Evaluation of bronchial hyper-reactivity through some new parameters of respiratory functional tests

Anxhela Gurakuqi (Qirko)[1,2]

[1]Department of Biomedical and Experimental Sciences, University of Medicine, Tirana, Albania;
[2]Interne Medicine Division and Respiratory Function Laboratory, University Hospital Center "Shefqet Ndroqi", Tirana, Albania.

Corresponding author: Anxhela Gurakuqi (Qirko), MD, PhD;
Address: Rr. "Dibres", No. 371, Tirana, Albania
E-mail: anxhela_g@yahoo.com

Abstract

Aim: Bronchial hyper-reactivity is one of the most important components of bronchial asthma, but it is present also in other diseases, and occasionally in normal people too. Different methods of bronchial provocation are used for the diagnosis of bronchial hyper-reactivity, with very long protocol procedures, very high cost of materials and medical staff, sometimes even risky, due to an eventual bronchospasm provoked to the patient. Presentation of the ratio RV/TLC as an indicator parameter of "air trapping", registered from plethysmography, and its role to evaluate in another dimension the bronchial hyper-reactivity, without any bronchial provocation of the patient.
Methods: Comparing physiopathology meaning of different parameters of lung function tests, not only after the provocation of airways tree "mimicking" the natural stimuli, but also the basic parameters including those offered from plethysmography, which is a technological evolution of spirometry.
Results: Evidence-based good correlation between methacholine provocation and effort provocation results with RV/TLC> 125% of predicted (the latter is an original preliminary study of the author), explains the relation of bronchial hyper-reactivity to different stimuli and "air trapping"- or the bronchospasm/obstruction of small airways.
Conclusion: New parameters offered from the technological evolution of lung function tests, like the RV/TLC ratio>125% of predicted value, open new perspectives and ways to evaluate the bronchial hyper-reactivity.

Keywords: air trapping, BHR, plethysmography, RV/TLC.

When the spirometry test results normal, especially when it does exist any suspicion for intermittent and/ or mild form of bronchial asthma, the detection of bronchial hyper-reactivity (BHR) after Methacholine provocation is often suggested, for a diagnostic reason.

It is well known that, according to the bronchial asthma definition, the BHR is one of the three components of its diagnosis: bronchial obstruction + bronchial reversibility + BHR (1).

Methacholine provocation is one of the many methods used in the Respiratory Function Laboratories for BHR detection. Methacholine reacts to its cholinergic receptors in the bronchial tree triggering bronchospasm through a parasympathetic way of provocation. The same way it is used also through acetylcholine provocation, and through carbachol provocation.

There do exist different natural stimuli, which are able to provoke bronchospasm.

According to those natural stimuli, there are used different ways of bronchial provocation (2), such as:

- Cold air inhalation, which "mimics" a natural cold weather exposure, triggering mucosal nerve's receptors;
- Distilled water (hypotonic) inhalation / or Sol. NaCl 4,5% (hypertonic) inhalation which triggers osmotic provocation of inflammatory cells in the mucosal layer, and their degranulation;
- Physical effort test (and hyperventilation), with the osmotic mechanism of bronchial provocation ;
- Mannitol provocation, triggering bronchospasm again through osmotic changes;
- Histamine provocation, which reacts to its own bronchial receptors, triggering bronchospasm;
- Specific provocations, using suspected allergens (mostly professional allergens like isocyanates, etc.). The patient inhales it, in a non-ventilated small room, and the spirometry is performed before, and directly after the provocation.

It is evident that different ways of provocation "mimic" the real-life exposure: cold & dry air, hyperventilation & stress (physical, emotional), chemical & physical stimuli of the airways triggering osmotic changes, degranulation & cytokine release. As a result, in all types of these stimuli, there is a kind of BHR. That is there is not only one form of BHR, but several forms of BHR.

On the other hand, BHR is found not only in bronchial asthma, but also in other diseases like: sarcoidosis, COPD, rhinosinusitis, respiratory viral infections, stenosis of mitral valve, gastro-esophageal reflux and even in 5% of normal people (3).

This is the reason that in many Respiratory Function Laboratories, in the same patient there are used different forms of bronchial provocations. For the following simple reason: to discover BHR(s) in different ways (4).

Certainly, the provocation tests at the same patient should be scheduled in different days (not in the same day), just to avoid the risk of any expected bronchospasm.

In this matter, herewith are mentioned some real-life examples experienced during specializations and work conducted in France and The Netherlands. Depending to the technical possibilities of Respiratory Function Laboratories and the requirements for a stable clinical condition of the patient (after obtaining his/her written consensus, too), in several cases the author of this article has assisted in more than one provocation of the same patient: 1st day methacholine provocation, 2nd day histamine provocation, 3rd day effort provocation, or hyperventilation with cold and dry air. All these tests were trying to get an evidence of BHR, aiming toward the diagnostic of bronchial asthma. Above all, to get an objective argumentation for starting an anti-inflammatory treatment (by inhalation or not), even though the basal spirometry consistently was "normal".

All these aforementioned procedures, trying to make an evidence of BHR, bear some weak points. They bear, first of all, the risk of a severe bronchospasm, which may be sometimes very risky for the patients involved. This is the reason why an informed consent is required to be signed from the patient

before anything else, a good clinical condition of them - selected from the doctor, and finally why all these provocations are needed to be performed in a well-equipped hospital unit, with a quick access to the reanimation room.

In order to reduce the time-consuming research for BHR and minimize also the cost for the medical staff and material (as an example, methacholine is very expensive), it is applied another alternative, very modern and interesting for the detection of BHR. This new alternative, in the first place, does not involve any risks like the bronchial provocation tests, and being very short in time and cost, it could be applied in many more patients, and could enlarge the number of people whom BHR needs to be evaluated.

The new alternative for the interpretation of BHR is based on some universal physiologic parameters, which any deviation regards the obstruction of bronchial lumen, in the very distal ramification of the bronchial tree, where the cartilages are lacking: bronchiolar level. The obstruction/spasm in that level makes impossible the quantity of the air (which has already entered in the alveoli) to get out, so the air remains in the alveoli, increasing the Residual Volume (RV). If RV/TLC is increased more than 125% of predicted values, it is considered as "air trapping".

The abnormal increase of the ratio Residual Volume (RV) to Total Lung Capacity (TLC) can be found in 2 cases: in the pulmonary emphysema and in bronchial hyper-reactivity, with or without asthma.

For many years in the past, emphysema was linked to the "trapped air" and hyperinflation visualized also in X-ray. In the background of an emphysema patient, in general, there is a long history of smoking, COPD, spirometry parameter's deviations, beside "Pink Puffer model" of clinical signs. Plethysmography measures the increase in TLC, mostly due to the RV increase, but always the ratio RV to TLC. The "trapped air" can be found not only in obstructive diseases, but also in fibrotic diseases, where anemphysema concomitant phenomenon of the degeneration of elastic network of the lung could be present, and where restrictive zones are associated with hyperinflated zones (emphysema bubbles). In these restrictive diseases (like professional exposure to mines, volatile harmful substances, etc.) the TLC is reduced, but due to the reasons mentioned above, the ratio RV/TLC could be increased.

Bronchial hyper-reactivity, with or without asthma, is another case where "trapped air" is identified. This is also the innovation concept presented in this article.

This category of patients clinically presents a chronic dry cough, without fever, with no radiological abnormalities, with a normal spirometry, and a suspicion for allergy background. In many cases the allergy tests result positive for any aero-allergen, complying with the atopy, but still a normal spirometry does not help. An attentive anamnesis should identify if the patient is having any ACE-inhibitor medication (cough provoking as a side effect) or presents any clinical signs of gastro-esophageal reflux, or rhino-sinusitis – for a differential diagnosis.

In such cases, the bronchial provocation tests (methacholine, histamine, etc.) are recommended, for obtaining a proof of BHR (5).

In many modern respiratory function laboratories, well-equipped with the Plethysmography, it can be measured the ratio RV/TLC. An "air trapping" found there, reflects very well an obstruction and/or bronchospasm of small airways (the very distal air-tree generation), which comply with the diagnosis of BHR, even better, without a provocation. If the doctor should provoke the bronchial tree, to get any sign of obstruction/bronchospasm after the provocation, why to increase the risk of the patient, the length of the research, and the cost of the whole procedure?

By simply getting an increase of RV/TLC more than 125%, we can identify an evidence of BHR. According to a study performed by a Canadian team, the positive results of Methacholine

provocation have e significant correlation with the ratio RV/TLC >125% (6).

In an on-going research made by our Albanian team, the preliminary data presented recently in Pediatric Allergy & Asthma Meeting in London (October 2017), also indicate a significant correlation between free-running test results (the BHR from effort) and the basal plethysmography ratio RV/TLC >125% (7).

The increasing use in the everyday clinical practice of the plethysmography measurement has increased the quality level of lung function respiratory tests, extending the number of parameters beyond spirometry. It is well-known in the community of allergology and pneumology specialists, a discrepancy between some really suggestive signs of BHR and/or asthma (mostly in very mild /intermittent forms) and a normal spirometry.

Having a quick measurement through plethysmography, this advanced technology lung function equipment, has brought many benefits, such as the aforementioned parameter: RV/TLC. Besides this, airway resistance is another new parameter interpreting directly the bronchospasm/obstruction. This parameter is very valuable mostly in children, because during resistance measurement the child could be relaxed, effortless, and does not need the same level of attention, understanding and cooperation like the forced expiration maneuver.

Reversibility test is another significant way reflecting how much changeable is the bronchial caliber (8), depending on the etiology of obstruction. Only bronchial asthma (with an associated BHR) is reversible more than 12% and 200 ml of FEV1 (10-15 min after 200-400mcg of Salbutamol), according to GINA guidelines (1). Generally, the two other obstructive airway diseases (COPD and emphysema) do not have any airway reversibility (except some rare cases of COPD). Obstructive spirometry with positive bronchodilator reversibility increases the probability of asthma (9).

Nowadays, there are attempts to include also the resistances in the reversibility test, but this has not been standardized in any international guidelines yet.

As a "normal" spirometry does not rule out the diagnosis of asthma, it is worthwhile to quote the British guideline on the management of asthma (9): *"In children, the relationship between asthma symptoms and lung function tests, including bronchodilator reversibility, is complex. Measures of gas trapping (residual volume and the ratio of residual volume to total lung capacity) may be superior to measurement of expiratory flow at detecting airways obstruction especially in asymptomatic children"* (10,11).

In conclusion, the fact that there is no "gold standard" for bronchial asthma diagnosis, the most important driving motivation should consist of continuous exploration of different ways, methods, tests and parameters, in order to identify as early as possible, the three components of asthma: obstruction + reversibility + BHR, at the very early stage of the disease. Because this disease starts at the small airways, with a tendency to progress toward medium and then to large airways, the functional parameters interpreting small airways, and "air trapping" of this level are very crucial.

Conflicts of interest: None declared.

References

1. 2018 GINA Report, Global Strategy for Asthma Management and Prevention. Available from: www.ginasthma.org/ 2018 (Accessed: January 10, 2018).
2. Van Schoor J, Joos GF, Pauwels RA, Indirect Bronchial Hyperresponsiveness in Asthma: Mecanisms, Pharmacology and Implications for Clinical Research. Eur Respir J 2010;16:514-33.

3. Schwartz J, Schlinder C, Zemp C. Predictors of Methacholine Responsiveness in a General Population. Chest 2002;122:812-20.

4. Brown LL, Martin BL, Morris MJ. Airway Hyperresponsiveness by Methacholine Challenge Testing, following Negative Exercice Challenge. J Asthma 2004;41:553-8.

5. Saga R, Mochizuki H, Tokuyama K, Morikawa A. Relationship between Bronchial Hyperresponsiveness and Development of Asthma in Wheezy Infants. Chest 2001;119:658-90.

6. Stanbrook MB, Chapman KR, Kesten S. Gas Trapping as a Predictor of Positive Methacholine Challenge in Patients with Normal Spirometry Results. Chest 1995;107:992-5.

7. Gurakuqi-Qirko A, Borici S, Ibranji S, Xhixha M, Shehu E, Hasanaj M, et al. The correlation between basal plethysmography ratio RV/ TLC with the decrease of FEV1 post effort, after free running test in allergic children with normal basal spirometry. Pediatric Asthma and Allergy Meeting (PAAM) London 2017, Poster Session: Asthma & Rhinitis, P025. Available from: www.eaaci.org/ meettings/ PAAM 2017/ Abstracts.

8. Ichinose M, Takahashi T, Sugiura H, Endoh N, Miura M, Mashito Y, et al. Baseline Airway Hyperresponsiveness and its Reversible Component: Role of Airway Inflammation and Airway Calibre. Eur Resp J 2000;15:248-53.

9. British Guideline on the management of asthma (BTS/ SIGN September 2016). Available from: www.brit-thoracic.org.uk (Accessed: January 10, 2018).

10. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF Jr, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. Am J Respir Crit Care Med 2004;170:426-32.

11. Verini M, Peroni DG, Rossi N, Nicodemo A, De Stradis R, Spagnolo C, et al. Functional assessment of allergic asthmatic children while asymptomatic. Allergy Asthma Proc 2006;27:359-64.