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Influence of cardiac dysfunction and systemic inflammation on pulmonary function and airway responsiveness in obese subjects

Abstract

Purpose: Obesity is associated with left ventricular diastolic dysfunction and altered heart rate variability, as well as pulmonary dysfunction. The relationship between asthma and cardiac dysfunction in severely obese subjects is unknown, although it has been hypothesized that cardiac dysfunction may contribute to increase airway hyper-responsiveness (AHR). This study aimed to determine if AHR is associated with left ventricular diastolic dysfunction and heart rate variability in severely obese subjects.

Methods: Sixty-one subjects with severe obesity (BMI ≥ 35 kg/m² with comorbidities) completed this study. All subjects completed respiratory questionnaires, spirometry, lung volume measurements, methacholine inhalation test, 24-hour Holter monitoring and a complete echocardiography evaluation. Blood samples were obtained for measurement of metabolic markers. Subjects with AHR, defined by a provocative concentration of methacholine inducing a 20% fall in FEV₁ (PC₂₀) < 8 mg/ml, were compared with those with no AHR (PC₂₀ ≥ 8 mg/ml).

Results: According to these criteria, 32 subjects had AHR and 29 had no AHR (mean PC₂₀ 1.70 mg/ml and 15.3 mg/ml respectively, $p < 0.001$). The groups were similar for anthropometric data and comorbidities. Fasting glucose, Hb1Ac, total cholesterol, LDL, triglycerides, Apo-B, C-reactive protein (CRP) and pro-BNP levels were also comparable between groups ($p > 0.05$). CRP level correlated with PC₂₀ (AHR, $r = 0.38$, $p = 0.03$). Indices of heart rate variability and overall cardiac function were similar in subjects with or without AHR but grade 2 left ventricular diastolic dysfunction was more prevalent in subjects with AHR ($p = 0.037$).

Conclusions: Altered cardiac function, dysglycemia and dyslipidemia do not seem to be significantly associated with AHR in severely obese subjects in contrast to systemic inflammation.

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An increased prevalence of symptomatic asthma has been described in obese subjects, although how obesity could influence the development or the clinical expression of AHR is still debated [1-8]. Possible suggested mechanisms by which obesity can alter airway function include mechanical factors, increased inflammatory state, and influence of co-morbid conditions such as diabetes, dyslipidemia and hypertension [9-12].

Lung function is altered in obesity, as shown by reduced functional residual capacity (FRC), reduced tidal volume (V_T) and small airway closure during tidal breathing [9]. Both visceral and subcutaneous fat can contribute to reduce lung volume and can possibly increase airway responsiveness [10, 13]. Obesity may be considered a chronic inflammatory state, often associated with increased markers of systemic inflammation [12]; however, there is no strong evidence that the latter can significantly impact local airway inflammation [14]. It has been previously reported that asthma, in obese subjects, constituted a specific phenotype and that there was a significant trend towards a lesser eosinophilic airway inflammatory pattern in severely obese subjects [15]. Several researchers have reported that asthma was more difficult to manage in obese subjects, particularly in severely obese patients, who showed a poorer response to asthma medications despite similar symptoms perception [16-20]. Furthermore, diabetes is commonly associated with obesity and a higher prevalence of insulin resistance has been found in obese children with asthma [21-22]. There is evidence that hyperinsulinemia can induce a hypercontractile smooth muscle phenotype [23] but the relationship between abnormal glucose metabolism and AHR is still unclear [23-25].

It has also been suggested that altered cardiovascular function could influence airway physiology [9]. Congestive heart failure may increase airway responsiveness, possibly by increasing airway wall water content [27-29]. Indeed, subtle pulmonary congestion associated with left ventricular diastolic dysfunction can possibly amplify peri-bronchial oedema, and exacerbate airway responsiveness by mechanisms such as bronchial/parenchymal uncoupling. Obesity is also associated with altered heart rate variability (HRV) [28-30]. Subjects with atopic dermatitis, allergic rhinitis and asthma show autonomic imbalance as observed for other diseases related to atopy or allergy [31-32]; however, the relationship between asthma and HRV is unknown in severely obese subjects [33]. So far, no study has used an integrative approach using these parameters within the same group of patients.

The primary outcome was to assess, using a comprehensive dataset, the determinants of the degree of airway responsiveness in light of the presence of left ventricular diastolic

dysfunction, altered heart rate variability and metabolic parameters in severely obese patients. We hypothesized that in severely obese subjects, airway hyper-responsiveness (AHR) is associated with the presence of left ventricular diastolic dysfunction and altered HRV. We also hypothesized that the severity of AHR correlates with systemic inflammation and dysglycemia.

Methods

Study population

Sixty-one severely obese subjects ($BMI \geq 35 \text{ kg/m}^2$ with comorbidities), aged 21 to 65 years, were enrolled from the Institut universitaire de Cardiologie et de pneumologie de Québec (IUCPQ) bariatric surgery program between October 2006 and June 2009. Subjects who were unable to provide informed consent, or who were pregnant or breast feeding, or had respiratory conditions (apart from AHR) that could interfere with the study design were excluded. The subjects were pre-interviewed by a physician from the bariatric surgery program and then contacted by our study group to take part of this study, which was approved by our Ethics Committee. All subjects signed an informed consent form.

Clinical Measurements

Anthropometric measures were recorded at the beginning of the study. Body weight was measured to the nearest 0.1 kg and height was measured to the nearest 0.01 meter. Body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared (kg/m^2). Atopic status was determined from skin prick tests, performed using a battery of common airborne allergens. A complete blood count, fasting blood glucose, Apo-B, pro-NT-BNP, lipid profile including total cholesterol concentration, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides as well as C-reactive protein (CRP) concentrations were obtained [34].

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured from flow-volume curves performed according to the American Thoracic Society (ATS) specifications, using an ATS-approved spirometer [35]. Baseline FEV_1 was calculated as the best of the three reproducible values (with a maximum change of 5%). Predicted values were obtained from Knudson [36]. Methacholine challenge was performed according to the method described by Juniper et al. up to a concentration of 16 mg/ml [37]. Lung volume and carbon monoxide (CO) diffusing capacity were measured by standard procedures using body plethysmography

TABLE 1: Patient characteristics

	AHR (PC ₂₀ <8 mg/ml) N = 32	No AHR (PC ₂₀ ≥8 mg/ml) N = 29	p value
Age (SD)	43 (11)	42 (11)	0.61
Sex, Female, n (%)	23 (71.9)	16 (55.2)	0.19
Height, cm (SD)	165.8 (11.2)	169.5 (9.1)	0.17
Weight, kg (SD)	128.9(30.8)	142.5 (28.7)	0.08
BMI, kg/m ² (SD)	46.0 (7.4)	48.3 (6.8)	0.21
Atopy, number (%)	17 (54.8)	15 (51.7)	0.20
Active smoking status, number (%)	5 (15.6)	5 (17.2)	0.21
Former smoker, number (%)	15 (46.9)	18 (62.1)	0.10
Smoking history, pack-year (SD)	20.8 (14.0)	16.8 (18.7)	0.49
Number of years quit smoking	8.4 (7.0)	12.9 (10.6)	0.17

Mean ± SD or number of patients (%)

AHR: airway hyper-responsiveness

PC₂₀: provocative dose (of methacholine) inducing a 20% fall of FEV₁

[38]. Methacholine challenge and body plethysmography were performed on different days.

Echocardiographic measures were recorded with a commercial ultrasound system (Sonos 5500; Hewlett Packard, Andover, MA). Standard parasternal, short-axis and apical views were performed in accordance with the recommendations of the American Society of Echocardiography and the same observer, who was blinded to other study evaluations, assessed all recordings and measurements. Left ventricular diastolic dysfunction, using transmitral and pulmonary veins recordings, was evaluated according to well-standardized criteria as previously reported [39–40]. HRV was derived from a 24-hour Holter monitoring system (Marquette Electronics., Milwaukee, WI) in all subjects during normal daily life activities. Numerous indices of HRV in the frequency and the time domains were determined: mean value of all RR intervals (mean NN), standard deviation of the RR intervals (SDNN), standard deviation of the mean NN intervals for each 5 minutes period (SDANN), square root of the mean squared difference of successive RR intervals (rMSSD), percentage of differences between adjacent normal RR intervals exceeding 50 ms (pNN50), high frequency (HF) and low frequency (LF) [40].

Statistical methods

Data are expressed as mean ± SD for continuous variables or as percentage ± SD for categorical data. Geometric mean was used for methacholine PC₂₀. AHR was defined as a provocative dose of methacholine inducing a 20% fall of FEV₁ < 8mg/ml (PC₂₀<8 mg/ml). For statistical analysis, a PC₂₀≥16 mg/ml

was considered as being equal to 16 mg/ml. Analyses of categorical variables were performed using the Fisher's exact test. According to the distribution of continuous data, Student's t-test or Wilcoxon's rank-sum test was used to compare groups. The normality assumption was verified with the Shapiro-Wilk test and the Brown and Forsythe's variation of Levene's test statistic was used to verify homogeneity of variances. The results were considered significant with p-values ≤ 0.05.

The relationships between variables were expressed using the Pearson's correlation coefficient. The results were considered significant with p-values ≤ 0.05. Data were analyzed using the statistical package program SAS v8.2 (SAS Institute Inc., Cary, NC). Data were analyzed using the statistical package program SAS v8.2 (SAS Institute Inc., Cary, NC).

Results

Sixty-two subjects agreed to take part in the study and sixty-one completed the study; one being excluded because of inability to perform all the tests. Thirty-two subjects suffered AHR (PC₂₀<8 mg/ml) while 29 had normal airway responsiveness (PC₂₀ ≥ 8mg/ml).

Anthropometric data were similar in severely obese subjects with and without AHR as were subjects with atopy, smoking status and smoking history (Table 1). Apart from AHR, obesity-related co-morbid conditions were comparable between groups (Table 2). In the group with AHR, 19/32 subjects (59.4%) had a physician-diagnosed or self-reported asthma compared to 8/29 (27.6%) in the group with normal

TABLE 2: Comorbidities

	AHR (PC ₂₀ <8 mg/ml) N = 32	No AHR (PC ₂₀ >8 mg/ml) N = 29	p value
Hypertension, n (%)	22 (68.8)	19 (65.5)	0.21
Type 2 diabetes, n (%)	13 (40.6)	14 (48.3)	0.17
Gastroesophageal reflux disease, n (%)	21 (65.6)	17 (58.6)	0.18
Sleep apnoea/hypopnoea syndrome, n (%)	30 (93.8)	26 (89.7)	0.30
Dyslipidemia, n (%)	17 (53.1)	14 (48.3)	0.19
Heart failure, n (%)	0	1 (3.6)	0.48
Coronary atherosclerosis, n (%)	3 (10.0)	3 (10.7)	0.34
Valvulopathy, n (%)	2 (6.5)	2 (7.1)	0.34
Daily use of statins, n (%)	14 (45.2)	13 (44.8)	0.20

Number of patients (%) AHR: airway hyper-responsiveness

PC₂₀: provocative dose (of methacholine) inducing a 20% fall of FEV₁

airway responsiveness ($p < 0.001$). Eleven subjects used daily bronchodilators in the hyper-responsive group compared to none in the normo-responsive group ($p < 0.001$). The number of subjects regularly using inhaled corticosteroids was not significantly different between groups (Table 3).

Blood measurements

Results of fasting blood glucose, lipid profile and C-reactive protein levels are showed in Table 4. The groups with and without AHR were similar for all parameters except for HDL level, which was higher in the hyper-responsive group ($p = 0.03$).

Methacholine challenge

Baseline FEV₁ before methacholine inhalation was $86.6 \pm 11.9\%$ in the hyper-responsive group and $94.0 \pm 12.7\%$ ($p = 0.02$) in the normo-responsive group. This significant difference was not found, however, on baseline evaluation of lung function (Table 4). Baseline FVC was $93.6 \pm 13.3\%$ and $98.7 \pm 13.8\%$, respectively ($p = 0.15$). Mean airway responsiveness to methacholine was 1.7 mg/ml, ranging from 0.01 mg/ml to 7.6 mg/ml in the hyper-responsive group and 15.3 mg/ml (10.4 to ≥ 16 mg/ml) in the normo-responsive group.

Lung volumes and CO diffusion

As expected, FEV₁/FVC ratio ($p = 0.02$) and forced mid 25-75% expiratory flow (FEF₂₅₋₇₅) were lower ($p = 0.003$) and residual volume was higher ($p = 0.02$) in the hyper-responsive

TABLE 3: Airway hyperresponsiveness diagnosis and medication

	AHR (PC ₂₀ <8 mg/ml)	No AHR (PC ₂₀ >8 mg/ml)	p value
Asthma diagnosis (self-reported), n (%)	19 (59.4)	8 (27.6)	< 0.001
Age of asthma diagnosis, years, (SD)	35 (15)	15 (13)	< 0.001
Daily use of inhaled bd ^a , n (%)	11 (34.4)	0	< 0.001
PRN use of inhaled bd ^a , n (%)	5 (15.6)	3 (10.3)	0.71
Daily use of inhaled corticosteroids or Inhaled corticosteroids/long-acting β -Agonist association, n (%)	9 (28.13)	3 (10.3)	0.11
Use of oral corticosteroid	0	0	-

^a: bd = bronchodilator

Number of patients (%) and mean $\pm$ SD for age of asthma diagnosis

AHR: airway hyper-responsiveness

PC₂₀: provocative dose (of methacholine) inducing a 20% fall of FEV₁

TABLE 4: Blood sample, methacholine test and lung volume results

	AHR (PC ₂₀ <8 mg/ml) n = 32	No AHR (PC ₂₀ ≥8 mg/ml) n = 29	p value
Blood sample results			
Fasting glucose, mmol/L (SD)	6.71 (2.93)	7.03 (2.82)	0.66
Hb _{1AC} , mmol/L (SD)	0.06 (0.01)	0.07 (0.01)	0.52
Total cholesterol, mmol/L (SD)	4.64 (0.93)	4.40 (1.00)	0.35
HDL, mmol/L (SD)	1.32 (0.35)	1.13 (0.31)	0.03
LDL, mmol/L (SD)	2.60 (0.83)	2.46 (0.78)	0.51
Triglycerides mmol/L (SD)	1.58 (0.58)	1.79 (0.85)	0.26
Apo-B, g/L (SD)	0.78 (0.17)	0.78 (0.22)	0.95
CRP, mg/L(SD)	9.56 (6.49)	9.02 (8.61)	0.78
NT-Pro-BNP, pg/mL(SD)	52.69 (42.90)	78.93 (119.37)	0.25
Methacholine test			
PC ₂₀ Methacholine,geometric mean, mg/mL, (range)	1.7 (0.01 to 7.6)	15.3 (10.4 to >16)	<0.001
Baseline respiratory flows and lung volumes			
FEV ₁ , % (SD)	90.1 (14.3)	95.2 (13.9)	0.17
FVC, % (SD)	98.2(13.9)	102.4 (14.9)	0.21
FEV ₁ /FVC ratio, % (SD)	92.8 (9.3)	97.8 (6.7)	0.02
FEF ₂₅₋₇₅ , % (SD)	75.3 (21.5)	92.4 (21.9)	0.003
TLC, % (SD)	104.0 (11.8)	101.32 (12.0)	0.39
RV, % (SD)	114.9 (26.4)	98.5 (25.6)	0.02
FRC, % (SD)	87.1 (13.3)	80.2 (17.1)	0.10
VC, % (SD)	103.5 (17.1)	102.60 (13.3)	0.84
D _L CO (SD)	105.8 (15.1)	104.9 (17.6)	0.83

Mean ± SD, median and range for PC₂₀: provocative dose (of methacholine) inducing a 20% fall of FEV₁

AHR: airway hyper-responsiveness

Hb_{1AC}: glycated hemoglobin HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, Apo-B: Apolipoprotein B, CRP: C-reactive protein, NT-Pro-PNB: pro-brain natriuretic peptide, FEV₁ : forced expiratory volume in one second, FVC : forced vital capacity, FEF₂₅₋₇₅: forced mid 25-75% expiratory flow, TLC: total lung capacity, RV: residual volume, FRC: functional residual capacity, VC: vital capacity, D_LCO: carbon dioxide lung diffusing capacity.

group compared with the normo-responsive group (Table 4). FEV₁ and FVC were also slightly lower in the hyper-responsive group but there was no statistically significant difference between groups. Carbon monoxide lung diffusing capacity (DLCO) was similar in both groups.

Cardiovascular measurements

Indices of HRV were similar in subjects with or without AHR (Table 5). A higher number of subjects with AHR depicted a more severe degree of left ventricular diastolic dysfunction (grade 2) compared with subjects without AHR (p=0.037); however, the overall degree of cardiac dysfunction had no sta-

tistically significant influence on the methacholine response (Figure 1A) or on CRP levels (Figure 1B).

Correlations

There was a significant correlation between CRP levels and PC₂₀ methacholine in the group of subjects with AHR (r = 0.38, p = 0.03, Figure 2). This could not be assessed in the normo-responsive group as most subjects had less than 20% fall in FEV₁ with a dose of methacholine of 16 mg/ml. Another analysis setting the cut-off at 4 mg/ml between the two groups and another sub-analysis excluding subjects on inhaled

TABLE 5: Cardiovascular measurements

	AHR (PC ₂₀ <8 mg/ml) N = 32	No AHR (PC ₂₀ >8 mg/ml) N = 29	p value
Diastolic dysfunction (%) Grade 0	3 (9.4)	8 (28.6)	0.037
Grade 1	10 (31.3)	12 (42.9)	
Grade 2	19 (59.4)	8 (28.6)	
Ejection fraction, %	64.2 (7.1)	62.2 (7.9)	0.31
NN, ms	723.1 (76.9)	731.5 (72.7)	0.67
Heart rate, bpm	83.8 (9.1)	82.8 (8.1)	0.63
SDNN, ms	110.97 (25.0)	108.4 (24.0)	0.68
rMSSD, ms	26.4 (9.7)	26.7 (10.2)	0.91
pNN50, %	3.5 (3.0)	3.3 (3.1)	0.86
HF (ms ²)	148.0 (108.2)	150.7 (136.6)	0.93
LF (ms ²)	316.8 (200.9)	389.0 (315.9)	0.29
LF/HF ratio	2.79 (1.73)	2.97 (1.44)	0.66

Mean $\pm$ SDPC₂₀: provocative dose (of methacholine) inducing a 20% fall of FEV₁AHR: airway hyper-responsiveness, NN: NN interval, SDNN: standard deviation of NN interval, rMSSD: square root of the mean squared difference of successive NNs, pNN50: percentage of differences between adjacent NN intervals that are >50 msec, HF and LF: high and low frequency heart rate variability

corticosteroids showed no changes in the findings (data not shown).

Discussion

No significant influence of HRV and left ventricular diastolic dysfunction, dysglycemia, and dyslipidemia on the prevalence or magnitude of AHR was found in severely obese subjects. In contrast, CRP, a marker of systemic inflammation, correlated, although weakly, with the latter. How obesity could influence the development of AHR is still debated [1-8]; however, recent data suggest that there is a causal relationship between obesity and asthma [1, 8, 41]. AHR, in the obese subject, may represent a specific phenotype with a particular pathophysiology and clinical presentation, somewhat different from « classical » asthma [1, 2, 16]. Obesity has been associated with altered cardiac function [28-30]; however, the relationship between AHR and cardiac dysfunction are still unknown in severely obese subjects. This is the first study investigating, using a comprehensive set of data, the relationship among asthma, obesity, metabolic variables, HRV and left ventricular diastolic dysfunction. Although severely obese subjects with AHR were found to have more common grade 2 LVDD compared with normo-responsive subjects, globally, altered cardiac dysfunction had no significant influence on methacholine responsiveness.

Left ventricular diastolic dysfunction has been reported to be associated with HRV in subjects with diabetes [39] and impaired left ventricular diastolic function may contribute to increased pulmonary artery wedge pressure [43-46]. This, in turn, could slightly alter total lung perfusion as well as the distribution of pulmonary blood flow, which may induce relative pulmonary congestion. This pulmonary turgor may contribute to increase airway responsiveness. The distinctive pathophysiology of AHR in severely obese subjects may have been influenced by left ventricular diastolic function as well as by the autonomic nervous system as evaluated with HRV. Our study does not support this hypothesis. Instead, we found that a high CRP level was associated with AHR in severely obese subjects. Although the clinical significance of this correlation is uncertain, it is in agreement with previous data demonstrating that low grade systemic inflammation is increased in obesity and is also associated with bronchial asthma, although its causal relationship with AHR is still debated [12, 14, 18, 20].

Obese subjects are more likely to experience dyspnea and a discrepancy is more likely to be observed between perceived symptoms and asthma diagnosis. Previous studies have shown that approximately one-third of both obese and non-obese subjects with physician-diagnosed asthma did not have asthma when objectively assessed [47] and over-diagnosis of asthma was no more likely to occur among obese than non-obese subjects [48]. In our group of severely obese subjects, some had AHR but no asthma diagnosis while others with an asthma

Figure 1

FIGURE 1. (A) Provocative concentration of methacholine inducing a 20% fall in FEV₁ (PC₂₀) and grade of left ventricular diastolic dysfunction in subjects with (PC₂₀ < 8 mg/ml) or without (PC₂₀ ≥ 8 mg/ml) airway hyperresponsiveness. (B) Distribution of C-reactive protein (CRP) according to degree of left ventricular diastolic dysfunction and airway responsiveness.

diagnosis or asthma medication showed negative tests for AHR, demonstrating the difficulty of attributing respiratory symptoms only to asthma in this population – this has also been shown to be the case with heart failure [48]. Asthma control may be overestimated in obese subjects, their respiratory symptoms being attributed to obesity *per se* as the increased work of breathing generates respiratory symptoms. This stresses the need to perform pulmonary function tests in this population.

No significant correlation was found between AHR and either dysglycemia or dyslipidemia. It has been proposed that changes in lipids and glucose metabolism could be associated with AHR in obese subjects [24, 25, 48, 49]; however, reported associations were weak. It has been speculated that the pro-inflammatory state of insulin resistance can contribute to systemic inflammation, explaining the pathogenesis of AHR in obese subjects [50]. In comparison with other studies, the diagnosis of AHR in our study was established following both a

FIGURE 2. Correlation between C-reactive protein (CRP) and airway responsiveness to methacholine (PC₂₀).

positive methacholine challenge and respiratory symptoms instead of physician-made or self-reported diagnosis.

Our study has some limitations. This was a cross-sectional study, and therefore not designed to investigate changes in AHR over time. A second limitation could be the limited number of subjects; however, we used a comprehensive set of data that has been associated with AHR and we were able to document associations with parameters such as CRP and grade 2 left ventricular diastolic dysfunction. A third possible limitation is that the methacholine challenge was stopped at 16 mg/ml in the normo-responsive group. For this reason, a PC₂₀ ≥ 16 mg/ml was considered as equal to 16 mg/ml in statistical analysis.

Conclusion

In conclusion, subtle cardiac dysfunction, dysglycemia or dyslipidemia do not appear to be associated with airway responsiveness in severely obese subjects. The fact that a greater proportion of subjects with grade 2 left ventricular diastolic dysfunction had AHR deserves further investigation.

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