

OBESITY

Increased Asymptomatic Airway Hyper-Responsiveness in Obese Individuals

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Objective. Asymptomatic airway hyper-responsiveness (AHR) represents a risk of further accelerated decline in lung function, and of asthma. Due to the fact that rare and contradictory results exist concerning the impact of obesity on BHR, we re-assessed the prevalence of bronchial hyper-responsiveness (BHR) in a large cohort of 60 lean, 84 overweight, and 360 class 1–3 obese non-asthmatic individuals, by coupled plethysmography and spirometry. **Methods.** Baseline-specific airway conductance (SGaw) and spirometric values were measured and then a methacholine challenge testing (MCT) was performed and considered as positive when a $\geq 200\%$ increase in specific airway resistance (SRaw = $1/SGaw$) was reached. **Results.** Compared to lean and overweight subjects, obese subjects of any class presented about a twice more frequent AHR ($\sim 50\%$ in obese vs. 17 and 26% in lean and overweight subjects, respectively). However, the bronchial sensitivity (methacholine dose doubling SRaw) and the shape of the relationship between SGaw and cumulative methacholine doses were the same in the five groups of individuals. **Conclusion.** The present data show a more frequent AHR in obese subjects. The association of plethysmography with spirometry, by taking into account the bronchodilator effect of the lung inflation (preceding the expiratory flow measurement) in some individuals, permitted to include some MCT which would have been otherwise excluded.

Keywords body plethysmography, bronchial hyper-responsiveness, methacholine challenge test, obesity, overweight

INTRODUCTION

Obesity and asthma are important health problems, and mounting evidence points to obesity being a risk factor for asthma (1), which represents one of the 18 comorbidities attributed to obesity and overweight (2). In France, the prevalence of obesity nearly doubled between 1981 and 2003, to reach the level of 10% of women and men (3).

Bronchial hyper-responsiveness (BHR) is defined as the excessive airway narrowing in response to provoking stimuli. It is a marker for the tendency of variable airway obstruction, and is a fundamental characteristic of asthma (4). However, a significant percentage of people showed asymptomatic airway hyper-responsiveness (AHR), which is defined as BHR without a history, or current symptoms, of asthma (5). A more rapid decline in pulmonary function has been shown in subjects with AHR and in patients with asthma as compared to normal subjects (5). This decline correlates with the severity of AHR (5). AHR would often precede the development of symptomatic asthma and can be considered as a risk factor for the disease (5).

A recent review (6) has reported contradictory results of studies on the impact of obesity on airway responsiveness in adults or children: some studies have shown that obesity is a risk factor for BHR, whereas others have reported no increase in airway responsiveness with increasing body mass index (BMI). The author listed the putative origins of the discrepancies between the studies as: role of gender,

choice of population samples (asthmatics—non-asthmatics), methods of assessment of weight excess, nature of the stimuli used to assess airway responsiveness, and outcome indicators used to assess airway narrowing. In non-asthmatic obese subjects, there are two works reporting negative results (4, 7) and three others demonstrating a correlation between airway responsiveness and BMI (8–10).

In our laboratory, we are used to assessing BHR with the body plethysmograph measurement of airway resistance coupled to spirometry during methacholine challenge testing (MCT) (11–13). This methodology makes it possible to take into account the bronchodilator effect of deep inspiration preceding forced expiration (14). Actually, this bronchodilator effect reduces decrease in FEV₁ in some patients, and may lead to erroneous conclusions in bronchial provocation tests. We thought that the use of this methodology in a large sample of lean, overweight, and obese individuals ought to be a valuable contribution to the assessment of a link between asymptomatic AHR and obesity.

METHODS

Subjects

Five hundred and four subjects were involved in this study. The subjects were classed according to their body mass index (BMI): lean, BMI from 18.5 to 24.9 kg/m² ($n = 60$); overweight, BMI from 25.0 to 29.9 kg/m² ($n = 84$); class 1, moderate obesity, BMI from 30.0 to 34.9 kg/m² ($n = 158$); class 2, severe obesity, BMI from 35.0 to 39.9 kg/m² ($n = 112$); class 3, morbid obesity, BMI over 40.0 kg/m²

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($n = 90$). Their smoking habits were noted. The lean subjects were referred by general practitioners or pneumologists to our Lung Function Laboratory for symptoms which may evoke an underlying slight BHR (chronic cough, exercise-induced dyspnea, recurrent lung infections). Their symptoms were not typical of asthma, as they did not describe acute dyspneic events and as their exercise-induced dyspnea did not worsen during the post-exercise recovery period (15). Bronchial challenge was performed in all of them on the demand of physicians, and this test does not necessitate a written informed consent in our hospital, like in others (16). On the other hand, the overweight or obese subjects were referred to our laboratory by pneumologists or surgeons for a check-up because of symptoms linked to their weight excess (snoring, suspicion of sleep apnea syndrome) or/and before bariatric surgery, but they did not report the following signs of asthma, i.e. acute dyspneic events with or without wheezing, repeated wheezing bronchitis, chronic cough, exercise-induced cough, wheezing, and/or dyspnea. A written informed consent was necessary for them as bronchial challenge was not indispensable, and the study was approved by the Institutional Committee of Aix-Marseille University.

A positive history of allergy was indicated if an affirmative response was given to either of the following questions: "Do you have allergies diagnosed by a health professional (aeroallergens)?" or: "Do you have any food allergies diagnosed by a health professional?". No prick tests were performed.

Clinical symptoms of rhinitis were searched by a questionnaire: "Do you have sneezing, nasal obstruction, or rhinorrhoea and pruritus?", and, when present: "How were these symptoms distributed over the year?".

Bronchial Challenge

Initially, the subjects underwent (MasterScreen Body Sebac, Viasys, France) measurements of specific airway conductance ($SGaw = 1/\text{Specific airway resistance} = 1/SRaw$) and functional residual capacity (FRC) (17, 18), and then spirometric measurements of forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1). The values were compared to predicted mean values (19).

MCT was performed by a previously described dosimetric method (11–13). We used an automatic dosimeter (MEFAR, Sebac France) with the following characteristics: pressure: 1.65 kg/cm^2 ; flow: 70 L/min ; particle size: $0.5\text{--}4.0 \mu\text{m}$. The puff and pause durations were adjusted at 1.2, and 5.0 sec, respectively. The subjects inhaled the spray directly from the dosimeter, previously filled with 3 ml of a 2 mg/ml methacholine solution. Plethysmographic parameters ($SGaw$, FRC) were measured after each inhalation, without any intermediate assessment of decrease in FEV_1 until the end of the MCT.

The first inhalation consisted of two puffs of $20 \mu\text{g}$, i.e. $40 \mu\text{g}$, of methacholine. Then, cumulative doses of methacholine were administered in the following way: +60, +100, +100, +100, +100 μg , to reach a total dose of 500 μg . The maximum dose administered was often <500 μg in hyper-reactive subjects. The MCT was

considered to be positive when there was a $\geq 200\%$ increase in $SGaw$ (20), although the most used criterion of BHR is a $\geq 20\%$ decrease in FEV_1 (16). The best final FEV_1 was chosen from three successive flow-volume curves. Four puffs of salbutamol (i.e. 400 μg) were given thereafter to subjects having a positive MCT. Dose-response curves made it possible to compare the bronchial sensitivities (i.e. methacholine doses doubling $SGaw$) and the relationships between $SGaw$ and cumulative methacholine doses between the groups.

Statistical Analysis

All data were analyzed by a SigmaStat 3.0 statistical software from SYSTAT Inc. Results were expressed as mean $\pm$ standard error of the mean (SEM). A two-way analysis of variance was performed to evaluate $SGaw$ values stratified by gender, allergies, rhinitis, or positive/negative MCT. A comparison was made between groups by one-way analysis of variance (ANOVA) test. Differences between groups were ascertained with the t independent test when data were normally distributed or with Mann-Whitney Rank Sum Test when they were not. Comparisons of qualitative variables were assessed through the Pearson's Chi-square test. The level of statistical significance was chosen at $p < .05$.

RESULTS

Subjects

The characteristics of the groups were homogeneous with respect to age, smoking status, reported allergies, and perennial rhinitis (Table 1). Lean subjects consulted for three main symptoms. They did not present evident signs of asthma. Their medical files revealed allergic rhinoconjunctivitis (10%), focal bronchiectasis (8%), hiatal hernia—gastroesophageal reflux (7%), or chronic sinusitis—nasal polyposis (7%). In overweight and obese subjects, Chi-square test revealed an overall increased proportion of women ($p < .001$), a larger suspicion of sleep apnea syndrome ($p < .001$), and more frequent pre-bariatric surgery check-up ($p < .001$) with body weight, whereas complaint of snoring tended to decrease with weight ($p < .001$).

Baseline Lung Function

Lung volumes decreased in parallel with BMI (Figure 1). Table 2 shows that the subjects were not obstructive before bronchial challenge with methacholine: they had normal FEV_1/FVC and $SGaw$ values, which did not differ between the five groups, whether in the total sample or, more specifically, in the subjects showing BHR. There was a significant tendency to an increase in Raw from lean to obese class 3 subjects (Table 2).

Bronchial Hyper-Responsiveness

There was a statistically significant interaction between class and positive MCT ($p = .01$). BHR was more frequent

TABLE 1.—Morphometric characteristics and medical status of subjects according to BMI classes.

	Lean <i>n</i> = 60	Overweight <i>n</i> = 84	Class 1 <i>n</i> = 158	Class 2 <i>n</i> = 112	Class 3 <i>n</i> = 90
Gender					
Men <i>n</i> (%)	26 (43)	43 (51)	65 (41)	38 (34)	19 (21)
Age (years)	54 ± 2	50 ± 2	50 ± 2	47 ± 2	51 ± 3
BMI (kg/m ²)	23.5 ± 0.2	28.0 ± 0.2	32.2 ± 0.2	36.7 ± 0.3	45.9 ± 1.6
Women <i>n</i> (%)	34 (57)	41 (49)	93 (59)	74 (66)	71 (79)
Age (years)	53 ± 1	51 ± 3	51 ± 2	52 ± 2	48 ± 2
BMI (kg/m ²)	21.5 ± 0.4	28.1 ± 0.2	32.4 ± 0.1	37.3 ± 0.2	45.6 ± 0.6
Indications					
SAS (%)		2	9	22	70
Snoring (%)		87	64	58	33
Bariatric surg. (%)		2	36	42	63
Chronic cough (%)	50				
EID (%)	27				
RLI (%)	23				
Smoking Status					
Current (%)	13	17	16	15	13
Past (%)	33	24	24	25	24
Never (%)	54	59	60	60	63
Reported allergies (%)	13.0	15.4	15.0	14.5	17.6
Perennial rhinitis (%)	10.0	16.0	18.0	18.5	21.0

Abbreviations: BMI: Body Mass Index, in kg/m². Values are means ± SEM, or percentages. Abbreviations: SAS = sleep apnea syndrome, EID = exercise-induced dyspnea, RLI = recurrent lung infections.

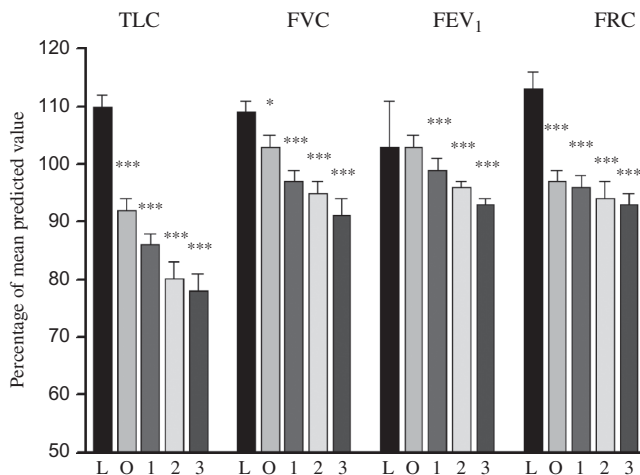


FIGURE 1.—Means ± SEM of spirometric values in each group of subjects: L: lean; O: overweight; 1: obese class 1; 2: obese class 2; 3: obese class 3. Abbreviations: TLC: total lung capacity; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 sec; FRC: functional residual capacity. Levels of significance of differences between lean and obese individuals: * $p < .05$; *** $p < .001$.

in the obese class 1–3 groups than in the lean and overweight groups ($p < .001$, Table 3). In some cases, the increase in SRaw was not accompanied by a significant decrease ($\geq 20\%$) in FEV₁. When the criterion of a $\geq 20\%$ decrease in FEV₁ was used, the percentages of positive MCT were slightly lower than those given in Table 3 (13, 18, 42, 44, and 49% in the lean, overweight, and obese class 1–3 groups, respectively), but the proportion of positive MCT was also higher in the obese groups with this criterion ($p < .001$). The distribution of the subjects having or not a $\geq 20\%$ decrease in FEV₁ was not significantly different in the five groups.

The proportions of symptoms having motivated the bronchial challenge were the same among the ten lean subjects presenting a positive MCT, i.e. chronic cough (4/10), exercise-induced dyspnea (3/10), and recurrent lung infections (3/10).

The indices of BHR (Table 3)—i.e. increase in SRaw, % of decrease in FEV₁, bronchial sensitivity—and the shape of the SGaw vs. methacholine dose (Figure 2) were not significantly different between the five groups, in subjects having a positive MCT. There was a statistically significant interaction between gender and positive MCT ($p = .02$): the repartition of women vs. men was different only between lean and obese class 3 groups ($p < .05$).

Interactions between either allergies or rhinitis and positive MCT were not statistically significant ($p = .54$ and $p = .63$, respectively).

DISCUSSION

The main finding of the present work was that subjects of the obese 1–3 groups presented a higher frequency of BHR than those of the lean and overweight groups. The occurrence of BHR was observed more frequently when the criterion of a $\geq 200\%$ increase in SRaw was used than with the usual criterion of a $\geq 20\%$ drop in FEV₁. As the lean subjects presented subtle signs of BHR while the overweight and obese subjects did not, the latter should have presented a less frequent BHR. It was not the case as, on the contrary, BHR was much more frequent in obese individuals, who were however asymptomatic (AHR).

Care was taken to check that the baseline airway patency of subjects with AHR was the same in the five groups.

TABLE 2.—Baseline bronchial values before methacholine challenge testing (MCT).

		Lean	Overweight	Class 1	Class 2	Class 3
All subjects	FEV ₁ /FVC, % (n = 504)	75.0 ± 1.0	82.4 ± 0.8	82.3 ± 0.6	82.1 ± 0.6	83.3 ± 0.7
	SRaw, cmH ₂ O.s (n = 504)	7.3 ± 0.2	7.2 ± 0.2	7.8 ± 0.2	7.5 ± 0.2	7.1 ± 0.2
	Raw, cmH ₂ O.l ⁻¹ .s	2.0 ± 0.1	2.4 ± 0.1***	2.8 ± 0.1***	2.9 ± 0.1***	3.0 ± 0.1***
Positive MCT	FEV ₁ /FVC, % (n = 215)	77.2 ± 3.3	79.2 ± 1.3	80.9 ± 0.9	80.6 ± 0.9	81.6 ± 0.9
	SRaw, cmH ₂ O.s (n = 215)	7.6 ± 0.7	7.9 ± 0.5	8.4 ± 0.3	8.0 ± 0.3	7.9 ± 0.3
	Raw, cmH ₂ O.l ⁻¹ .s	2.0 ± 0.2	2.6 ± 0.1*	3.0 ± 0.1***	3.1 ± 0.1***	3.3 ± 0.1***

Abbreviations: FEV₁/FVC: forced expiratory volume in one sec/forced vital capacity; SRaw: specific airway resistance. Results are expressed as means ± SEM. *: $p < .05$, ***: $p < .001$.

TABLE 3.—Characteristics of positive Methacholine Challenge Testing (MCT).

	Lean	Overweight	Class 1	Class 2	Class 3
Positive MCT: n =	10	22	79***	57***	47***
% of positive tests	17	26	50	51	52
Increase in SRaw, %	277 ± 39	243 ± 20	249 ± 10	240 ± 12	233 ± 12
FEV ₁ , % of decrease	26 ± 4	23 ± 2	30 ± 1	32 ± 2	30 ± 2
Bronchial sensitivity, µg	181 ± 48	256 ± 42	193 ± 18	167 ± 18	198 ± 22

Abbreviations: SRaw: Specific airway resistance; FEV₁, % of decrease: decrease in forced expiratory volume in one sec when SRaw was increased by ≥200%; Bronchial sensitivity: methacholine dose doubling SRaw. Results are expressed as means ± SEM. ***: $p < .001$.

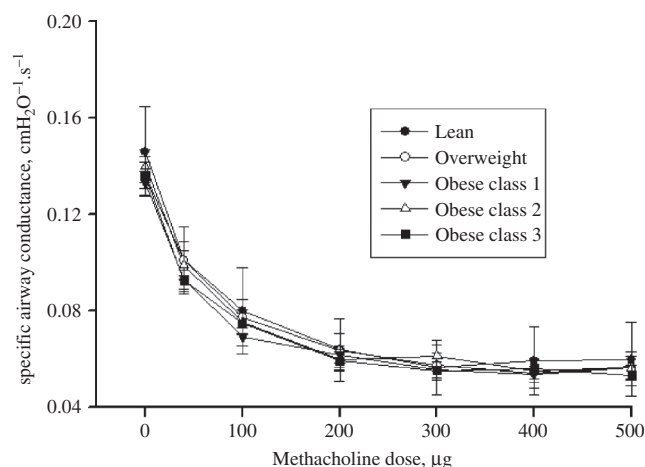


FIGURE 2.—Means ± SEM of specific airway conductance (SGaw) vs. methacholine dose in each group of subjects having a positive MCT. SGaw did not differ between the groups at each step of methacholine challenge.

Methodological Points

On the one hand, the factors having a possible influence on BHR, e.g., ageing, smoking, symptoms evoking atopy (21) and airway patency (22) were found to be the same in the five groups.

Obese patients (with obstructive sleep apnea) have smaller upper airways (23), but we did not detect in our study a higher SRaw in obese subjects when compared to lean subjects. In another article, it has been shown also that obesity, per se, had no significant impact on SGaw (7). However, a lower patency of upper airways in obese individuals may increase Raw as a consequence of a lower thoracic gas volume ($\text{Raw} = \text{SRaw}/\text{thoracic gas volume}$; thoracic gas volume $\sim$ FRC). In our study, there was a significant increase in Raw from lean to obese class 3 subjects.

On the other hand, the proportion of women increased with the BMI because of the method of recruitment of our subjects: actually, women are more often seeking bariatric surgery than men (24), when the percentage of obese individuals is the same in both genders, i.e. $\sim 10\%$ in France (3). Previous studies have suggested that the female sex could promote BHR through a greater cholinergic reactivity and hormonal differences (21). In the present study, this gender-linked factor could have resulted in the higher occurrence of positive MCT in the obese class 3 individuals, but not in the obese class 1-2 ones, when compared to lean subjects.

To conclude in a positive MCT, we used an additional criterion developed previously (20), i.e., a minimum of 200% increase in initial SRaw. This target was slightly exceeded in all the groups ($\sim +250\%$). The most frequently used criterion to conclude in BHR is a $\geq 20\%$ decrease in FEV₁ (16). The average decrease in FEV₁ was $\geq 20\%$ in the five groups at the end of MCT. However, the FEV₁ decrease was $<20\%$ in some subjects of the five groups, without any different distribution of this index among them. This observation agrees with the data of a study reporting that the post-MCT deep inspiration effect is not abnormal in obese individuals (9).

Asymptomatic Hyperresponsiveness

None of the subjects included in the present study complained of asthma, but a non-negligible number of them presented a positive MCT.

Although BHR can be documented in almost all patients who experience symptoms of asthma, a significant percentage of persons show AHR (5). The prevalence of AHR in the general population varies greatly from one survey to another: most surveys report prevalence under 15% (25). In the present study, the prevalence of BHR in

the lean individuals was 13% when the criterion of a $\geq 20\%$ decrease in FEV₁ was used, i.e. close to the upper limit of 15% given in the above-cited review. Plethysmographic assessment of specific airway resistance increased the number of positive MCT until 17% in our experimental series.

It has been shown that weight gain over a ~ 4 -year period in men with (a low or) a high BMI was associated with the development of BHR (26), which may explain the fairly high percentage of positive MCT (26%) in the overweight group of the present study.

Increase in AHR with Obesity

We found a higher occurrence of positive MCT in the obese class 1–3 groups than in the lean and overweight groups. As stated in the introduction, the literature on BHR and obesity is poor, and, in most cases, it includes both asthmatic and non-asthmatic individuals (1).

One study conducted with the forced oscillation technique on small cohorts of non-asthmatic obese vs. non-obese adults (4) has resulted in a reduction of lung volumes without altered sensitivity or maximal response to methacholine. The authors attributed the enhanced perception of dyspnea of obese subjects to the greater stiffness of the respiratory system (increase in respiratory system reactance). Another work reported no correlation between BMI and bronchial responsiveness to methacholine, either in normal or obese subjects (7). On the other hand, a positive relationship between airway responsiveness and BMI has been reported in non-asthmatic obese individuals (8–10).

Other works have been performed in populations including asthmatic and non-asthmatic individuals. In a study performed on a large sample of adults, it has been shown that severe obesity was a significant risk factor for recent asthma but not for BHR (27). In contrast, an increase in BHR with BMI has been reported in men, but not in women, in a very large group of 11,277 participants, including a small percentage of obese subjects (28). Similarly, obesity was found to be associated with BHR and appeared to be a risk factor for asthma in another study showing that BHR increased from class 1 to class 3 (29), whereas, in our study, it was higher in obese individuals than in lean and overweight ones, but it was not related to the seriousness of obesity.

Contradictory results, performed on small groups of subjects, appeared also concerning the beneficial effect of weight loss on BHR. One study demonstrated an improvement in BHR in obese asthmatic patients after bariatric surgery (30), whereas two others concluded that there was no change in BHR after either bariatric surgery (31) or an intensive weight loss program (32).

Putative Mechanisms Linking Obesity to BHR

Several mechanisms may modify the airway smooth muscle function to explain the fact that obesity predisposes towards BHR (1). Obesity appears to either cause or aggravate asthma.

Increased abdominal and chest wall mass in the obese individual causes lower than normal functional residual capacity, which may unload the airway smooth muscle, and thereby allow it to shorten excessively when activated (1). In the present study, there was a progressive decrease in lung volumes from lean to obese class 3 subjects (about 110 to $<80\%$ of predicted total lung capacity), which accounts for the effect of static factors on BHR. The TLC reported in overweight and obese individuals of our study is lower than those reported in another recent study (33): means were 110, 92, 86, 80, and 78% in lean, overweight, and class 1–3 in our study, vs. 99, 97, 93, 92, and 88% in theirs. They did not use the same predicted values (Ref. (34) vs. Ref. (19)), but they are quite close to each other. They determined TLC by adding FRC and inspiratory capacity, which is not the usual method to obtain TLC ($TLC = CV + RV$).

Concerning dynamic factors, the tidal action of spontaneous breathing imposes tidal stress on airway smooth muscle, and these tidal strains happen to be the most potent of all physiological bronchodilator factors. The obese individual breathes at higher frequencies, but with substantially smaller tidal volumes when compared to the lean individual, and as a result, this potent bronchodilator mechanism is compromised and predisposes towards increased airway responsiveness compared with the lean individual (1). We did not record ventilatory patterns of our subjects and so we cannot argue for or against this second factor. However, we verified that baseline airway patency did not differ between overweight and obese subjects.

Other mechanisms promoting BHR in obesity have been invoked (chronic systemic inflammation, adipocyte-derived factors) (1).

CONCLUSION

The present work, conducted on a large sample of non-asthmatic individuals, demonstrates a more frequent AHR in obese subjects than in lean or overweight ones. The present data show that the frequency of AHR is increased by obesity. Obesity and weight gain may precede the development of asthma (35). As AHR would contribute to accelerate the decline in lung function and would often precede the development of symptomatic asthma (5), its high occurrence in obesity should urge to incorporate weight reduction strategies, with a view to reducing the economic burden of asthma and improving general health.

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DECLARATION OF INTEREST

The authors report no conflicts of interest.

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