

Assessment of allergen-induced respiratory hyperresponsiveness before the prescription of a specific immunotherapy

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ABSTRACT

Background: Asymptomatic sensitization is a frequent condition that must be considered before the indication of allergic-specific immunotherapy.

Objective: The aim of this study was to appreciate and correlate the local and spirometric changes elicited by the allergen-specific nasal provocation test (NPT) to define practical and feasible guidelines for the allergist/immunologist to demonstrate specific respiratory hyperresponsiveness before the indication of allergic-specific immunotherapy.

Methods: A total of 172 subjects (children and adults) with a diagnosis of allergic rhinitis were submitted to flow-volume spirometry immediately before and after the NPT performed with *Dermatophagoides antigens*. The differences between the pre- and postspirometric estimated values of peak expiratory flow rate ($PEF_{dif\%}$), forced expiratory volume in 1 second ($FEV_{1dif\%}$), and forced vital capacity ($FVC_{dif\%}$) were correlated with the results of the nasal provocation test symptom score (NPT-SS).

Results: There were 119 subjects (69%) with $NPT-SS > 2$. Among these patients who were reactive, the mean NPT-SS was 6.3. The Spearman's correlation between $PEF_{dif\%}$ and NPT-SS was $r = -0.44$ ($p = 0.01$); the Spearman's correlation between $FEV_{1dif\%}$ and NPT-SS was $r = -0.22$ ($p = 0.01$), and the Spearman's correlation between $FVC_{dif\%}$ and NPT-SS was $r = -0.21$ ($p = 0.04$).

Conclusion: The combined utilization of the allergen-specific NPT-SS with the spirometry (or PEF meter) is a safe methodology to evaluate allergen-specific nasal and bronchial hyperresponsiveness (which sometimes acts as a bronchial provocation test) in patients with allergic rhinitis and asthma due to hypersensitivity who are candidates for allergen-specific immunotherapy.

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The etiologic investigation of patients with respiratory allergy is the main step before the prescription of an allergen-specific immunotherapy.¹ The detection of specific immunoglobulin E (IgE) is essential but not sufficient to establish the diagnosis of allergy.² Asymptomatic sensitization is a frequent condition that may mislead the diagnosis of allergy.³ The crescent sensibility of the laboratory assays to detect specific IgE has expanded the diagnosis of sensitization more common in subjects who have complete tolerance to the studied allergen.⁴ The clinical diagnosis of al-

lergy must differentiate asymptomatic sensitizations to irrelevant antigens from the relevant immunoreactive allergens to which the patient is intolerant. When considering the high heterogeneity of sensitization profiles and the patients with only local sensitization, the best way to establish this differentiation is the challenge test, which reproduces the clinical symptoms.^{5–7}

The allergen-specific nasal provocation test (NPT) is a valuable *in vivo* examination designed to support the etiologic diagnosis of allergic rhinitis and, when combined with spirometry, may also establish the diagnosis of paradoxical vocal fold motion.^{8,9} The use of NPT in patients with asthma is considered safe, despite possibly being associated with significant bronchial reactions when evaluated by the forced expiratory volume at 1 second (FEV_1), specific conductance, lung volumes, and the O_2 saturation.^{10–12} Curiously, the studies do not mention the peak expiratory flow (PEF). In fact, the concept of a close connection between allergic rhinitis and asthma as supported by the Allergic Rhinitis and its Impact on Asthma document makes us predict that an upper respiratory allergic reaction may be accompanied by alterations in the lower respiratory

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organs.¹³ The routine use of respiratory challenges as a confirmation step for the indication for allergic-specific immunotherapy seems to be the ideal procedure, but, in many services, it may be a utopia. Most publications regarding nasal challenges use sophisticated nasal patency measuring devices, such as the acoustic rhinometry or rhinomanometry, whereas in real life most allergists do not even routinely use a spirometer in their practice. To simplify the allergen challenge step of candidates for allergen-specific immunotherapy, we associated a validated symptom score for allergen-specific NPT and the expiratory spirometric parameters (including the PEF) measured by flow-volume spirometry by searching for a correlation between the upper and lower airways immediate responses.

METHODS

Study Design and Subjects

The study was approved by the ethical review board of the Irmandade de Misericórdia de Campinas and registered at the Plataforma Brasil (CAAE 07971212.0.0000.5480), and was conducted according to the principles of the Declaration of Helsinki. Informed assent and consent were obtained before enrollment. Patient data were kept confidential. No investigational drugs were used.

We examined 172 subjects (115 female; ages 4–74 years, mean [standard deviation] 30.3 ± 16 years; including 19 children younger than 13 years). The subjects were not using any medication for at least for 2 weeks before the examination. All the subjects had a previous clinical diagnosis of allergic rhinitis and evidence of IgE-mediated hypersensitivity to *Dermatophagoides pteronyssinus* by serum analysis of specific-IgE, skin-prick test, and skin scrape test performed as previously described.¹⁴ No subject had a previous diagnosis or symptoms of asthma.

NPT

The allergen-specific NPT was performed in subjects who had demonstrated no abnormalities in the previous spirometry (pre-NPT). 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 the subject. The subject was instructed to inhale before allergen application, to hold his or her breath during application, and to exhale immediately after application. A symptom score (NPT-SS), which ranged from 0 to 12 for immediate reactions, was implemented after each NPT as described by Lebel *et al.*,¹⁵ who described as significant a score of >2 . The appearance of lower respiratory symptoms and signs was also observed.

Spirometry

The values obtained by spirometry for each subject pre-NPT and 15 minutes post-NPT were recorded as spirometric data. The subjects were acclimatized for at least 30 minutes 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 loops. FVC, FEV₁, FEV₁-FVC ratio, and PEF were measured by flow-volume spirometry (WinspiroPRO 3.6.3 USB spirometer; MIR Medical International Research, Rome, Italy). The spirometer software also was used to calculate the %pred results for each lung function value in the reference population according to his or her age and height, and the relative difference of the %pred results between the pre-NPT and the post-NPT values (dif%).¹⁶

Statistical Analyses

Paired correlation charts between the NPT-SS and the %pred results of each spirometric parameter were plotted, and Spearman's rank correlation was used to analyze results. Statistical analyses were performed with GraphPad Prism for Windows (version 5.0; GraphPad Software, Inc., San Diego, CA).

RESULTS

Symptom Score

There were 119 subjects (69%) with a NPT-SS > 2 . Among the subjects who were reactive, the mean NPT-SS was 6.3.

Spirometric Parameters

PEF

There were 12 subjects (7%) who had a decrease of PEF of $>20\%$ ($PEF_{dif\%} = 21\text{--}42\%$; mean $PEF_{dif\%} = 25.9\%$). Among these subjects, the mean relative decrease of PEF after NPT ($PEF_{dif\%}$) was 25.9%. There were 33 subjects (19.1%) who had a decrease of PEF of $\geq 15\%$. Among these subjects who were reactive, the mean relative decrease of PEF after NPT ($PEF_{dif\%}$) was 20.5%. In this group, the Spearman's correlation between $PEF_{dif\%}$ and NPT-SS was $r = -0.44$ ($p = 0.01$) (Fig. 1).

FEV₁

Two subjects (1.1%) had a decrease of FEV₁ $\geq 20\%$. Among these subjects, the mean $FEV_{1\ dif\%}$ was 22.5%. There were 5 subjects (2.9%) who had a decrease of FEV₁ $\geq 15\%$. Among these subjects, the mean $FEV_{1\ dif\%}$ was 15.4%. There were 112 subjects (65.1%) who had a decrease of FEV₁ $\geq 1\%$. Among these subjects, the

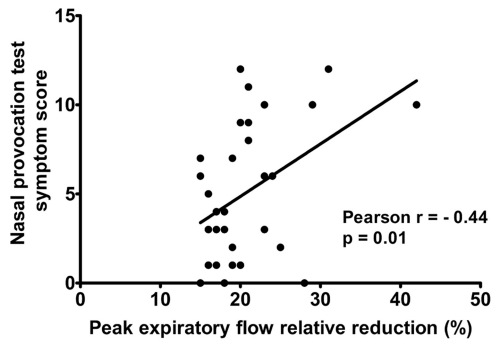


Figure 1. A paired correlation chart between the symptom score of the NPT with *D. pteronyssinus* and the PEF relative decrease after NPT in subjects with allergic rhinitis and a decrease in PEF $\geq 15\%$.

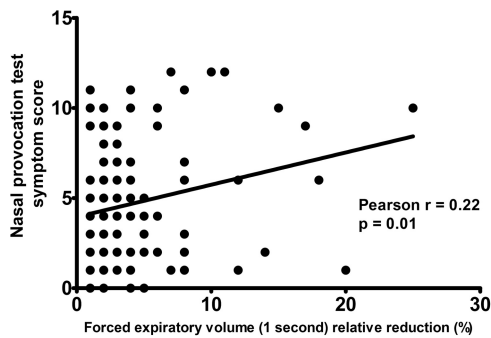


Figure 2. A paired correlation chart between the symptom score of the NPT with *D. pteronyssinus* and the FEV₁ relative decrease after NPT in subjects with allergic rhinitis and a decrease in FEV₁ $\geq 1\%$.

mean FEV_{1 dif%} was = 4.4%. In this group, the Spearman's correlation between FEV_{1 dif%} and NPT-SS was $r = -0.22$ ($p = 0.01$) (Fig. 2).

FVC

There were 2 subjects (1.1%) who had a decrease of FVC $\geq 20\%$. Among these subjects, the mean relative decrease of FVC after NPT (FVC_{dif%}) was 21%. There were five subjects (2.9%) who had a decrease of FVC $\geq 15\%$. Among these subjects, the mean relative decrease of FVC after NPT (FVC_{dif%}) was 17.8%. There were 123 subjects (71.5%) who had a decrease of FVC $\geq 0\%$. Among these subjects, the mean relative decrease of FVC after NPT (FVC_{dif%}) was 3.5%. In this group, the Spearman's correlation between FVC_{dif%} and NPT-SS was $r = -0.21$ ($p = 0.04$) (Fig. 3).

FEV₁-FVC

There were no subjects who had a decrease of FEV₁-FVC $\geq 20\%$. There was one subject (0.5%) who had a decrease of FEV₁-FVC $\geq 15\%$. There were 75 subjects (71.5%) who had a decrease of FVC $> 0\%$. Among these subjects, the mean relative decrease of FEV₁-FVC after NPT (FEV₁-FVC_{dif%}) was 3.8%. There was no

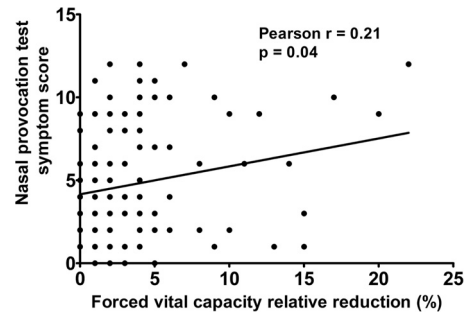


Figure 3. A paired correlation chart between the symptom score of the NPT with *D. pteronyssinus* and the FVC relative decrease after NPT in subjects with allergic rhinitis and a decrease in FVC $\geq 0\%$.

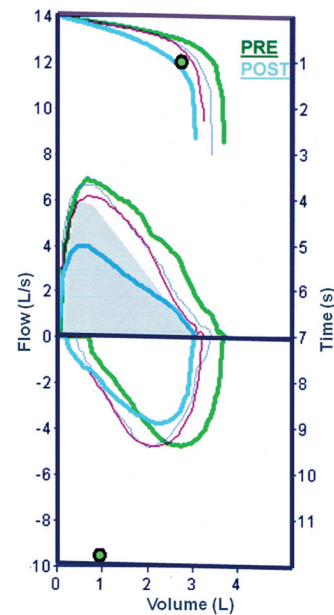


Figure 4. Flow-volume and volume/time charts of the subject who was most reactive pre- and post-NPT with *D. pteronyssinus* (a 28-year-old woman who had an NPT-SS = 10; PEF_{dif%} = -42%; FVC_{dif%} = -17%; FEV₁-FVC_{dif%} = -9%, and FEV_{1 dif%} = -25% after allergen-specific NPT).

significant correlation between FEV₁-FVC_{dif%} and NPT-SS.

DISCUSSION

The allergen-specific NPT is a simple, valuable, and neglected examination. Our results agreed with the literature about the safety of the allergen-specific NPT. In our series, only 2 subjects (1.1%) demonstrated a decrease of FEV₁ $> 20\%$ and presented respiratory symptoms (dyspnea, sibilance, and cough), which improved after the use of a short-acting bronchodilator inhaler. Shown in Fig. 4 are the flow/volume and the volume/time charts of the subjects who were most reactive before and after allergen-specific challenge (a 28-year-old woman with NPT-SS = 10, PEF_{dif%} =

-42%, $FVC_{dif\%} = -17\%$, $FEV_{1-FVC_{dif\%}} = -9\%$, and $FEV_{1_{dif\%}} = -25\%$ after allergen-specific NPT).

As a safe and specific challenge, the utilization of the NPT may be useful in patients with allergic rhinitis before the prescription of allergen-specific immunotherapy. The criterion to monitor NPT is nasal patency measurement, such as the anterior manometry and/or the acoustic rhinometry when considering the immediate, intermediate, and late-phase reactions.¹⁷ However, due the high costs and complexity of the equipment to perform these examinations, as well the assistance of trained technicians, these examinations are usually restricted to research facilities. With the lack of the patency devices, the allergen-specific NPT may be performed in the medical examination room with a simple score of symptoms that may help to quantify the allergic nasal reactions.¹⁵ Similarly, the evaluation of bronchial hyperresponsiveness may be beneficial before performing immunotherapy as an assessment risk for asthma, but the combined use of NPT and spirometry is not meant to substitute for bronchial challenge. During the NPT procedure, the subject was instructed to inhale before allergen application, to hold his or her breath during application, and to exhale immediately after application to prevent the allergen from reaching the bronchus. So, the interpretation of the results may be biased because of the capability of each subject to hold his or her breath. The evaluation of the bronchial hyperresponsiveness is usually performed by means of a flow-volume spirometry. Despite the fact that the acquisition and the maintenance of a spirometer are not expensive, it may not be affordable for low-income health services that are operating in developing countries. An inexpensive solution, in the absence of a spirometer, is to use the peak-flow meter to monitor bronchospasm.

Asymptomatic episodes of bronchospasm are common in mild intermittent asthma and may be present in patients with allergic rhinitis without any lower respiratory symptoms.¹⁸ These episodes may be diagnosed by the bronchial challenge test, a well-established technique that uses the inhalation of specific allergens or nonspecific agents with defined cutoff values.¹⁹ Usually the cutoff for an inhalation challenge test is a decrease of $FEV_{1} > 20\%$.²⁰ Because we do not have a defined cutoff value to establish the significance of the spirometric alterations after an NPT, we compared the spirometric parameters with the bronchial challenge test cutoff, stratified the results, and searched a possible correlation with the results of NPT-SS. A significant correlation between the variation of intensity between the allergen-specific NPT-SS values and the expiratory spirometric parameters after the nasal challenge is a convincing demonstration of the impact of the nasal allergic reactions over the bronchial responsiveness and asthma.¹³

The spirometric parameter that had the most significant correlation to NPT-SS was PEF, which may be easily estimated with the help of a PEF meter. The PEF meters are portable and inexpensive devices produced by several companies with different designs and accuracies. The most modern are digital and also measure the FEV_{1} . Several studies validated the accuracy of the portable PEF meters in accordance with the American Thoracic Society criteria.²¹⁻²³

In summary, the simultaneous utilization of the NPT-SS and the flow-volume spirometry (and for extension the PEF meter) is a simple and low-cost examination combination that may be inexpensively implemented in low-income health services to evaluate allergen-specific nasal and bronchial hyperresponsiveness in candidates for allergen-specific immunotherapy.

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