Systemic inflammation and higher perception of dyspnea mimicking asthma in obese subjects

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Background: There are a variable number of obese subjects with self-reported diagnosis of asthma but without current or previous evidence of airflow limitation, bronchial reversibility, or airway hyperresponsiveness (misdiagnosed asthma). However, the mechanisms of asthma-like symptoms in obesity remain unclear.
Objectives: We sought to evaluate the perception of dyspnea during bronchial challenge and exercise testing in obese patients with asthma and misdiagnosed asthma compared with obese control subjects to identify the mechanisms of asthma-like symptoms in obesity.
Methods: In a cross-sectional study we included obese subjects with asthma (n = 25), misdiagnosed asthma (n = 23), and no asthma or respiratory symptoms (n = 27). Spirometry, lung volumes, exhaled nitric oxide levels, and systemic biomarker levels were measured. Dyspnea scores during adenosine bronchial challenge and incremental exercise testing were obtained.
Results: During bronchial challenge, patients with asthma or misdiagnosed asthma reached a higher Borg-FEV_1 slope than control subjects. Moreover, maximum dyspnea and the Borg–oxygen uptake ($V'O_2$) slope were significantly greater during exercise in subjects with asthma or misdiagnosed asthma than in control subjects. The maximum dyspnea achieved during bronchial challenge correlated with IL-1β levels, whereas peak respiratory frequency, ventilatory equivalent for CO_2, and IL-6 and IL-1β levels were independent predictors of the Borg-$V'O_2$ slope during exercise ($r^2 = 0.853$, $P < .001$).
Conclusions: A false diagnosis of asthma (misdiagnosed asthma) in obese subjects is attributable to an increased perception of dyspnea, which, during exercise, is mainly associated with systemic inflammation and excessive ventilation for metabolic demands. (J Allergy Clin Immunol 2016;137:718-26.)

Key words: *Obesity, dyspnea, asthma, inflammation*

Abbreviations used
AMP: Adenosine-5′-monophosphate
FENO: Fraction of exhaled nitric oxide
HRR: Heart rate reserve
$V'O_2$: Oxygen uptake

Asthma and obesity are common disorders with a prevalence that has increased substantially over recent decades. Obesity is a growing worldwide problem that has reached epidemic proportions. The World Health Organization estimates that more than 600 million adults were obese in 2014.[1] Asthma is also a major health problem, which is estimated to affect about 300 million persons worldwide, with the global prevalence of asthma ranging from 1% to 18% of the general population.[2]

Several cross-sectional and prospective longitudinal studies have suggested a link between obesity and asthma.[3-5] It has been reported that obesity is associated with a dose-dependent increase in the odds of incident asthma[6] and that weight reduction leads to a significant improvement in asthma symptoms.[7] Moreover, in adults with self-reported symptoms of asthma, obesity was associated with asthma severity indicators, such as respiratory symptoms, use of health care services, or medication requirements, after adjusting for potential confounders.[8]

However, most of these studies have used self-reported diagnosis of asthma with no confirmation based on objective measurements of variable airflow obstruction or bronchial hyperresponsiveness.[9,10] This raises the possibility that asthma might not be adequately diagnosed (misdiagnosed asthma). In fact, analysis of 16,171 participants from the Third National Health and Nutrition Examination Survey showed that subjects in the highest body mass index quintile had the greatest risk of exercise-related dyspnea and self-reported asthma, despite having the lowest risk for airflow obstruction.[11] Moreover, other studies have not demonstrated associations between obesity and asthma severity.[12,13] This is particularly relevant when we consider the possibility that obesity can cause dyspnea through other mechanisms, leading to a misdiagnosis of asthma.

Aside from airflow obstruction, obesity has been shown to adversely affect respiratory mechanics, decrease respiratory muscle function and lung volume, and increase the work and energy cost of breathing,[9,14] which, either independently or in combination, could also cause asthma-like symptoms. Furthermore, the perception of dyspnea can be related to other factors that are common in obese subjects, such as deconditioning[15] or psychological and emotional stress.[16] An additional possible mechanism involves the effect of inflammation on perception of symptoms. Adipose tissue from obese subjects secretes several regulatory adipokines and proinflammatory cytokines,[17] leading to a chronic mild systemic inflammatory state.[18] Several reports suggest that some of these mediators contribute significantly to neuronal mechanisms of inflammatory hypernociception[19] and

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Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication April 18, 2015; revised September 29, 2015; accepted for publication November 9, 2015.
Available online January 5, 2016.
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The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections
0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.11.010

that specific receptors have been localized in brainstem regions involved in respiratory control.[20]

On the basis of these observations, we hypothesized that an increased perception of dyspnea might be related to the misdiagnosis of asthma in obese subjects. Our objective was to evaluate the perception of dyspnea during bronchial challenge and exercise testing in obese subjects with asthma, misdiagnosed asthma, and no asthma or respiratory symptoms to identify the mechanisms of asthma-like symptoms in obesity.

METHODS

Study subjects

We selected obese subjects (body mass index >30 kg/m^2) between the ages of 18 and 65 years from outpatient obesity clinics in the Endocrinology Department at La Paz University Hospital between January 2012 and December 2012. Exclusion criteria were the existence of a previous diagnosis of chronic obstructive pulmonary disease, bronchiectasis, sleep apnea, hypoventilation syndrome, heart disease, or psychiatric disorders; asthma exacerbation within the previous 3 months; use of oral glucocorticoids; contraindication for performing bronchial challenge or exercise testing; and the inability to comprehend or carry out the study procedures.

Selected obese subjects were classified as asthmatic, misdiagnosed asthmatic, or control subjects according to their clinical reports and current evaluation. Patients with a diagnosis of asthma established at least 6 months earlier, according to the Global Initiative for Asthma criteria,[21] were considered asthmatic subjects. Subjects with self-reported asthma but no previous evidence of airflow limitation, bronchial reversibility, or airway hyperresponsiveness were considered to have misdiagnosed asthma. Moreover, these subjects were re-evaluated at the time of enrollment to confirm that they did not meet Global Initiative for Asthma criteria and were therefore included in the misdiagnosed asthma group. The remaining subjects were considered control subjects.

The study was approved by the La Paz Hospital Medical Ethics Committee (PI-795), and informed consent was provided by all subjects.

Clinical and functional evaluation

Height and body weight were recorded, and body mass index was calculated as body weight divided by the square of the calculated height (in kilograms per meter squared). Body composition was evaluated by using bioelectrical impedance analysis (Bodystat, Isle of Man, United Kingdom). Smoking history, age at asthma diagnosis, and current asthma treatment were recorded. Specific questionnaires for depression (Beck depression inventory)[22] and anxiety (State-Trait Anxiety Inventory)[23] were administered to all patients.

Spirometry was performed with a pneumotachograph, and static lung volumes were measured with a constant-volume body plethysmograph (MasterLab Pro; Vyasis Healthcare, Hoechberg, Germany), according to current recommendations.[24,25] European Coal and Steel Community–predicted values were used.[26] Before testing, patients omitted short-acting inhaled bronchodilators for 8 hours and long-acting β-agonists for 12 hours.

Fraction of exhaled nitric oxide (FENO) values were measured immediately before spirometry by using a chemiluminescence analyzer (CLD88sp, Eco Medics, Dürnton, Switzerland), according to American Thoracic Society/European Respiratory Society recommendations.[27]

Systemic biomarkers

Quantitative determination of C-reactive protein was done by using a latex agglutination turbidimetric immunoassay on the ADVIA 2400 analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany), with a lower detection limit of 0.003 mg/dL and an intra-assay coefficient of variation of 1.2%. Fibrinogen was assessed by using a coagulation analyzer (Roche, Mannheim, Germany) according to the Clauss method and calculated from EDTA to citrate plasma values. The detection range was 0.5 to 12.0 g/L, and the intra-assay variability was 2.8%.

Serum levels of IL-1β, IL-6, IL-8, TNF-α, leptin, and adiponectin were determined by using a Milliplex MAP immunoassay by Millipore (Merck KGaA, Darmstadt, Germany) with a Luminex xMAP analyzer (Luminex, Austin, Tex). The lower detection limits were 0.5 pg/mL for IL-1β, 0.4 pg/mL for IL-6, 0.1 pg/mL for IL-8, 0.1 pg/mL for TNF-α, 4.7 pg/mL for leptin, and 6.0 pg/mL for adiponectin. The intra-assay coefficients of variation ranged from 2% for adiponectin to 16% for leptin.

8-Isoprostane levels were measured by using an enzyme immunoassay (Cayman Chemical Company, Ann Arbor, Mich) with a detection limit of 2.7 pg/mL and an intra-assay coefficient of variation of 11.7%. Neuropeptide Y levels were measured by using a competitive enzyme immunoassay (Abnova, Taipei City, Taiwan) with a detection limit of 0.18 ng/mL and an intra-assay coefficient of variation of less than 10%.

Adenosine bronchial challenge

Adenosine-5′-monophosphate (AMP) bronchial challenge was performed after a short dosimeter protocol[28] by using a bronchial aerosol provocation system (APS; Jaeger, Würzburg, Germany) with a Medic Aid SideStream nebulizer (Medic-Aid, Bognor Regis, United Kingdom). Each subject was instructed to inhale the aerosols by taking slow deep breaths from functional residual capacity to total lung capacity without breath holding. The first aerosol was 0.9% saline, followed by quadrupling doses of AMP from 0.02 to 36.86 mg. FEV_1 was measured 2 minutes after each dose, and the highest of 3 acceptable measurements within 150 mL was retained to create dose-response curves. Just before the spirometric measurements, intensity of dyspnea was assessed by using a modified Borg scale,[29] which is a categorical scale scored from 0 to 10 with specific descriptors of dyspnea, where 0 represents the sensation of normal breathing (absence of dyspnea) and 10 corresponds with the most severe (maximal) difficulty breathing that the subject had previously experienced or could imagine. Each subject was instructed to record the degree of dyspnea they felt at that moment.

The test was discontinued when there was a decrease in FEV_1 of 20% or greater compared with the control inhalation (0.9% saline solution) or until the maximum dose was inhaled. When FEV_1 had decreased by 20% or greater from postdiluent baseline values, the challenge result was considered positive and the PD_{20} value was determined by means of linear extrapolation on a semilogarithmic scale. The bronchial reactivity index was defined as the log of the percentage decrease in FEV_1/log final AMP dose after adding 10 to eliminate negative values.[30] We also recorded the maximum Borg score, the perception of breathlessness at a 20% decrease in FEV_1, and the Borg score change divided by the cumulative AMP dose and by the change in FEV_1 over the postdiluent value ($\Delta Borg/\Delta FEV_1$).

Exercise testing

A week after the AMP bronchial challenge, a symptom-limited incremental exercise test was performed on an electronically braked cycle ergometer (Ergobex, Bexen, Spain), according to the standards of the American Thoracic Society/American College of Chest Physicians statement.[31] The initial 2 minutes consisted of resting data collection followed by 1 minute of unloaded cycling. Subsequently, workload was increased by 15 W/min until maximal symptom-limited exercise was achieved. Pedaling rates were maintained between 50 and 60 revolutions per minute. Expired gases and ventilation were measured on a metabolic cart by using a pneumotachograph positioned at the mouth with O_2 and CO_2 analyzers (Oxycon Alpha, Jaeger). This allowed for breath-by-breath measurements of oxygen uptake ($V'O_2$), carbon dioxide production ($V'CO_2$), minute ventilation, respiratory rate (f), and tidal volume. The predicted values of Jones et al[32] were used for the exercise measurements. In all patients heart rate, heart rhythm, blood pressure, and oxygen saturation were continuously monitored. In addition, full 12-lead electrocardiograms were monitored during each minute of exercise and recovery. Oxyhemoglobin saturation was continuously monitored by using a finger Oscar II pulse oximeter (Datex, Helsinki, Finland). Maximal work rate was defined as the highest work rate that the subject was able to maintain for at least 30 seconds. Anaerobic threshold was estimated by using the V-slope method.[31]