

OBESITY

Cross-Sectional Assessment of the Roles of Comorbidities in Resting and Activity-Related Dyspnea in Severely Obese Women

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Objectives. Obesity has been associated with a lesser degree of asthma control that may be biased by other comorbidities. The objectives of this cross-sectional study were to describe resting and activity-related dyspnea complaints according to the presence of obesity-related comorbidities (asymptomatic airway hyperresponsiveness (AHR), asthma, gastroesophageal reflux disease (GERD) and sleep-disordered breathing (SDB)). We hypothesized that obese women can exhibit both resting and activity-related dyspnea, independently of the presence of asthma. **Methods.** Severely obese (body mass index (BMI) > 35 kg m⁻²) women prospectively underwent description of resting and activity-related dyspnea (verbal descriptors and Medical Research Council (MRC) scale), pulmonary function testing (spirometry, absolute lung volumes, and methacholine challenge test), oesogastro-duodenal fibroscopy, and overnight polygraphy. Thirty healthy lean women without airway hyperresponsiveness were enrolled. **Results.** Resting dyspnea complaints were significantly more prevalent in obesity (prevalence 41%) than in healthy lean women (prevalence 3%). Chest tightness and the need for deep inspirations were independently associated with both asthma and GERD while wheezing and cough were related to asthma only in obese women. Activity-related dyspnea was very prevalent (MRC score > 1, 75%), associated with obesity, with the exception of wheezing on exertion due to asthma. Asymptomatic AHR and SDB did not affect dyspneic complaints. **Conclusions.** In severely obese women referred for bariatric surgery, resting dyspnea complaints are observed in association with asthma or GERD, while activity-related dyspnea was mainly related to obesity only. Consequently, asthma does not explain all respiratory complaints of obese women.

Keywords airway responsiveness, asthma, gastroesophageal reflux disease, obesity, pulmonary function tests, sleep-disordered breathing

INTRODUCTION

Dyspnea is a frequent complaint in obese patients. Up to 80% of severely obese patients present some degree of activity-related dyspnea (1) while some obese patients may also exhibit some resting complaints, as suggested by a single study performed in 23 nonasthmatic obese men (2). Whether obesity explains per se resting and activity-related respiratory complaints is an important issue because these symptoms are recorded to evaluate asthma control. Obesity-related comorbidities, such as gastroesophageal reflux disease (GERD) and sleep-disordered breathing (SDB), have also been associated with respiratory complaints and even asthma-like symptoms (3–7), further biasing the recording of “asthma” symptoms. It may explain why obesity has

been associated with a lesser degree of asthma control in some studies and why obese asthmatic patients are less responsive to asthma treatment (8, 9).

To this end, a first pragmatic approach is the systematic recording of both resting and activity-related respiratory complaints (the verbal descriptors of dyspnea) in obese patients while taking into account their potential modifiers such as “asymptomatic” airway hyperresponsiveness (AHR), asthma, GERD, and SDB. The role of AHR was also evaluated because Laprise and Boulet have shown that subjects with asymptomatic AHR had a greater increase in airway responsiveness and frequency of development of asthma symptoms (10).

We focused on females since two studies using factor analysis identified a cluster of asthmatic obese women with noneosinophilic airway inflammation (specific phenotype) (11, 12) and since dyspnea descriptors have previously been described in females (13).

Consequently, the objectives of our cross-sectional study were the description of resting and activity-related dyspnea

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complaints according to the presence of obesity-related comorbidities (AHR, asthma, GERD and SDB). Dyspnea descriptors were also obtained in a healthy group (without AHR and SDB) of lean women for comparison.

PATIENTS AND METHODS

All the obese and lean women have previously been described as this investigation (Dyspnea-Obesity (DYS-OB) study) constituted an ancillary study of the breathing asthma obesity (Breathing Obesity Asthma (BOA)) trial devoted to explore the pathophysiology of airway responsiveness/asthma in obese women (Clinical Trials number: NCT00577733) (14). This was a cross-sectional study in which informed written consent was obtained from all subjects, and ethical approval (CPP IDF II, ID-RCB: 2007-A00363-50) was received also.

Design—Patients

The objectives of this study were to describe resting and activity-related dyspnea complaints according to the presence of obesity-related comorbidities, and therefore to assess whether asthma is responsible for these dyspnea complaints. To this end, obese women were enrolled and their comorbidities were defined. Age-matched lean healthy women were also included to define the normalcy of respiratory complaints. The study was a prospective cross-sectional evaluation of consecutive obese women (body mass index (BMI) > 35) without respiratory disease (excepting asthma) or chronic heart failure, referred for bariatric surgery (preoperative evaluation). The presence of baseline airflow limitation with a Forced Expiratory Volume in 1 second (FEV₁) < 60% predicted was a non-inclusion criterion.

Healthy women with normal BMI (18.5–25) and no smoking or mild (<5 pack-year) ex-smoking history were recruited by our Center of Clinical Investigation by advertisement. The presence of AHR (methacholine challenge test) or SDB (polygraphy) or GERD (symptoms and/or treatment) was an exclusion criterion.

Dyspnea Evaluation

Activity-related dyspnea was evaluated by the Medical Research Council (MRC) scale (grade 1–5) that assesses the impact domain of dyspnea (15), which was chosen due to its simplicity and available data in the literature for comparison.

Word Descriptors of Dyspnea in Patients

These descriptors assess the perceptual-sensory experience domain of dyspnea (15). An initial interview of 30 women was obtained in order to define their more frequent descriptors during a previous study (16). The list of word descriptors obtained by Ofir and colleagues in obese women (13) translated from English was also administered. The selected descriptors for the DYS-OB study were those that were described or selected by at least three women. Unexpectedly, some descriptors like “increased work or

effort” or “heavy breathing” were not kept in the final list, suggesting that this specific sensation was not a good verbal descriptor of activity-related dyspnea in obesity and/or that the descriptor had no real meaning in the French translation (description such as “difficulty” was rather used by our patients), which has also recently been observed when translating English to Portuguese dyspnea descriptors in obese patients (17).

Descriptors were recorded only in presence of a respiratory complaint (negative effect of dyspnea) both in lean and obese women.

Pulmonary Function Tests

Spirometry, flow-volume curves, static lung volumes (using body plethysmography or helium dilution), and airway resistance (calculated from specific resistance at 0.5 L s⁻¹ (sRaw0.5) obtained by plethysmography (18)) were obtained according to international recommendations using an automated pulmonary function testing system. Measurements were standardized as percentages of predicted normal values and corrected for ethnicity as recommended (19).

Bronchoprovocation tests and withdrawal of medications were in accordance with American Thoracic Society guidelines (20). The study was terminated when FEV₁ decreased by 20% at any cumulated dose (50, 200, 400, 800, 1600 and 2400 µg) (21) or when the maximum dose of methacholine had been administered. AHR was defined by a dose-response slope (DRS) ≥ 2.39 % decrease µmol⁻¹ (22).

Comorbidity Definitions

AHR/asthma. After functional testing and detailed standardized medical interview, AHR and asthma were defined as the absence of AHR, asymptomatic AHR (AHR plus no symptom of asthma) nonsuggestive respiratory complaints, and asthma (AHR plus recurrent wheeze or chest tightness or cough (worse particularly at night) that are suggestive symptoms).

SDB. Unattended overnight polygraphy was performed using a computerized data acquisition system and the respiratory disturbance index (apnea / hypopnea index (AHI)) was defined according to international recommendations (23). SDB was defined by a respiratory disturbance index ≥ 5 hour⁻⁵.

GERD. It applies to individual with reflux of gastric contents into the esophagus causing (1) symptoms sufficient to reduce the quality of life and/or (2) esophageal injury (24). Based on the clinical interview and the result of oesogastro-duodenal fibroscopy (performed only in obese patients), GERD levels were defined as follows: no GERD, possible GERD (suggestive symptoms: endoscopy-negative reflux disease), and confirmed GERD (symptoms plus suggestive endoscopic findings such as erosive esophagitis) (24, 25).

Statistical Analyses

Data are summarized as relative frequencies for categorical variables with 95% confidence interval (CI)

when stated, mean (SD) for normally distributed variables, and median (Quartile 1; Quartile 3) for non-normal data. Comparisons between groups were performed using Chi-square, Fisher's, Student *t*, Mann-Whitney, Wilcoxon or Kruskal-Wallis tests according to the variable's type and distribution. Correlations were estimated using Spearman coefficients. Other statistical tests are described in the *Results* section. Corrections for multiple comparisons were done to examine the impact of the number of tests

on *p* value (Benjamini and Yekutieli's correction (26)). A *p* value < .05 was deemed significant, except when stated. Statistical analyses were performed using SAS software (version 9.2, SAS Institute, Inc, Cary, NC, USA).

RESULTS

One hundred and eighteen consecutive obese women referred for bariatric surgery were included from January

TABLE 1.— Clinical characteristics of the obese and lean groups of women.

Characteristics	Healthy lean women, <i>n</i> = 30	Obese women, <i>n</i> = 118	<i>p</i> value
Ethnicity			1
Caucasian, <i>n</i>	26	98	
African, <i>n</i>	4	18	
Asian, <i>n</i>	0	2	
Age, years	34 ± 12	36 ± 10	.32
Height, m	1.64 ± 0.06	1.63 ± 0.06	.37
Weight, kg	59 ± 6	123 ± 20	ND
BMI, kg.m ⁻²	21.9 ± 1.8	46.1 ± 6.8	ND
Smoking history			
Current smoker, <i>n</i> (%)	0	31 (26)	ND
Past smoker, <i>n</i> (%)	5	24 (20)	ND
Pack-years	4 ± 1	11 ± 9	ND
Never smoker, <i>n</i> (%)	25	63 (53)	ND
Asthma			
Ever asthma, <i>n</i>	0	31	ND
Current asthma, <i>n</i>	0	24	ND
Childhood asthma*, <i>n</i>	0	10	ND
Overweight at asthma diagnosis, <i>n</i>		22	
Treatment, <i>n</i>		20	
On demand SABA		8	
LABA, ICS, LTRA		8 / 10 / 2	
Pulmonary function tests #			
TLC, % predicted	105 ± 14	98 ± 14	.030
FRC, % predicted	103 ± 18	76 ± 18	<.001
RV, % predicted	99 ± 27	96 ± 25	.59
ERV, % predicted	108 ± 21	48 ± 26	<.001
FEV ₁ , % predicted	103 ± 12	96 ± 16	.037
FVC, % predicted	107 ± 13	99 ± 16	.014
FEV ₁ /FVC	0.84 ± 0.05	0.84 ± 0.06	.78
FEF _{25-75%} , % predicted	87 ± 20	82 ± 26	.36
FEF _{25-75%} / FVC	0.90 ± 0.20	0.93 ± 0.28	.62
Raw _{0.5} , kPa.s.L ⁻¹ (<i>n</i>)	0.17 ± 0.09 (30)	0.29 ± 0.13 (94)	<.001
sRaw _{0.5} , kPa.s (<i>n</i>)	0.49 ± 0.27 (30)	0.72 ± 0.38 (94)	.004
Metacholine challenge test			
DRS, % decrease/μmol	1.04 [0.72;1.40]	2.15 [0.87;17.32]	<.001
Nocturnal polygraphy			
Epworth Sleepiness score	7.4 ± 4.4	(1 missing)	.070
AHI, hour ⁻¹	0.3 [0.0;1.2]	9.3 ± 4.2	ND
Absence of SDB (AHI<5), <i>n</i> (%)	30 (100)	1.0 [0.0;7.0]	ND
Mild SDB (5≤AHI<15), <i>n</i> (%)	0	81 (69)	ND
Moderate SDB (15≤AHI<30), <i>n</i> (%)	0	22 (19)	ND
Severe SDB (AHI≥30), <i>n</i> (%)	0	9 (8)	ND
GERD		5 (4)	
Absence, <i>n</i>	NA	67 (57)	
Possible, <i>n</i>	NA	11 (9)	
Confirmed, <i>n</i>	NA	40 (34)	

*Childhood asthma defined by asthma onset before 13 years of age.

#Lung volumes were obtained by body plethysmography (*n* = 94) or helium dilution (*n* = 24).

Notes: Results are expressed as mean ± SD or median [interquartile] as appropriate.

ND: statistical analysis not done (differences related to inclusion criteria); NA: not available; SABA: short-acting beta agonist; LABA: long-acting beta agonist; ICS: inhaled corticosteroid; LTRA: leukotriene receptor antagonist.

DRS: dose-response slope.

The *p* values in bold are those that remained significant after statistical correction for multiplicity of testing.

2010 to June 2011. Thirty healthy lean women were also recruited. Clinical and functional characteristics of the women are described in Table 1. Pulmonary function of obese women was characterized by a decrease in expiratory reserve volume (ERV), functional residual capacity (FRC), and an increase in airway resistance.

Prevalence of Obesity-Related Comorbidities

In our population of severely young severely obese women, the prevalence of asymptomatic AHR, asthma, GERD, and SDB was 35/118 (30%, 95% CI: 22–38%), 22/118 (19%, 95% CI: 13–27%), 51/118 (43%, 95% CI: 35–52%), and 36/117 (31%, 95% CI: 23–40%), respectively.

Dyspnea Descriptors

The dyspnea descriptors of the obese and lean women are described in Table 2, and the descriptors according to comorbidities of the obese women are described in Table 3.

Resting Dyspnea

Resting dyspnea was very prevalent in obese women as compared to healthy lean women. Among obese women, 48/118 (41%, 95% CI: 32 to 50% – 5% missing data) complained of at least one resting symptom, while only one lean women reported a resting complaint (3%, 95% CI: 1 to 17%; $p < .0001$).

In obese women, a Cochran-Mantel-Haenszel test (repeated tests of independence) further demonstrated that chest tightness, unsatisfactory inspiration, and the need for deep inspirations (measured variables) were independently associated with GERD, as explanatory variable ($p = .005$, $p = .008$, and $p = .044$, respectively) after controlling on asthma. By contrast, using the same analysis strategy, wheezing and cough descriptors were not related to GERD ($p = .20$ and $p = .13$, respectively).

Overall, resting respiratory complaints were associated with asthma, GERD, or both.

We further assessed whether descriptors obtained at rest can be associated with abnormalities evidenced by respiratory function tests. Air hunger and feeling of suffocation were associated with a lower level of PaO₂ impaired oxygenation ($p = .004$ and $p = .020$, respectively).

Activity-Related Dyspnea

Among obese women, 88/118 (75%, 95% CI: 66 to 82–7% missing data) complained of at least one symptom on exercise, while only two lean women reported an activity-related complaint (7%, 95% CI: 2 to 21%; $p < .0001$) without impact on activity (MRC grade 1, all lean women). Wheezing on exercise was the only complaint related to a comorbidity of obesity, namely asthma. As a consequence, other respiratory complaints were probably related to obesity. This sensory experience of dyspnea in obese women (mainly rapid and shallow breathing) was associated with an impact on daily activities since activity-related dyspnea was highly prevalent (MRC ≥ 2 : 84/118, 71%, 95% CI: 62 to 79%).

DISCUSSION

The main results of our cross-sectional study in severely obese women are (1) resting dyspnea complaints are frequent in obese women and observed in association with asthma and/or GERD while (2) activity-related dyspnea complaints are highly prevalent in obese women and mainly associated with obesity, with the exception of wheezing on exercise that is related to asthma.

Assessment of Comorbidities

Our first attempt was to establish comorbidity diagnoses with certainty. With the exception of asymptomatic AHR

TABLE 2.— Respiratory descriptors at rest and on exercise in obese and lean women.

Dyspnoea descriptors, <i>n</i> *	Whole Obese population <i>n</i> = 118	Control population <i>N</i> = 30	<i>p</i> value (Fisher's Exact Test)
At rest			
Chest tightness	18 (15%)	0 (%)	.013
Unsatisfactory inspiration	19 (16%)	0 (0%)	.013
Air hunger	23 (19%)	0 (0%)	.004
Need for deep inspirations	26 (22%)	1 (3%)	.016
Inspiration difficulty	10 (8%)	0 (0%)	.12
Expiratory difficulty	12 (10%)	0 (0%)	.07
Feeling of suffocation	18 (15%)	0 (0%)	.013
Wheezing	26 (22%)	0 (0%)	.001
Cough	13 (11%)	0 (0%)	.07
On exercise			
Wheezing	24 (20%)	0 (0%)	.002
Feeling of suffocation	38 (32%)	0 (0%)	<.001
Rapid breathing	83 (70%)	1 (3%)	<.001
Shallow breathing	71 (60%)	2 (7%)	<.001
MRC scale, 1/2/3+4	34/58/26	30/0/0	<.001

Note: Missing data: 6 to 8 obese women did not respond to all resting descriptors, and 8 to 11 obese women did not respond to all exercise descriptors. The *p* values in bold are those that remained significant after statistical correction for multiplicity of testing.

TABLE 3.— Respiratory descriptors at rest and on exercise in obese women according to comorbidities.

Dyspnoea descriptors, <i>n</i>	Whole population <i>n</i> = 118	AHR		SDB (7 missing data)		GERD			<i>p</i> value
		Without <i>n</i> = 61	Asymptomatic <i>n</i> = 35	Asthma <i>n</i> = 22	<i>p</i> value	Without <i>n</i> = 75	With <i>n</i> = 36	<i>p</i> value	
At rest									
Chest tightness	18 (15%)	10	0*	8	<.001	14	3	.259	11
Unsatisfactory inspiration	19 (16%)	10	2	7	.060	13	6	1.000	12
Air hunger	23 (19%)	10	2	11	<.001	19	3	.071	12
Need for deep inspirations	26 (22%)	13	2	11	<.001	20	5	.222	12
Difficulty on inspiration	10 (8%)	5	0	5	.014	8	1	.267	7
Difficulty on expiration	12 (10%)	4	1	7	.003	9	2	.497	7
Feeling of suffocation	18 (15%)	8	2	8	.019	14	3	.259	9
Wheezing	26 (22%)	12	0*	14	<.001	19	6	.466	13
Cough	13 (11%)	4	0*	9	<.001	12	1	.059	8
On exercise									
Wheezing	24 (20%)	10	0*	14	<.001	16	7	1.000	11
Feeling of suffocation	38 (32%)	18	7	13	.019	26	11	1.000	19
Rapid breathing	83 (70%)	45	19	19	.055	54	28	.484	34
Shallow breathing	71 (60%)	37	17	17	.197	43	28	.033	29
MRC scale, 1/2/3+4	34/58/26	17/30/14	14/15/6	3/13/6	.315	24/31/20	6/26/4	.011	9/23/8

*These complaints have been selected to define asymptomatic AHR versus asthma that explains these results (absence of complaint in asymptomatic AHR).
Note: The *p* values in bold are those that remained significant after statistical correction for multiplicity of testing.

prevalence that remains controversial in obese subjects (29, 30), the observed prevalence of asthma (19%), GERD (43%), and SDB (31%) are in line with those expected in our French population referred for bariatric surgery. The observed prevalence of asthma is in agreement with the results of a meta-analysis that demonstrated a two-fold increase in asthma prevalence in obese women (31). The overall prevalence of GERD in France is 31.3% (27), and clinical GERD, defined by the presence of either heartburn or regurgitation, was present in 50% (34/68) of patients selected for bariatric surgery in a French series (32). In another French series, polysomnography before bariatric surgery showed that 40% (31/77) of the patients suffered from SDB (33).

Resting Dyspnea

We deliberately distinguished resting and activity-related dyspnea complaints because they often do not share common pathophysiological backgrounds. To our best knowledge, only one study specifically addressed the question of whether obese subjects can complaint of resting dyspnea. In this study, among 23 healthy obese men free of coexisting conditions that could have influenced the presence and severity of dyspnea, the 15 men who reported breathing difficulties at rest had lower maximum voluntary ventilation and lower maximal expiratory flows at low lung volumes (2). The dyspneic group also included a greater proportion of smokers and had a higher BMI, which may account for some of the symptoms and differences in lung function. Unfortunately, verbal descriptors of dyspnea experience were not provided in this latter study (2). In severely obese young women, resting dyspnea was clearly associated with asthma. We further show that asthma-like resting complaints are also encountered in GERD, independently of the presence of asthma. GERD is known to aggravate respiratory complaints in asthmatic patients, and has occasionally been described as the only dyspnea cause (34, 28).

Activity-Related Dyspnea and Comorbidities

Despite a frequent activity-related dyspnea complaint in obese patients (71% in our study with MRC scale > 1) that is in agreement with previous studies (1), dyspnea causes are ill-determined (35). We recently demonstrated that psychological status did not affect activity-related dyspnea assessment by the MRC scale in obese patients (16). Consequently, one may wonder whether comorbidities of obesity, such as AHR, SDB, and GERD, may explain dyspnea. Similar to other investigators (21), we suggest that obese women are characterized by an increased prevalence of AHR. While dyspneic complaints at rest were clearly related to asthma in obese women, we did not find any increase in activity-related dyspnea in women with asymptomatic or symptomatic AHR, i.e. asthma. Exercise-induced bronchospasm is frequent in asthmatics but often occurs at high levels of exercise intensity (36), which may be prevented by the sedentary lifestyle of obese patients (37).

The prevalence of SDB is increased in obese patients. Nocturnal dyspnea has been described in this setting, but whether SDB contributes to activity-related dyspnea has not been established. Recent studies have shown that SDB is associated with poor asthma control (38), which may be associated with worsened dyspnea. In the present study, we show that Apnea Hypopnea Index (AHI) was not associated with dyspnea level.

Limitations of the Study

Due to the cross-sectional design of our study, our results are based on statistical relationships that did not mean causality. Evaluation of the women after surgery is a complex issue, because even if weight reduction is significant, they often do not recover a normal BMI. Furthermore, the effects of BMI on lung function seem to develop over time (years for human beings (39)), implying that the effect of weight reduction should also be assessed after several years. Obviously, our results are restricted to the female gender with severe obesity, maybe more symptomatic due to surgery referral, and finally some other comorbidities of obesity may also have contributed to dyspneic complaints.

Clinical Consequences

The first message is that resting dyspnea is frequent (~40%) and is related to either asthma or GERD, and two frequent comorbidities of obesity. The second message is that activity-related dyspnea is highly prevalent (~70%) and seems related to obesity per se (35), with the exception of wheezing on exertion related to asthma. Asthma control assessment relies on the recording of both resting and exercise-induced symptoms that can limit daily activities. The present study shows that obese patients can exhibit respiratory complaints that are due to GERD, a frequent obesity-related comorbidity, or due to obesity. As a consequence, these complaints, which are not related to asthma, may bias the assessment of asthma control. Along this line, it has been shown that obese patients with difficult-to-treat asthma had more co-morbid factors than non-obese patients, in particular, GERD and SDB (40).

In conclusion, in severely obese women referred for bariatric surgery, resting and activity-related dyspnea complaints are very prevalent and can be related to GERD and obesity, respectively, independently of the presence of asthma.

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DECLARATION OF INTERESTS

The authors declare no competing interest. This governmental organization had no direct financial interest in the subject discussed in the submitted manuscript.

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