



## Relation and Concordance of Two Methods for the Evaluation of Airway Hyperresponsiveness in Obese Adolescents

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### ABSTRACT

**Cieslak F, Lopes WA, Titski ACK, Timossi LS, Levandoski G, Vilela Junior GB, Rosário Filho NA, Leite N.** Relation and Concordance of Two Methods for the Evaluation of Airway Hyperresponsiveness in Obese Adolescents. **JEPonline** 2013;16(3):59-68. This study determined the relation and concordance of two methods for the evaluation of airway hyperresponsiveness in 15 obese adolescents (9 females and 6 males). Forced expiratory volume (FEV<sub>1</sub>) was evaluated at baseline and at 3, 5, 10, 15, and 30 min after a physical exercise test. Inhalation of 4.5% hypertonic saline was performed using a large-volume ultrasonic nebulizer continuously at 0.5, 1, 2, 4, and 8 min until the FEV<sub>1</sub> decrease was ≥15% in relation to baseline. The exercise-induced bronchospasm (EIB) was considered positive if the FEV<sub>1</sub> decrease was <10% in relation to the baseline. For the concordance of the FEV<sub>1</sub> fall of ≥10% for exercise with the FEV<sub>1</sub> fall of ≥15% of hypertonic saline (k=0.67; P=0.05), the linear regression intermethod was used (R<sup>2</sup>=0.751; P<0.001). The intraclass correlation coefficient was strong (ICC=0.86; P<0.001). The findings indicate that the two methods for the detection of airway hyperresponsiveness probably have the same trigger point, indicating that both methods promoted bronchial hyperosmolarity and possess a degree of concordance.

**Key Words:** Adolescent, Airway Hyperresponsiveness, Obese

## INTRODUCTION

The prevalence of obesity has increased substantially in many developing countries that it is now considered a worldwide epidemic (24). In the pediatric population, the presence of obesity is related to the development of symptoms related to cardiovascular diseases and asthma (13,16). Obesity has been verified as a risk factor for asthma based on the fact that excess adipose tissue in the body mass can cause changes in the mechanical properties and inflammatory responses of the respiratory system (13,15,20). Thus, asthma symptoms are the result of increased physiological responses of structures to protect the airways (i.e., bronchial hyperresponsiveness) (23,24).

Bronchial hyperresponsiveness can be defined as an exaggerated response to environmental stimuli, leading to constriction of the airways, while reactivity refers to the degree of spirometric changes in response to a stimulus (23,24). There are several methods to quantify hyperresponsiveness, including provocation tests using histamine or methacholine, exercise, inhalation of cold air under hyperventilation, and inhalation of hypertonic saline. All these tests are also used as objective markers of asthma (4,8,10,21).

While several studies have been performed to evaluate the relationship between obesity and pulmonary function tests in adults (1,11,27), bronchoprovocation using exercise and hypertonic saline solution inhalation have not been compared in obese adolescents (26). Thus, the purpose of this study was to evaluate the relation and concordance of the two provocation methods (exercise and hypertonic saline inhalation) used to investigate airway hyperresponsiveness in obese adolescents.

## METHODS

### Subjects

This study included 15 obese individuals (mean age,  $13.4 \pm 2$  yrs; 9 females and 6 males). The patients were selected from Pneumology Outpatient Service of Curitiba Clinics Hospital of the Federal University of Parana, Curitiba, PR, Brazil. All subjects received individual clarifications about the objectives, procedures, possible benefits, and risks related to the implementation of the study, and subsequently, confirmed their participation on a voluntary basis. Informed consent was obtained from parents since the subjects were children. The research protocol of the study was in accordance with the guidelines proposed in Resolution 196/96 of the National Health Council. The research was approved by the Ethics Committee of the Clinical Hospital, Federal University of Paraná (Protocol Number: 1818.235/2008-11).

Subjects were included in the study if they satisfied the following criteria: (a) participation in all assessments; (b) presentation of the consent form signed by parents or guardians; (c) individuals classified as obese; (d) self-reported absence of respiratory infections 4 wks prior to the provocation test, based on medical examinations before the beginning of evaluations; (e) self-reported absence of history of drug treatment and cardiovascular, respiratory, musculoskeletal and/or metabolic disorders; and (f) self-reported abstinence from use of drugs or food with caffeine 2 hrs before the tests.

### Clinical Procedures

A digital scale (Plenna<sup>®</sup>, MEA-03140, USA) with a resolution of 0.1 kg was used to measure body weight. The subjects were assessed barefoot with as little clothing as possible. Height was measured using a stadiometer (Sanny<sup>®</sup>, Standard, Brazil) with a resolution of 0.1 cm. All subjects were measured barefoot and in inspiratory apnea with the head positioned in the Frankfort plane (9). Body

mass index (BMI) was calculated from the measured weight and height. The criteria adopted for BMI classification were based on the critical values used to determine the nutritional status of children and adolescents proposed by the CDC (12).

The assessment of pubertal subjects was performed by self-assessment using maturation stage figures as proposed by Tanner (25). Girls were evaluated in terms of breast development and pubic hair growth and boys in terms of testicular size and pubic hair growth. This method shows satisfactory agreement with the medical evaluation of obese individuals (14).

### **Evaluation of Pulmonary Function Before Provocation Tests**

The International Study of Asthma and Allergies in Childhood (ISAAC) (5) was used. Lung function was measured by a spirometer (Microlab<sup>®</sup>, Micromedical, UK) in the sitting position using a nose clip. The variables measured were lung forced vital capacity (FVC) and forced expiratory volume in one second (FEV<sub>1</sub>) in liters (l). There were three spirometric maneuvers and the one with the highest values for FEV<sub>1</sub> and FVC was selected (18). The percentages of predicted values of FEV<sub>1</sub> and FVC for age and sex were calculated according to Polgar and Promodhat (19), from which the ratio of FEV<sub>1</sub> to FVC was estimated.

Before the tests were conducted, the techniques necessary for the spirometric maneuvers to examine lung function (with at least one baseline spirometry before to have reproducible outcomes) followed the guidelines for pulmonary function testing in which the subjects did not present FEV<sub>1</sub> <75% on the day of the tests (3,7). The tests were performed in the afternoon from 1400 to 1700 hrs in an environment maintained at a temperature of 20 to 25°C with air humidity below 50%.

### **Exercise Test**

The physical exercise test was performed on a treadmill (Ecafix<sup>®</sup>, 700X, USA) using the protocol proposed by the American Thoracic Society (3,7). The protocol consisted of walking/jogging at an intensity >85% of the maximum heart rate (HR max) for 8 min. To control intensity, the slope of the treadmill was adjusted to 10% and the speed to that estimated using the equation, speed (mi·hr<sup>-1</sup>) = 1.16 + 0.02 × [Height (cm)] (22). Heart rate was monitored using a cardiac monitor (Polar<sup>®</sup>, S625X, Kempele, Finland). FEV<sub>1</sub> was measured at 3, 5, 10, 15, and 30 min after exercise. The exercise-induced bronchospasm (EIB) was considered positive if there was a greater than 10% fall in FEV<sub>1</sub> compared to the pre-exercise value (8,26).

### **Hypertonic Saline Test**

To evaluate airway hyperresponsiveness, 4.5% hypertonic NaCl was inhaled using an ultrasonic nebulizer (DeVilbiss<sup>®</sup>, Somerset, PA, USA). The nebulizer was weighed before and after the end of each nebulization by replacing the hypertonic solution to the initial weight and volume, since the fluid level inside the vessel interferes with the flow. The subjects were seated comfortably and encouraged to maintain a good posture to provide the proper administration of saline. They were asked to breathe normally through the mouthpiece containing an exhalation valve and a nose clip, thus avoiding hyperventilation. The instruction was to swallow excess saliva, to prevent the saliva from entering the tube. The elevation of the tube above the height of the subject's mouth and buccal inversion with the exhalation valve down were also used to prevent saliva from entering the inhalation tube. The solution remaining in the tube at the end of inhalation was re-included in the metered volume for later weighing. The saline solution was withdrawn from the vial with a 25-ml syringe using a sterile needle, maintaining the presence of air within the tube even during test execution.

The duration of inhalation was increased gradually (0.5, 1, 2, 4, and 8 min totaling 15.5 min) until there the FEV<sub>1</sub> fall was ≥15% (21,26) or the maximum accumulated time was 15.5 min. The spirometric measurements were undertaken 1 min after inhalation. The total inhaled substance was examined by weighing the meter with the hose after each nebulization and verifying the difference from the initial weight.

### Evaluation of Pulmonary Function After Provocation Tests

After the provocation tests, the subjects' FEV<sub>1</sub> (1) was measured and the intensity of bronchial hyperresponsiveness was calculated as the maximum percentage of FEV<sub>1</sub> fall (maximum % of FEV<sub>1</sub> fall), using the following equation:  $Fall_{max} FEV_1 = (FEV_{1before} - FEV_{1after}) \times 100 / FEV_{1before}$ .

### Statistical Analysis

Shapiro-Wilk's test was used to analyze the normality of the parametric data. To compare frequency measures between methods Z and McNemar's tests were applied. The relationships of the variables measured by different methods were verified by linear regression and the intraclass correlation coefficient. The identification of concordance between the methods was evaluated by the Kappa index of concordance (2) and Bland-Altman (6) plots (P<0.05). All statistical analyses were performed using Statistica 7.0 (Statsoft, Tulsa, USA).

## RESULTS

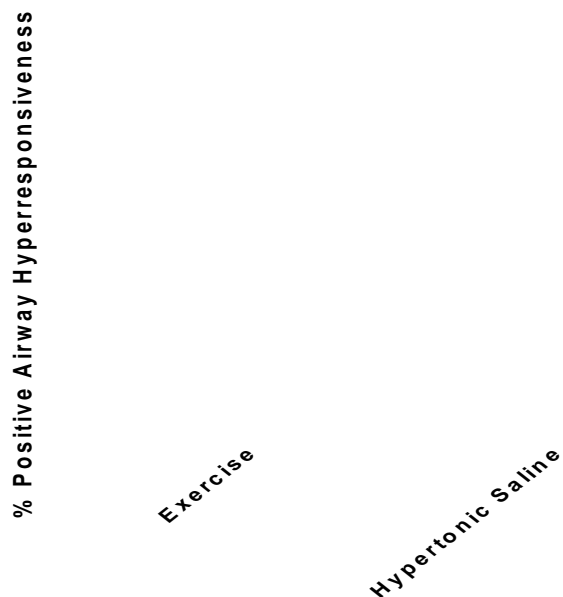
Six asthmatics and 9 non-asthmatics were identified in this study. All subjects were classified as pubescent according to the maturational stage. Table 1 shows the mean and standard deviation for anthropometric and spirometric variables. Normality was confirmed date in the parametric variables.

**Table 1. Anthropometric and Spirometric Variables of Subjects at the Baseline.**

<b>Variables</b>	<b>Mean ± Standard Deviation</b>
<b>Weight (kg)</b>	81.11 ± 13.84
<b>Height (cm)</b>	161.91 ± 8.41
<b>Body mass index (kg·m<sup>-2</sup>)</b>	30.87 ± 4.23
<b>FEV<sub>1</sub> (l)</b>	2.99 ± 0.60
<b>FEV<sub>1</sub> (% of expected value)</b>	91.00 ± 12.41
<b>FVC (l)</b>	3.55 ± 0.78
<b>FVC (% of expected value)</b>	103.88 ± 13.04
<b>FEV<sub>1</sub>/FVC (%)</b>	84.62 ± 7.40

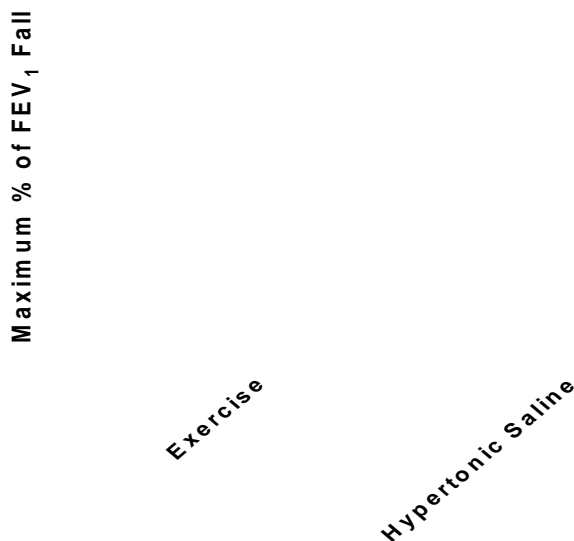
Frequency of bronchial hyperresponsiveness during exercise and hypertonic saline inhalation are presented in Figure 1. Positive bronchoprovocation was more frequent in obese asthmatics than in obese non-asthmatics, but no significant differences were observed for provocation by exercise ( $X^2 =$

2.550;  $P = 0.118$ ) and hypertonic saline ( $X^2 = 1.086$ ;  $P = 0.293$ ). Although exercise was more positive, no significant difference was identified by the Z test ( $Z = 1.107$ ;  $P = 0.268$ ).



**Figure 1. Frequency of Airway Hyperresponsiveness in Exercise and Hypertonic Saline Solution Models.**

Figure 2 shows the values of the maximum % of FEV<sub>1</sub> fall in exercise and hypertonic saline solution methods. Although the exercise method (Median [Minimum-Maximum] = - 8.28% [- 53.56%; - 2.45%]) showed lesser variability than the hypertonic saline solution method (Median [Minimum - Maximum] = - 5.56% [- 50.45%; + 50.51%]), no significant difference was identified by the McNemar's test ( $X^2 = 3.200$ ;  $P = 0.073$ ).



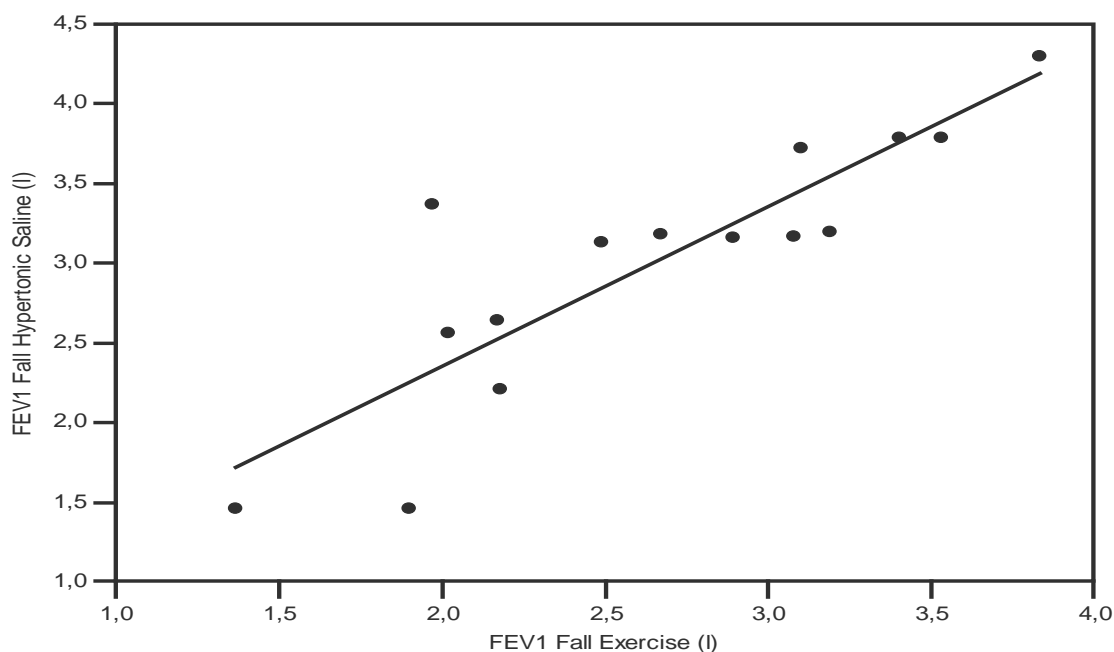
**Figure 2. Frequency of Maximum % in FEV<sub>1</sub> Fall in Exercise and Hypertonic Saline Solution Inhalation Models.**

Concordance of FEV<sub>1</sub> fall of  $\geq 10\%$  for the exercise method with that of  $\geq 15\%$  for hypertonic saline solution inhalation method ( $k = 0.67$ ;  $P = 0.05$ ) is presented in Table 2.

**Table 2. Kappa Index of Comparison of Exercise and Hypertonic Saline Solution**

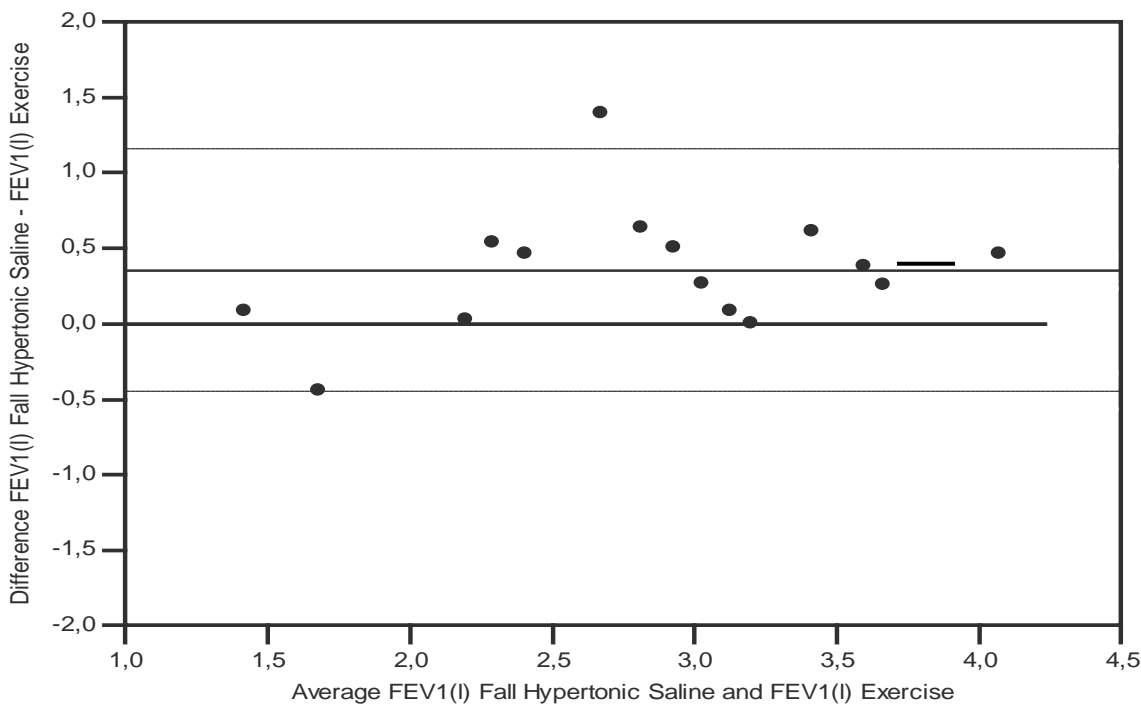
Methods	Hypertonic Saline Solution	Hypertonic Saline Solution
	(-15%)	(+15%)
Exercise (-10%)	6.7% (1)	33.3% (5)
Exercise (+10%)	0% (0)	60% (9)

Figure 3 shows the regression coefficient between both methods. The FEV<sub>1</sub> fall for the exercise method and that for the hypertonic saline method were significantly related ( $R^2 = 0,751$ ;  $P < 0.001$ ). The intraclass correlation coefficients were significant for both methods (ICC = 0.86;  $P < 0.001$ ; IC95% = 0.603 - 0.945).



**Figure 3. Dispersion Chart % in FEV<sub>1</sub> Fall in Exercise and Hypertonic Saline Solution Inhalation Models.**

The concordance analyses between the different methods of airway hyperresponsiveness are presented in Figure 4. The results indicate concordance between FEV<sub>1</sub> fall for exercise and FEV<sub>1</sub> fall for hypertonic saline inhalation (bias = 0.409;  $P = 0.130$ ; Lower Limit = -0.445; Upper Limit = 1.158).



**Figure 4. Bland-Altman in Relation of FEV<sub>1</sub> Fall in Exercise and Hypertonic Saline Solution Models.**

## DISCUSSION

Recent evidence has demonstrated associations between obesity and asthma with bronchial hyperresponsiveness (23,24,26). In obesity, the mechanical properties of the respiratory system are changed because of the effect of the fat on the thorax and diaphragm. This results in restricted chest movement and compliance with possible increases in airway hyperresponsiveness (20). The results of the present study show that the hypertonic saline inhalation and exercise methods can be satisfactorily used to evaluate airway hyperresponsiveness in obese adolescents. These findings are important because they show that these indirect tests are interesting alternatives to the bronchoprovocation test.

With the difficulty of obtaining direct methods, provocation tests using physical exercise and hypertonic saline solution inhalation have been used to assess more frequent hyperresponsiveness (16,21,26). Despite being an analogous method, the exercise method demonstrated a loss of airway fluid to the external environment due to physiological hyperpnoea. Hypertonic saline solution inhalation reproduces this mechanism, with the advantages of being performed with tidal volume and does not require patient cooperation to achieve the maximum load of effort (8,21).

The results of this study indicate a higher frequency of bronchial hyperresponsiveness to bronchial provocation by the exercise method (40%) than that by the hypertonic saline solution inhalation method (26.7%), but differences were not significant ( $Z = 1.107$ ;  $P = 0.268$ ). Another survey conducted by Ulger et al. (26) found similar data for bronchoprovocation by the exercise (31.6%) and hypertonic saline solution inhalation (18.4%) methods. A plausible response to this frequency variation between both methods is related to a lower sensitivity for the exercise method (FEV<sub>1</sub> fall

>10%) than for the hypertonic saline solution inhalation method (FEV<sub>1</sub> fall  $\geq$ 15%). However, the literature indicates that this represents an adequate sensitivity to the bronchial provocation test by the exercise method (8). Nevertheless, the comparison values of the maximum % of FEV<sub>1</sub> fall were not statistically different ( $X^2 = 3.200$ ;  $P = 0.073$ ) between the methods, demonstrating the similarity between the measurement techniques.

The tests used in this study induced bronchoconstriction and showed a good level of concordance for the Kappa Index ( $k = 0.67$ ;  $P = 0.05$ ). A good concordance between the techniques (2) shows that these frequencies can cause positive bronchoprovocation in obese adolescents even without a diagnosis of asthma, regardless of the technique applied (26). Additionally, linear regression analysis ( $R^2 = 0.751$ ;  $P < 0.001$ ), intraclass correlation coefficient (ICC = 0.86;  $P < 0.001$ ), and the Bland–Altman (6) technique showed adequate concordance (bias = 0.409;  $P = 0.130$ ) between methods; analysis of these models has been recommended by the literature as appropriate procedures for comparison of the data (2,6).

The hypertonic saline solution inhalation method seems to cause bronchoconstriction by increasing sodium, which results in changes in the membrane channels that involve calcium mechanism and bronchospasm (17). Similarly, bronchoprovocation by the exercise method may be explained partly by the increase in sodium concentration in the membrane, characterizing it as one of the theories related to water loss bronchoconstriction through hyperventilation (10). Therefore, these data suggest similarities in the physiologic responses of both methods for determining airway hyperresponsiveness in obese adolescents.

## CONCLUSIONS

This study showed that the two methods for detection of airway hyperresponsiveness have a high degree of concordance, probably indicating that both methods promote bronchial hyperreactivity as the triggering mechanism of bronchospasm. These findings allow for clinical implications, and this investigation provides important information to understand bronchoprovocation techniques and management of airway hyperresponsiveness in obese adolescents. However, concordance with gold standard measures and other populations needs to be determined in further studies.

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