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Body mass index and airway hyper-responsiveness in individuals without respiratory disease

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Key words

Airway hyperresponsiveness, body mass index; lung volumes, obesity, pulmonary function testing

Summary

Background. *Overweight and obesity are major health issues in Western societies. They are related with a higher risk of different co-morbidities but their relationship with airway hyperresponsiveness (AHR) is still under discussion. Nevertheless, they are related to higher severity in asthma and other respiratory diseases. The aim of the study was to analyze the AHR in individuals with normal lung function without respiratory disorders, according to body mass index (BMI) calculation.* ***Methods.*** *We performed clinical observation and basal lung function tests (LFT) in 595 consecutive individuals in order to exclude respiratory disease. 377 individuals fulfilled the criteria of normal values according international guidelines. They were submitted to standardized treadmill exercise test followed by bronchodilator test. FVC, FEV1, FEF 25/75, RV and Raw were obtained at different conditions according to BMI groups (I: lean; II: normal; III: overweight; IV: obese).* ***Results.*** *55.2% of the sample was overweight or obese, and a significant relationship was found with female gender and older ages ($p=0.0046$ and $p<0.0001$ respectively). The positive response to exercise test or bronchodilator β2 agonists was not significantly frequent compared with the other groups. In obese individuals the exercise markedly reduced basal Raw and increased FEF 25/75. Lean individuals showed higher basal values of RV that was reduced upon exercise. Response to β2 agonists showed no differences according to weight biotypes.* ***Conclusion.*** *BMI hampers lung function in normal individuals, and seems not to be related to AHR. Regular exercise should be encouraged in overweight and obese individuals, since it increases their bronchial permeability as shown in lower frequency of positive exercise tests. The same is advisable for lean individuals for different reasons. Their increased basal RV and Raw improve upon exercise. Despite overweight and obesity are being related to a low-grade of basal systemic inflammation, there was no association with a higher basal bronchial hyperresponsiveness in these individuals.*

Introduction

Many studies have shown that there is a connection between increased BMI and asthma (1,2). With bronchial asthma being defined by GINA (Global Initiative for Asthma) as a chronic inflammation of the airways (3) and obesity as a pre-inflammatory condition (4), there has been a special interest in examining how the two are related. Additionally, reported incidence of asthma and obesity has increased in several countries (5-12) and the fact is that adult patients with asthma tend to be more obese than those without. In the last few years asthma has in-

creased in both children and adults (11), with incidence rates growing as societies become more westernized (11,12).

Obesity is a public health issue, especially associated to Western countries. In most European countries its rates have increased around 10 to 40% over the last few decades (8). In 2004, Lobstein and partners, in a study based on data from european countries, showed that the highest percentage of overweight children (aged between 7 and 10) occurred in the Mediterranean (10). According to International Obesity Task Force data (2003-2005, related to people aged between 18 and 64), in Portugal the percentage of overweight people was 39.4% (45.2% for men and 34.4% for women) and the percentage of obese people was 14.2% (15% for men and 13.4% for women) (9).

Obesity is generally considered a cardiovascular risk factor, but obesity also has an adverse impact on the respiratory system, namely as a result of changes in lung function, respiratory mechanisms, muscular strength and resistance, air exchange, and breathing control (6). Various studies conducted with both children and adults point to the correlation between asthma and obesity, showing that obesity precedes asthma, the relative risk of developing asthma increases with BMI, and obesity makes asthma difficult to control or increases its seriousness (13,14).

The possible processes that explain the correlation between asthma and obesity are in summary, the following: mechanical effects of obesity, systemic and chronic inflammation, energy regulating hormones, co-morbidity and common etiology (13).

In terms of the mechanical effects of obesity, the decrease in the lung-thorax compliance is one of the primary consequences of obesity (6,14). Associated to the change in chest wall elasticity, comes the decrease in residual functional capacity, residual exhalation volume and the width of the airways, the restriction in deep breathing, a marked contraction of the smooth respiratory muscle and of the affected physiological bronchodilation mechanism (13,15,16). These changes lead to a reduction in lung capacity, an increase in bronchial hyperresponsiveness and lung blood levels and a ventilation-perfusion mismatch (13,14).

We know that obesity is a low-level systemic inflammation condition. Obese people's adipose tissues include various pro-inflammatory molecules such as cytokines, chemokines, complementary proteins and acute phase proteins (adipokines) (13,17). There appears to be a significant correlation between the immune function of the adipocytes and the T-lymphoctye and macrophage function, mainly in the creation of inflammatory cytokines (17). We also highlight the importance of the energy regulating hormones in relating asthma to obesity, especially in terms of leptin and adiponectin (13). Leptin is important in appetite-regulation, inducing a feeling of satisfaction or fullness and an increase in metabolic rate. This hormone occurs in markedly higher levels in obese people (13,16). Recent studies have suggested that leptin increases the hyperresponsiveness of the airways, albeit through a mechanism that is independent of Th2 inflammation 13,16,18. Adiponectin, an insulin regulating hormone, occurs at reduced levels in obesity. This hormone has key anti-inflammatory functions in obesity, as it inhibits the production of pro-inflammatory cytokines and increases the production of IL-10 and the IL-1 inhibitor (19). Increasingly, there is a suggestion that adiponectin significantly reduces bronchial hyperresponsiveness, inflammation of the airways and the occurrence of Th2 cells in lungs (20-22).

Most of the works published on the effect of BMI on respiratory function has been based on asthmatic patients. There are very few studies based on people without a respiratory disease or severe breathing problems. In fact it is a point of discussion whether obesity is a risk factor for AHR.

The aim of the study was to analyse the AHR in individuals with normal breathing function and without respiratory disorders or illness, according different phenotypes obtained from the BMI calculation.

Material and methods

This was a prospective study conducted between January to December 2006, obtained by the analysis of 595 consecutive both sex individuals sent by medical general practitioner (GP) in order to exclude bronchial and respiratory disease. All of them were submitted to a pletismographic test (MasterLab Jaeger), undertaken by the same cardio-respiratory technician. The following protocol was implemented:

1. Baseline measurements of dynamic volumes, static volumes and airways resistance, as the best of two measures.
2. Treadmill exercise test (Exer), while breathing ambient air (20ºC) with a nose clip to ensure mouth breathing, and cardio monitoring. In order to achieve approximately 80% of the maximum predicted heart rate (220-age in years) after a 1 minute warm-up at a lower work

rate, the patients performed a near maximal constant load exercise for 6 minutes in a treadmill. At least two acceptable FEV1 values were obtained at 1 and 5 minutes after cessation of exercise and the lowest FEV1 value was selected to calculate the fall from baseline by the following equation: % fall in FEV1 = (pre-exercise FEV1 - lowest FEV1 post-exercise) / pre-exercise FEV1 x 100%. Those with a fall in FEV1 ≥15% were considered positive for exercise test.

3. Bronchodilator test (BD), administering an inhaled short acting β2 inhibitor (100 μg of albuterol) through a spacer; the lung function was re-assessed 15 minutes later. It was considered a positive bronchodilator response an increase in FEV1 and/or FVC ≥12% of control.

The procedures and the technique were according to ATS/ERS Task Force criteria, as well as the interpretation of the results (23-26). The following lung function parameters were analyzed: forced vital capacity (FVC), forced expiratory volume at 1 second (FEV1), mean forced expiratory flow between 25% and 75% of FVC (FEF 25/75), residual volume (RV) and airway resistance (Raw).

All the non-smokers individuals with normal basal lung function tests (FEV1 and FVC ≥80%) and that had no clinical evidence of respiratory disease or other relevant illnesses were included on the study.

This sample was divided into 4 groups, according to the International Classification of adult BMI – WHO (5) (Tab. 1).

The difference between gender and age groups was analysed using the χ^2 test. Kruskal-Wallis test was used to establish the statistical significance of each respiratory factor and Mann-Whitney test was used to assess the statistical differences within each BMI group. To study the impact of physical exercise and bronchial dilation on lung function, the Wilcoxon Signed Ranks test was used. The statistical assessment was performed using the SPSS 15.0® program (2006 SPSS Inc, Chicago, Ill, USA). $p<0.05$ was considered as the statistical relevance standard.

Table 1 - BMI groups according to WHO classification

Group	Classification	BMI(kg/m^2)
I	Underweight	<18.50
II	Normal range	18.50 – 24.99
III	Overweight	25.00 – 29,9
IV	Obese	≥30.00

Results

Of the 595 people who were tested, 377 met the criteria defined (238 were women and 139 were men), non-smokers, all without illness and with normal respiratory function base levels. The average age was 41.33±17.92. The average BMI was 25.94±4.71.

Table 2 shows the demographic data and lung function test results according to BMI groups. The results of lung function parameters in the three steps of evaluation are shown in figure 1.

55.2% of the individuals were overweight or obese (Group III and IV), and a significant relationship with female gender ($p=0.0046$) and older ages was found ($p<0.0001$).

Group II had the highest FVC basal value. This parameter increased with exercise in almost all the sample, albeit with greater significance in Group I. The bronchodilator test improved FVC in all groups but mainly in Groups II, III and IV.

FEV1 deteriorated with exercise in Groups II and III. In Group I, this parameter improved but not significantly. The bronchodilator test improved FEV1 in all Groups, but more noticeable in Groups II, III and IV.

In terms of the distal air flow, FEF 25/75 average basal values were highest in Group I. Exercise improved FEF 25/75 for individuals in Groups III and IV, mainly in the latter. Individuals in Groups I and II (underweight or normal) and who are as previously mentioned younger, showed marginally worse levels with exercise.

In lean individuals basal RV values were higher compared to the other groups. They were slightly reduced by exercise in opposite to obese individuals although without statistical significance.

Basal airway resistance mean values were higher in group IV, and markedly reduced by exercise.

Positive exercise challenge test was uncommon among the total sample, with the overweight and obese individuals showing curiously the lowest frequencies (Fig. 2). Responsiveness to bronchodilator was presented at higher rates, but without significant differences between groups.

Discussion

This study differs from the previous ones, given that the study population included individuals who had normal respiratory function according to the criteria established by ATS/ERS Task Force (23,24), and had no respiratory disease.

Table 2 - Summary table with main lung function test results by BMI grouping. Values are shown as average percentage with standard deviations

	Group I	Group II	Group III	Group IV
N	16	153	128	80
Female	8	87	84	59
Male	8	66	44	21
Average age	10.56±4,89	34.62±16,66	47.84±15,39	49.9±13,66
FVC	86.61±6.03	98.19±11.64	96.77±12.56	96.74±11.92
FVC – exercise	100.36±7.44	98.43±7.18	99.45±6.67	98.75±6.25
FVC – BD	102.80±7.19	102.11±6.91	103.18±7.70	103.23±7.05
FEV1	100.43±8.37	106.56±11.02	104.77±11.98	104.36±13.27
FEV1 – exercise	100.75±6.38	99.95±5.69	101.39±5.28	101.71±6.16
FEV1 – BD	102.34±5.17	103.07±5.59	103.33±6.01	104.61±6.59
FEF 25/75	119.89±23.98	110.42±29.49	103.32±28.00	102.06±24.40
FEF 25/75 – exercise	108.40±12.94	105.77±16.51	107.68±16.08	113.03±20.85
FEF 25/75 – BD	106.29±15.37	107.95±18.03	105.84±21.23	110.88±20.31
RV	116.61±22.26	100.64±29.62	93.68±25.35	90.11±30.53
RV – exercise	98.57±41.43	112.69±44.79	101.17±33.31	111.93±75.59
RV – BD	92.33±21.82	106.32±48.64	98.54±27.48	103.09±43.24
RAW	135.85±51.39	93.51±43.59	125.00±68.35	146.03±84.09
RAW – exercise	125.49±32.89	108.25±39.81	102.22±36.56	96.21±36.98
RAW – BD	103.88±20.41	96.37±30.84	94.37±31.82	89.84±32.29

In order to measure airways reactivity, there are several tests that can be performed; the methacoline and exercise challenging tests are the most widely used, but the first one is better established (26). Although challenge tests with methacholine are more sensitive in the diagnosis of AHR than tests with exercise, the last ones are more specific and may reflect more directly the ongoing airway inflammation (27). Also, there are patients with mild bronchial AHR to methacoline who have negative exercise challenges and others who have positive exercise challenges but negative methacholine challenges; this can be indicative of different mechanisms involved in AHR (27). We chose the exercise challenge test because it is the most physiological and reflect a natural trigger to AHR; also, to this date there are very few studies that investigated exercise induced bronchospasm.

Our results suggest that BMI affects lung function in people without a respiratory disorder. This agrees with the data of several other studies, in which it was found that the lung capacity varied inversely with the body weight (2, 28-31). The changes in resistance, as a function of BMI, are also in agreement with these studies, suggesting that obese people have higher airways resistance (32-34). One curious found in our study is that underweight people also showed higher base level resistance. These data could be explained by the fact that the BMI groups were defined by different criteria, depending on the study, and most of the samples had mainly obese people.

In our study the different BMI groups did not appear to have more frequently AHR despite having normal respiratory function according to the ATS/ERS criteria (23,24). Obesity was not linked to an increase in AHR. Therefore, we conclude that although there is no clear rise in the frequency of hyperresponsiveness, we suspect that depending on the clinical conditions which led to obese patients developing asthma, this would be more serious, as a result of the bronchial inflammation induced by the increased synthesis of leptin by the adipocytes and the systemic inflammation caused by obesity, as a result of increased TNF-α, IL-6 and sIL-6R levels (6,13,17), as suggested by a study published by our group (35). This can also explain the higher base level of airways resistance in obese and also overweight people. These groups of individuals showed less bronchial obstruction following exercise and the best response to bronchodilators. Obese and overweight subjects tend to have decreased pulmonary

Figure 1 - Effects of BMI on FVC, FEV1, FEF25/75, RV and resistance (RAW), according to lung function tests.The horizontal lines are the between-group comparisons from Wilcoxon Signed Ranks and Mann-Whitney tests.The vertical lines are the error bars (2 SD)

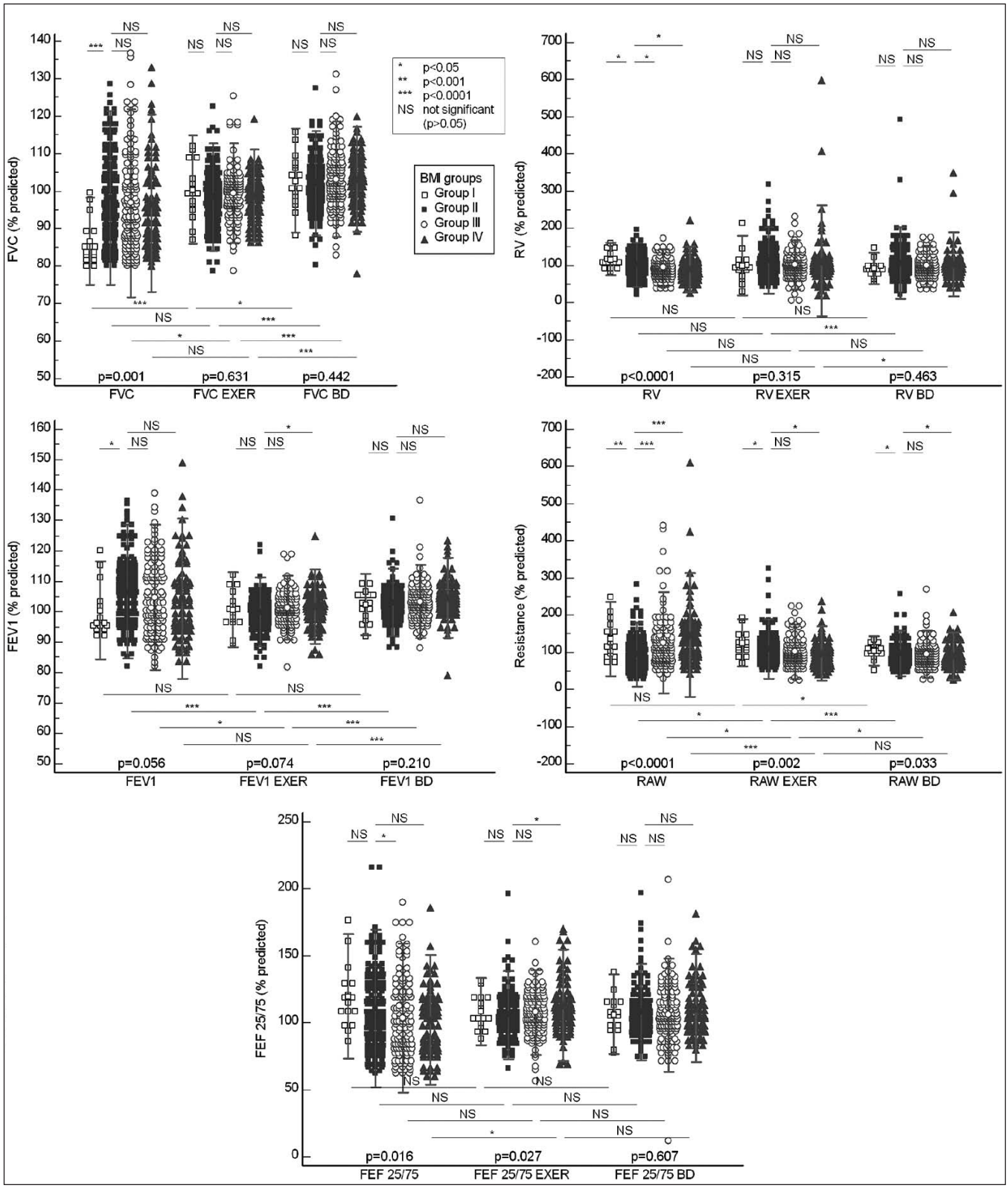
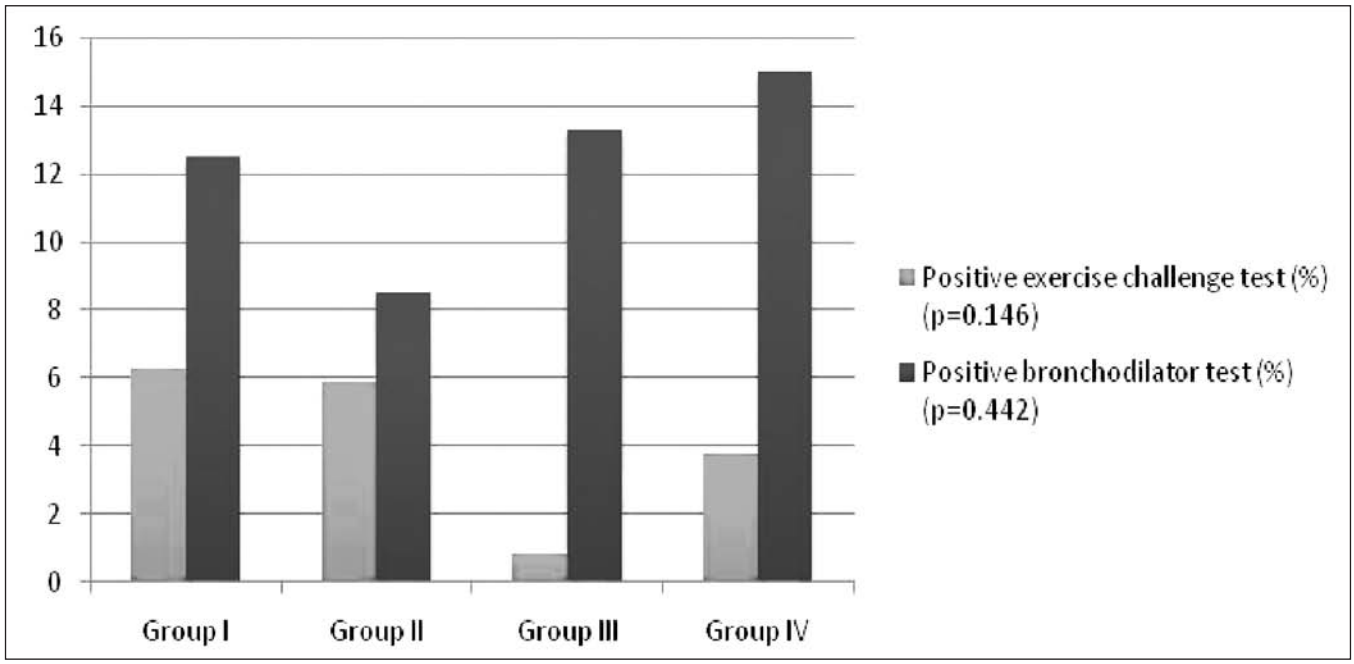


Figure 2 – Exercise challenge and positive bronchodilator tests (as a %), distributed by BMI Groups



volumes and less thoracic wall distensibility (36); they have a more sedentary life and are not used to exercise, so with physical activity they have to exercise muscles, otherwise not employed, and better coordinate their respiratory movements, which can explain a better bronchomotricity.

The role of obesity on AHR is controversial, as arise from the analysis of several studies. In 2006, a study undertaken by Johnston and cols concluded that obese rats showed increased lung response to ozone, and that the inhalation of this gas increased resistance, hyperresponsiveness and inflammation of the airways (37). These results were then reproduced in human, where some studies showed higher increase in AHR and a reduction in lung function response to ozone in overweight as opposed to underweight individuals (38,39). Chinn and cols, 2002, showed that there was a significant correlation between bronchial hyperresponsiveness to methacoline and BMI, but only in men (40). Another study published in 2002, conducted in men participating in the Normative Aging Study, associated both a low BMI and a high BMI with the development of AHR to methacholine (41). Although our study did not find a relation between BMI and AHR, underweight and obese individuals had the lowest basal FEV1 and FCV levels and the highest basal resistance levels, and exercise improved the general lung function parameters. The differences between the studies referred before and our study can be explained by the less sensitivity and more specificity of exercise challenge tests in the diagnosis of AHR (27), as already explained. Also, we have highlighted before that obese people do not have a regular physical activity, so exercise can bring a better respiratory coordination and muscles utilization, facts that can explain the respiratory improvement with exercise in these individuals. Other studies showed no correlation between BMI and AHR. Schachtern and partners in 2001 did not find any connection between serious obesity and AHR to histamine challenge, despite obesity being a factor for asthma and wheezing (42). Weight loss did not lead to a reduction in bronchial hyperresponsiveness to methacoline in a group of obese women (43).

Various studies have attempted to establish the relationship between obesity and asthma, and have reached diverse conclusions. In 2005 a review of several studies concluded that adult asthma patients are more obese than those without asthma, but in children and adolescents this correlation is less marked (1). The prevalence of asthma is higher in obese individuals, as obesity underlines a worse clinical history (16). Longitudinal studies show that obesity precedes asthma and that the risk of asthma amplifies with increasing BMI (44,45). Obesity is related to

a worse clinical history and makes the asthma more difficult to control (13,43). One interesting study was conducted with perimenopausal women, which established that underweight and obese women showed the highest risk of having impaired lung function and of developing asthma. In underweight women the explanation was that the fatty tissue produces less oestrogen, while in obese women the explanation arises from insulin-resistance, as this is a pro-inflammatory factor (46).

Our results stress that BMI seems not be related to higher risk of AHR, namely in overweight and obese individuals. They must be asked for regular exercise, because they increase their bronchial permeability besides the lower positivity to exercise test. Lean individuals should also be asked for regular exercise, because they decrease the values of basal RV and Raw. Despite the lower frequency of positive broncoresponsiveness tests in our study among overweight and obese individuals we strong believe that if asthma occurs in those, it definitely contributes to a severe clinical phenotype, developed on a previous low-grade inflammatory state already described.

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