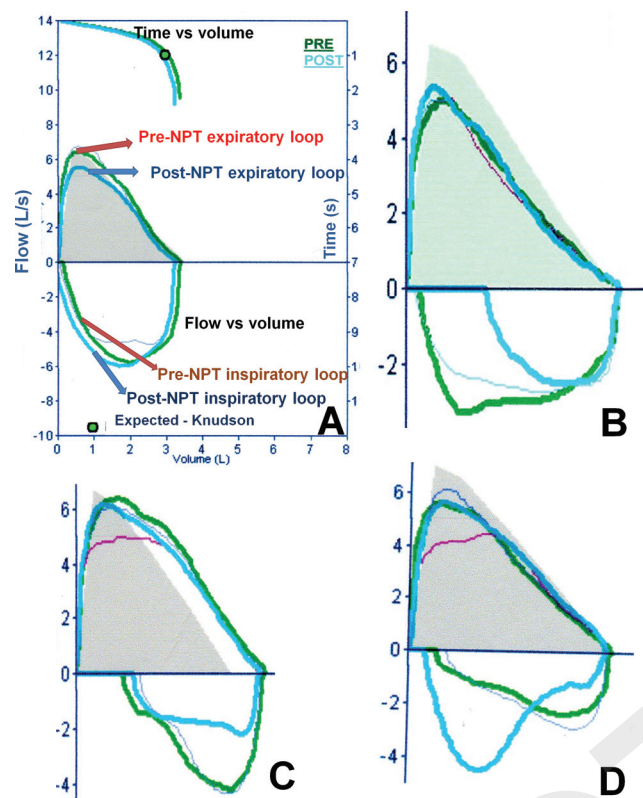


Figure 1. Flow-volume loops appearance of combined allergen-specific nasal provocation test with spirometry. (A) Normal pre-NPT inspiratory and expiratory loops (red); (B) truncation of post-NPT inspiratory loop; (C) flattening of post-NPT inspiratory loop; and (D) inverse truncation of post-NPT inspiratory loop. NPT, nasal provocation test.

isons were performed using a two-tailed paired *t*-test. The data were reported as the arithmetic mean with 1 SD. Mean differences were considered significant at $p < 0.05$. Paired correlation charts between NPT-SS and the differences between the %pred pre-NPT and post-NPT ($FIVC_{df\%}$, $FIV_{2df\%}$, and $FIV_1/FIVC_{df\%}$) values were plotted, and the Pearson's correlation was used to analyze the results. Statistical analyses were performed using GraphPad Prism for Windows (Version 5.0; GraphPad Software, Inc., San Diego, CA).

RESULTS

Nasal Provocation Test Symptom Score

The mean NPT-SS was $4.7 (\pm 2.8 \text{ SD})$. The distribution was shown to be normal using the D'Agostino and Pearson omnibus normality test ($p = 0.17$).

Inspiratory Loops Abnormalities

There were 18 subjects (28.5%) who showed remarkable alterations on their post-NPT inspiratory loops. The main alterations were decreased in total area (16 subjects), truncation (6 subjects), and flattening (8 sub-

jects). Two subjects presented an inverse truncation, with flattening of the initial inspiratory loop and a compensatory increase of the ending of the loop, suggesting a sudden opening of the vocal fold in the middle of inspiration. In these subjects, we did not observe a decrease in the total inspiratory area (see Figs. 1 and online supplement E1).

Spirometric Values

The absolute cutoff suggestive of PVFM for each parameter was defined as the value of $df\%$ under which there was no subject without inspiratory loops abnormalities. The absolute cutoff suggestive of a normal inspiratory loop was defined as the value of $df\%$ above which there was no subject with inspiratory loops abnormalities. The range of the spirometric values and suggestive cutoffs are summarized in Table 1. The complete data including the subject's ages (years), NPT-SS, and spirometric values obtained before and after allergen-specific NPT (%pred and $df\%$) are displayed in online supplement Table E1.

$FIVC_{df\%}$ (difference of percent of predicted Forced Inspiratory Volume Capacity)

The mean difference between the pre-NPT $FIVC_{\%pred}$ and post-NPT $FIVC_{\%pred}$ values obtained from the whole group of 63 subjects was significant using a two-tailed paired *t*-test (-4.1 ; 95% confidence interval [$CI_{95\%}$], -6.8 to -1.4 ; $p = 0.0034$). Four subjects with inspiratory loop abnormalities (22%) had an increase in FIVC. Twelve subjects with inspiratory loop abnormalities (66.6%) had a decrease in FIVC of $>10\%$. Four subjects with inspiratory loops abnormalities (22.2%) presented a decrease of FIVC of $>25\%$. There were five subjects with normal inspiratory loops (11%) with a decrease of FIVC of $>10\%$. There were no subjects with normal inspiratory loops with a decrease of FIVC of $>25\%$. There was no significant correlation between NPT-SS and $FIVC_{df\%}$.

$FIV_1/FIVC_{df\%}$ (difference of percent of predicted Forced Inspiratory Volume Capacity in one second/ Forced Inspiratory Volume Capacity)

The mean difference between the pre-NPT $\%pred$ and post-NPT $\%pred$ $FIV_1/FIVC$ values obtained for the whole group of 63 subjects was significant using a two-tailed paired *t*-test (-2.7 ; $CI_{95\%}$, -5.3 to -0.05 ; $p = 0.045$). Half of the 18 subjects with inspiratory loop abnormalities showed no significant alterations (decrease of $<5\%$) to their $FIV_1/FIVC$ ratio. Nine subjects (50%) with inspiratory loop abnormalities presented a decrease of $FIV_1/FIVC$ of $\geq 13\%$. Six subjects (33%) with inspiratory loop abnormalities presented a decrease of $FIV_1/FIVC$ of $\geq 19\%$. There were no subjects with normal inspiratory loops with a decrease of $FIV_1/FIVC$ of $\geq 13\%$.

Table 1 Ranges of differences between pre-NPT and post-NPT percentage of predicted spirometric values and suggestive absolute cutoffs related with PVFM or normal inspiratory loops

	Range of Values in Subjects with Normal Post-NPT Inspiratory Loop	Range of Values in Subjects with Abnormal Post-NPT Inspiratory Loop	Absolute Cutoff Suggestive of a Normal Inspiratory Loop	Absolute Cutoff Suggestive of PVFM
FIVC _{df%}	−25% to +16%	−39% to +10%	None	Decrease of >25%
FIV ₁ /FIVC _{df%}	−17% to +18%	−59% to +2%	None	Decrease of >17%
FIV _{2df%}	−25% to +32%	−59% to −9%	Decrease of <9%	Decrease of >25%

NPT = nasal provocation test; pre-NPT = spirometric data obtained prior to NPT; post-NPT = spirometric data obtained after NPT; FIVC = forced inspiratory vital capacity; FIV₂ = forced inspiratory volume in 2 s; FIV₁/FIVC = ratio between forced inspiratory volume in 1 s and FIVC; %pred = percentage of predicted for age, gender, and height; df% = difference between pre-NPT percentage of predicted and post-NPT percentage of predicted spirometric data; PVFM = paradoxical vocal fold motion.

FIVC of >17%. There was a significant correlation ($p = 0.01$) between NPT-SS and FIV₁/FIVC_{df%} for the whole group (Pearson's $r = -0.31$; CI_{95%}, −0.52 to −0.077).

FIV_{2df%} (difference of percent of predicted Forced Inspiratory Volume in two seconds)

The mean difference between the pre-NPT_{%pred} and post-NPT_{%pred} FIV₂ values obtained from the whole group of 63 subjects was significant using a two-tailed paired t -test (−7.2; CI_{95%}, −11 to −3.4; $p = 0.003$). All of the 18 subjects with inspiratory loop abnormalities had a decrease of FIV₂ of $\geq 9\%$ (mean, −26.2; CI_{95%}, −33.1 to −19.4). Fourteen subjects (77.7%) with inspiratory loop abnormalities presented with a decrease of FIV₂ of $\geq 15\%$. Nine subjects (50%) with inspiratory loop abnormalities presented with a decrease of FIV₂ of >25%. There were five subjects (11%) with normal inspiratory loops with a decrease of FIV₂ of >9%. There were no subjects with normal inspiratory loops with a decrease of FIV₂ of >25%. There was a significant correlation ($p = 0.03$) between NPT scores and FIV_{2df%} (Pearson's $r = -0.26$; CI, −0.48 to −0.01).

DISCUSSION

Allergen-specific NPT is considered the gold standard for the diagnosis of allergic rhinitis, but it is a neglected test.^{22,23} However, because of its inability to test more than one allergen simultaneously, allergen-specific NPT is not used for triage purposes. Instead, it is used for specific indications such as the diagnosis of allergic rhinitis in subjects with just local production of IgE²⁴ or to confirm the relevance of a particular antigen before prescription of desensitization therapy.²⁵ NPT can also be used to study nonallergic conditions such as aspirin intolerance or nonspecific nasal hyperresponsiveness.^{26,27} The use of allergen-specific NPT combined with spirometry was already reported to study asthmatic response but, in these articles, there

was no reference to inspiratory loops.^{28,29} The inspiratory loop in spirometry is also a valuable and neglected source of information. Usually, the medical practitioner pays more attention to the expiratory components of the test because medical protocols use these results to guide the diagnosis and treatment of asthma.³⁰ This lack of attention is not, however, totally a physician's fault. Sometimes, while applying the spirometry, the examiners focus on the expiratory loops and do not emphasize to the subject the need to exert maximal inspiratory effort. Adequate encouragement of forced inspiration is crucial to establish the presence/absence of truncation or flattening of the inspiratory loop.³¹ Because the shape of the inspiratory loop may distinguish an episode of asthma from an episode of PVFM, the observance of such details should be mandatory.¹ Among acute respiratory disorders, PVFM is also one of the most forgotten on the differential diagnosis. It is not uncommon to attend subjects with PVFM whose symptoms have already been inappropriately imputed in emergency rooms to asthma or a psychosomatic disorder. In fact, it is not usual for an emergency department to keep a spirometer on hand to distinguish a PVFM attack from asthma.¹ The diagnosis of PVFM is not easy to establish because the attacks are intermittent and, most of the time, the subjects remain asymptomatic. The diagnosis of PVFM is made during the attacks based on laryngoscopic evidence of inspiratory and/or early expiratory vocal cord adduction. The gold standard is fiberoptic laryngoscopy or endospirometry, but these exams do not show the etiology of the process.³² The etiology of PVFM is complex, often multifactorial, and still remains an insufficiently explored field, which results in more subjects being referred for nonspecific treatments such as speech therapy. Although PVFM is often misdiagnosed as asthma, there is also a close relationship between the two conditions. Newman and colleagues found that 56% of

their 95 PVFM subjects had coexistent asthma.³³ The fact that some patients complained of inspiratory shortness of breath after allergen-specific NPT also alerted us to the possibility that a specific trigger might represent an additional etiology for PVFM. This study was designed to establish a temporal relationship between an allergen dispensed by a nasal challenge and spirometric alterations suggesting PVFM. This relationship was indicated in 18 of 63 subjects (28.5%) with a recognized sensitivity to the specific allergen. These alterations were not present at the initial spirometric evaluation, suggesting an allergen-specific laryngeal hypersensitivity.

This is the first report in the literature of a study of spirometric results (performed with emphasis on the inspiratory loop) that was performed with the same group of subjects and compared an asymptomatic baseline status versus an allergen-specific postchallenge status. Murri and colleagues compared spirometric values between a group of subjects with PVFM and another normal control group.¹⁸ In contrast to the findings of Murri, who found a significant difference in the percent (FVC%) between the groups, there was no significant difference between the pre-NPT FVC% and post-NPT FVC% in our subjects (results not shown), but the two studies were performed with different designs and, therefore, the comparison is just relative.

It is also convenient to remark that the spirometric parameters measured by the Winspiro flowmeter (previously called Fleischmann's tachymeter) are not the directly measured classic volume values but are derived from a mathematical cohesion supported by the fact that, at a laminar flow, the pressure difference and the flow rate are linear to each other. The advantage of this method is the precise measurement at low flows and absence of influence of air density or humidity.

Among the spirometric parameters of our subjects, FIV_{2dF%} showed to be more consistent to suggest a normal inspiratory loop or PVFM. A decrease in FIV₂ of <9% was not associated with any abnormal inspiratory loop. A decrease of >25% in FIV₂ or FIVC on post-NPT spirometry was highly suggestive of PVFM, as well as a decrease in FIV₁/FIVC of >17%.

The combination of allergen-specific NPT with spirometry can enrich the information sought by both tests. It is a useful way to show a direct link between specific sensitivity and laryngeal hyperresponsiveness in allergic subjects and, consequently, can be used as an indicator for the therapeutic approach, among others, immunotherapy. In this work, we observed a temporal association between allergen exposure and PVFM. This association suggests a new use for spirometry as a supplementary diagnostic parameter to the allergen-specific NPT. It also suggests a specific indication for NPT/spirometry on the diagnosis of allergen-specific PVFM. The information provided by this

test combination is valuable for allergists because it lends support to the indication of desensitization therapy, as well as the referral of patients with PVFM to an otolaryngologist with a suggestion for fiberoptic laryngoscopy. Reciprocally, these data alert otolaryngologists that patients with PVFM must also be investigated for allergies.

REFERENCES

1. Nolan PK, Chrysler M, Phillips G, et al. Pulse oximetry coupled with spirometry in the emergency department helps differentiate an asthma exacerbation from possible vocal cord dysfunction. *Pediatr Pulmonol* 42:605–609, 2007.
2. Schulze J, Weber S, Rosewich M, et al. Vocal cord dysfunction in adolescents. *Pediatr Pulmonol* 47:612–619, 2012.
3. Forrest LA, Husein T, and Husein O. Paradoxical vocal cord motion: Classification and treatment. *Laryngoscope* 122:844–853, 2012.
4. Turner PJ, and Foreman JC. Hyperresponsiveness in the human nasal airway: New targets for the treatment of allergic airway disease. *Mediators Inflamm* 8:133–146, 1999.
5. Aronsson D, Tufvesson E, Ankerst J, and Björner L. Allergic rhinitis with hyper-responsiveness differ from asthma in degree of peripheral obstruction during methacholine challenge test. *Clin Physiol Funct Imaging* 28:81–85, 2008.
6. Rondón C, Campo P, Herrera R, et al. Nasal allergen provocation test with multiple aeroallergens detects polysensitization in local allergic rhinitis. *J Allergy Clin Immunol* 128:1192–1197, 2011.
7. Sheahan P, Walsh RM, Walsh MA, and Costello RW. Induction of nasal hyper-responsiveness by allergen challenge in allergic rhinitis: The role of afferent and efferent nerves. *Clin Exp Allergy* 35:45–51, 2005.
8. Pelikan Z. Late and delayed responses of the nasal mucosa to allergen challenge. *Ann Allergy* 41:37–47, 1978.
9. Lebel B, Bousquet J, Morel A, et al. Correlation between symptoms and the threshold for release of mediators in nasal secretions during nasal challenge with grass-pollen grains. *J Allergy Clin Immunol* 82:869–877, 1988.
10. López S, Rondón C, Torres MJ, et al. Immediate and dual response to nasal challenge with *Dermatophagoides pteronyssinus* in local allergic rhinitis. *Clin Exp Allergy* 40:1007–1014, 2010.
11. Fabbri N, Abib-Junior E, Vian BS, et al. A new approach to bioequivalence studies for nasal sprays: A nasal challenge considering histamine intermediate-late phase reaction. *J Bioequiv Availab* 2011:S1. (DOI:10.4172/jbb.S1-006.)
12. Lopuhaä CE, Out TA, Jansen HM, et al. Allergen-induced bronchial inflammation in house dust mite-allergic subjects with or without asthma. *Clin Exp Allergy* 32:1720–1727, 2002.
13. Hicks M, Brugman SM, and Katial R. Vocal cord dysfunction/paradoxical vocal fold motion. *Prim Care* 35:81–103, 2008.
14. Bucca C, Rolla G, Brussino L, et al. Are asthma-like symptoms due to bronchial or extrathoracic airway dysfunction? *Lancet* 346:791–795, 1995.
15. Christopher KL, Wood RP, Eckert RC, et al. Vocal-cord dysfunction presenting as asthma. *N Engl J Med* 308:1566–1570, 1983.
16. Morrison M, Rammage L, and Emami AJ. The irritable larynx syndrome. *J Voice* 13:447–455, 1999.
17. Ayres JG, and Gabbott PL. Vocal cord dysfunction and laryngeal hyperresponsiveness: A function of altered autonomic balance? *Thorax* 57:284–285, 2002.

18. Murry T, Cukier-Blaj S, Kelleher A, and Malki KH. Laryngeal and respiratory patterns in subjects with paradoxical vocal fold motion. *Respir Med* 105:1891–1895, 2011.
19. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 63(suppl 86):8–160, 2008.
20. Olivier CE, Argenta DGP, Santos RAPG, et al. Skin scrape test: An inexpensive and painless skin test for recognition of immediate hypersensitivity in children and adults. *Open Allergy J* 6:9–17, 2013.
21. Olivier CE, Lorena SL, Pavan CR, et al. Is it just lactose intolerance? *Allergy Asthma Proc* 33:432–436, 2012.
22. Knudson RJ, Slatin RC, Lebowitz MD, and Burrows B. The maximal expiratory flow-volume curve. Normal standards, variability, and effects of age. *Am Rev Respir Dis* 113:587–600, 1976.
23. Litvyakova LI, and Baraniuk JN. Nasal provocation testing: A review. *Ann Allergy Asthma Immunol* 86:355–364, 2001.
24. Gosepath J, Amedee RG, and Mann WJ. Nasal provocation testing as an international standard for evaluation of allergic and nonallergic rhinitis. *Laryngoscope* 115:512–516, 2005.
25. Rondón C, Fernandez J, Canto G, and Blanca M. Local allergic rhinitis: Concept, clinical manifestations, and diagnostic approach. *J Investig Allergol Clin Immunol* 20:364–371, 2010.
26. Tantilipikorn P, Vichyanond P, and Lacroix JS. Nasal provocation test: How to maximize its clinical use? *Asian Pac J Allergy Immunol* 28:225–231, 2010.
27. Micheletto C, Visconti M, Tognella S, et al. Urinary LTE4 is higher after nasal provocation test with L-ASA in bronchial than in only nasal responders. *Eur Ann Allergy Clin Immunol* 39:162–166, 2007.
28. Godnic-Cvar J, Somogyi-Zalud E, and Plavec D. Nasal challenge with histamine decreases nonspecific bronchial reactivity in workers exposed to respiratory irritants. *Am J Ind Med* 35:420–425, 1999.
29. Baki A, and Uçar B. Diagnostic value of the nasal provocation test with *Dermatophagoides pteronyssinus* in childhood asthma. *Allergy* 50:751–754, 1995.
30. Pelikan Z. Asthmatic response induced by nasal challenge with allergen. *Int Arch Allergy Immunol* 148:330–338, 2009.
31. Koolen BB, Pijnenburg MW, Brackel HJ, et al. Comparing Global Initiative for Asthma (GINA) criteria with the Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT). *Eur Respir J* 38:561–566, 2011.
32. Sterner JB, Morris MJ, Sill JM, and Hayes JA. Inspiratory flow-volume curve evaluation for detecting upper airway disease. *Respir Care* 54:461–466, 2009.
33. Newman KB, Mason UG III, and Schmalzing KB. Clinical features of vocal cord dysfunction. *Am J Respir Crit Care Med* 152:1382–1386, 1995. □

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