Mechanical effects of obesity on airway responsiveness in otherwise healthy humans

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Torchio R, Gobbi A, Gulotta C, Dellacà R, Tinivella M, Hyatt RE, Brusasco V, Pellegrino R. Mechanical effects of obesity on airway responsiveness in otherwise healthy humans. J Appl Physiol 107: 408–416, 2009. First published June 18, 2009; doi:10.1152/japplphysiol.00083.2009.—We investigated whether obesity is associated with airway hyperresponsiveness in otherwise healthy humans and, if so, whether this correlates with a restrictive lung function pattern or a decreased number of sighs at rest and/or during walking. Lung function was studied before and after inhaling methacholine (MCh) in 41 healthy subjects with body mass index ranging from 20 to 56. Breathing pattern was assessed during a 60-min rest period and a 30-min walk. The dose of MCh that produced a 50% decrease in the maximum expiratory flow measured in a body plethysmograph (PD50MCh) was inversely correlated with body mass index ($r^2 = 0.32, P < 0.001$) and waist circumference ($r^2 = 0.25, P < 0.001$). Significant correlations with body mass index were also found with the maximum changes in respiratory resistance ($r^2 = 0.19, P < 0.001$) and reactance ($r^2 = 0.40, P < 0.001$) measured at 5 Hz. PD50MCh was also positively correlated with functional residual capacity ($r^2 = 0.56, P < 0.001$) and total lung capacity ($r^2 = 0.59, P < 0.001$) in men, but not in women. Neither PD50MCh nor body mass index correlated with number of sighs, average tidal volume, ventilation, or breathing frequency. In this study, airway hyperresponsiveness was significantly associated with obesity in otherwise healthy subjects. In obese men, but not in women, airway hyperresponsiveness was associated with the decreases in lung volumes.

methacholine response; body mass index; lung volumes; sighs; deep breath

THE FIRST REPORT DOCUMENTING a possible relationship between obesity and bronchial asthma was published by Seidell et al. in 1986 (35). Despite a number of studies published worldwide (5–7, 9, 13, 15, 25, 36, 49), the scientific community is still divided on whether obesity causes or promotes asthma and, if it does, what the underlying mechanisms are (8).

Cross-sectional and longitudinal studies conducted in adults and children suggest that bronchial asthma occurs more frequently in obese than lean individuals (6, 7, 9, 15, 25, 36, 49). In addition, gaining or losing weight appears to be associated with an increase or decrease in the relative risk for incident asthma (5, 12). However, there have been weaknesses and confounding factors in these studies. Among these are the self-reported diagnosis of the disease and anthropometric data (8), the association of obesity with respiratory symptoms or drug consumption rather than objective measurements (36), the different trends for obesity and asthma (50), and the absence of synergistic effects of obesity and asthma on lung function (30). Another source of variability is sex, as bronchial asthma or airway hyperresponsiveness have been variably found to be associated with obesity only in females (6, 7), or only in males (15, 25), or in both sexes (20).

As opposed to epidemiological investigations, animal studies are more conclusive (40). In different murine models of obesity, resulting from either genetic mutations or increased amounts of fat in the diet, the response to intravenous constric-

tor agents was unequivocally enhanced and so was the response to ozone (22, 26, 33, 41). In addition to providing evidence that obesity itself carries the potential to contribute to airway hyperresponsiveness and perhaps bronchial asthma in humans, these studies also shed light on possible underlying mechanisms. Adipose tissue in overweight and obese animals is capable of expressing a series of proinflammatory substances such as leptin, IL-6, TNF-α, TGF-β, eotaxin, C-reactive protein (CRP), and others. Because many of these mediators are also implicated in asthma, the possibility exists that chronic release of these agents from the adipocytes might contribute to exacerbate bronchial asthma. However, a recent study of obese and nonobese asthmatic subjects found that systemic and local pulmonary inflammation may be unrelated, suggesting that the systemic release of inflammatory mediators from the adipose tissue may not play a consistent role in asthma (43).

Another mechanism potentially linking obesity to bronchial asthma is a reduction in lung volumes caused by excess adipose tissue primarily within the abdomen. A decrease in functional residual capacity (FRC) by itself is associated with a reduction of airway caliber and a shorter length of airway smooth muscle. Because the airway smooth muscle can adapt its contractile apparatus without losing force-generation ca-

pacity, even when substantially shortened (18), and airway resistance is inversely related to the fourth power of airway radius (19), the response to constrictor stimuli is amplified at low lung volume. Reductions in tidal volume ($V_t$) and total lung capacity (TLC) may also contribute to increased airway responsiveness in obesity because they would reduce the stretching effects of breathing on airway smooth muscle (14), thus favoring airway narrowing. Low lung volume breathing associated with airway hyperresponsiveness has been documented in both animal and human studies. In sheep corseted

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for 4 wk, a decrease in FRC of about 25% increased the rate of stress generation in bronchial smooth muscle (27). In humans, voluntary decrease of operant lung volume was associated with an increase in airway resistance upon exposure to a constrictor agent (11). Similar findings have been reported with supine posture (28) and chest wall strapping (44). However, this enhancing effect of lung restriction on airway responsiveness could be offset by an increase in the number and depth of sighs, which occurs when lung volume is reduced (10).

For these reasons, we first studied whether airway responsiveness is increased in obesity as a result of the associated reduction in lung volumes. After documenting this, we examined the relative roles of the decreased FRC, TLC, and minute ventilation in determining the extent of airway hyperresponsiveness in obesity, with respect to sex. We also assessed whether airway responsiveness might be increased as a result of a reduction in the number of sighs in obese individuals. The hypothesis was that a low number of sighs would prevent airways subtending poorly ventilated lung regions from re-inflating, thus contributing to increased bronchial tone upon exposure to a constrictor agent.

MATERIALS AND METHODS

Subjects

Forty-one healthy subjects (Table 1) with a wide range of body mass index (BMI) participated in the study after giving informed consent. The trial was approved by the S. Luigi Hospital (Orbassono-TO, Italy) Ethical Committee. None were smokers or had a history of cardiopulmonary disease, rhinitis, diabetes, sleep apnea, or gastroesophageal reflux disease (GERD) (47). Three patients (2 men and 1 woman) were under treatment with angiotensin-converting enzyme inhibitors and two (1 man and 1 woman) with low doses of calcium blockers. None of the women were under estroprogestinic anticontraceptive therapy.

Lung Function Measurements

Spirometry, flow-volume curves, and absolute lung volumes were obtained using a body plethysmograph (Autobox; SensorMedics, Yorba Linda, CA) (29, 48). Briefly, after at least four regular breaths, thoracic gas volume was measured with the subjects panting against a closed shutter at a frequency slightly <1 Hz while supporting their cheeks with hands. Soon after tidal breathing was resumed, the subjects performed a forced expiratory maneuver from TLC to residual volume (RV). This provided a measure of the forced expiratory volume in 1 s (FEV1) and forced vital capacity. Care was taken that the duration of the forced expiration was ≥6 s. Maximum flow was measured at 60% of predicted TLC after plotting mouth flow against plethysmographic volume (Vmax). FRC was obtained from thoracic gas volume corrected for any difference between the volume at which the shutter was closed and the average end-expiratory volume of the four preceding regular tidal breaths. TLC was obtained by adding the linked inspiratory vital capacity to RV. Predicted values for spirometry and lung volumes were taken from Quanjer et al. (31).

Respiratory mechanics during tidal breathing were measured by the forced oscillation technique in the sitting position. Flow was measured at the mouth by a screen-type pneumotachograph (DCXL10DS; Sensor Technics, Puchheim, Germany). All signals were sampled at 200 Hz. Sinusoidal pressure oscillations of 5-Hz frequency and ~2-cmH2O amplitude were applied at the mouth with the subjects breathing quietly while firmly supporting their cheeks with their hands. The forcing signal was generated by a personal computer connected to an analog-to-digital (A/D)-D/A board (DAQ-CARD 6036E; National Instruments, Austin, TX) and sent to a single-chip power amplifier (TDA7391; STMicroelectronics, Geneva, Switzerland) connected to a 16-cm diameter loudspeaker (model CW161N; Ciare, Ancona, Italy) mounted on a rigid box. The loudspeaker was connected to the mouthpiece through a short connecting tube (22 cm long, 19 mm ID). A low-resistance, high-inertance tube was used to connect the pressure generator to the atmosphere to allow the subject to breathe. The dead space of the tube was minimized by a 15-l/min bias flow applied between the pressure generator and the pneumotachograph. The frequency response of both systems was assessed according to Brusasco et al. (4) and found to be flat up to 30 Hz. The real and imaginary parts of input impedance at 5 Hz (Rrs and Xrs, respectively) were computed by using a least squares algorithm (23, 24).

Breathing pattern at rest and during exercise was measured by a low resistance mesh flowmeter (0.81 cm3 H2O s−1 cm−1) placed at the outlet of a full-face mask (ResMed, Bella Vista, NSW, Australia). The dead space of the mask was 125 ml. Pressure drop across the mesh was measured by a piezoresistive transducer (PXL02X5DN, 0–2.5 cm H2O; Sensym, Milpitas, CA). The flow signal was digitized at a frequency of 100 Hz with the help of a small battery-operated device.

Table 1. Subjects’ main anthropometric and functional data

<table>
<thead>
<tr>
<th></th>
<th>All Subjects (n = 41)</th>
<th>Men (n = 18)</th>
<th>Women (n = 23)</th>
<th>P Value, Men vs. Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>40 (24–60)</td>
<td>40 (24–56)</td>
<td>41 (26–60)</td>
<td>0.9503</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166 (147–187)</td>
<td>174 (164–187)</td>
<td>160 (147–178)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>34 (20–56)</td>
<td>33 (21–56)</td>
<td>34 (20–50)</td>
<td>0.7462</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>107 (73–152)</td>
<td>114 (83–152)</td>
<td>102 (73–142)</td>
<td>0.0568</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>117 (92–160)</td>
<td>117 (92–160)</td>
<td>115 (85–150)</td>
<td>0.7457</td>
</tr>
<tr>
<td>FEV1, % pred</td>
<td>101 (63–125)</td>
<td>98 (63–122)</td>
<td>103 (89–125)</td>
<td>0.2647</td>
</tr>
<tr>
<td>VC, % pred</td>
<td>105 (60–137)</td>
<td>99 (60–119)</td>
<td>111 (90–137)</td>
<td>0.0101</td>
</tr>
<tr>
<td>TLC, % pred</td>
<td>101 (75–126)</td>
<td>97 (75–119)</td>
<td>104 (82–126)</td>
<td>0.0597</td>
</tr>
<tr>
<td>FRC, % pred</td>
<td>81 (42–129)</td>
<td>84 (60–129)</td>
<td>80 (42–125)</td>
<td>0.4256</td>
</tr>
<tr>
<td>RV, % pred</td>
<td>99 (60–132)</td>
<td>98 (60–125)</td>
<td>94 (64–132)</td>
<td>0.8675</td>
</tr>
<tr>
<td>DLCO, % pred</td>
<td>94 (63–115)</td>
<td>96 (80–111)</td>
<td>93 (63–115)</td>
<td>0.4385</td>
</tr>
<tr>
<td>ESS, units</td>
<td>5.3 (1.0–9.0)</td>
<td>5.1 (1.0–9.0)</td>
<td>5.5 (1.0–9.0)</td>
<td>0.331</td>
</tr>
<tr>
<td>GERD score, units</td>
<td>1.4 (0–10)</td>
<td>1.5 (0–8)</td>
<td>1.3 (0–10)</td>
<td>0.8000</td>
</tr>
<tr>
<td>PD25MCh, log mcg</td>
<td>3.40 (2.24–4.63)</td>
<td>3.49 (2.30–4.63)</td>
<td>3.33 (2.24–4.56)</td>
<td>0.3684</td>
</tr>
</tbody>
</table>

Applicable data are means (min-max). BMI, body mass index; FEV1, forced expiratory volume in 1 s; VC, slow vital capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; DLCO, single breath-diffusing lung capacity for carbon monoxide; ESS, Epworth sleepiness score for daytime sleepiness; GERD, gastroesophageal reflux disease; PD25MCh, dose of methacholine that determined a decrease by 50% of baseline value in maximum expiratory flow corrected for thoracic gas compression volume at 60% of predicted TLC; % pred, percentage of predicted values. Predicted values are from Quanjer et al. (31).
and then sent to a personal computer by a wireless radio link. A wireless XBee device (Maxstream, Lindon, UT) on the basis of standard ZigBee/IEEE 802.15.4 networking protocol was used to establish a fast peer-to-peer networking connection. The system was calibrated at the beginning and the end of each measurement. For the measurements at rest, the subjects with loosened garments sat comfortably in a chair watching a 1-h television documentary on nature. No one was allowed to enter the room during the study. For measurements during walking, the subjects were instrumented with the same face mask and walked on a 100-m long corridor at a comfortable pace for 30 min.

Experimental Protocol

Subjects were studied on three occasions, at least 1 wk apart, in the following temporal order.

Study 1. On the first occasion, spirometry and lung volume measurements were obtained according to the American Thoracic Society and European Respiratory Society (ATS-ERS) recommendations (29, 48). Weight, height, waist, and hip circumferences were measured. The Epwort sleepiness scale (ESS) (21), and a questionnaire on symptoms of GERD was administered (47). Finally, a standard methacholine (MCh) challenge was conducted by inhaling doubling doses of a solution of MCh chloride dry-powder (Lofarma, Milan, Italy) in distilled water from 300 to 2,400 μg. Aerosols were generated by an ampoule-dosimeter system (MB3 MEFAR, Brescia, Italy) delivering particles with a median mass diameter ranging between 1.53 and 1.61 μm. Aerosols were inhaled during quiet tidal breathing in the sitting position. The dose of MCh causing a decrease of $V_{\text{max}}$ by 50% of control (PD50MCh) was calculated by linear interpolation between two adjacent points of the (log)dose-response curve or extrapolation.

Study 2. On the second occasion, the subjects underwent a single-dose bronchial challenge by using the PD50MCh previously determined. At baseline and 2 min after MCh input, impedance by the forced oscillation technique was measured for 5 min before and 2 min after a deep breath (DB).

Study 3. On the third occasion, the subjects attended the laboratory in the midafternoon for measuring breathing pattern at rest and during walking.

Data Reduction and Statistical Analysis

Rrs and Xrs at baseline and after MCh were computed as follows. The pre-DB values were obtained by averaging the values of at least 10 regular tidal breaths before the DB (Rrs pre-DB and Xrs pre-DB.

![Fig. 1. Tidal volume ($V_T$), and resistance and reactance (Rrs and Xrs, respectively) recorded before and for 2 min after the deep breath (DB) during methacholine challenge. The single dots of resistance and reactance are average values for each breath. The vertical line separates values collected before (left) from after the DB (right). The oblique line after the DB represents the linear regression coefficient of the values after DB plotted against time until a plateau was reached. The intercept with the vertical axis is the computed value at the time DB ended. Its ratio to the pre-DB value represents the acute effects of DB on resistance and reactance (vertical line). The slope was taken as an index of the recovery of resistance and reactance after DB.](http://jap.physiology.org/doi/10.1152/jappl.00498.2009)
respectively). The post-DB values of Rrs and Xrs measured from the end-DB to the time point at which a clear plateau was observed were submitted to a linear regression analysis to obtain an intercept at the time the DB was terminated (RrsInt and XrsInt, respectively) and a slope (RrsSlope and XrsSlope, respectively) (28, 44). A typical example is shown in Fig. 1. From these measurements we estimated the recovery rates of Rrs and Xrs with time after the DB during airway narrowing (RrsSlope and XrsSlope, respectively).

Breathing pattern at rest and during walking was assessed by measuring VT and inspiratory and expiratory times. Breathing frequency (BF) and min ventilation (V˙E) were then calculated. A sigh was defined as a VT three times larger than average VT during the 60-min rest (1).

A minimum sample size of 37 subjects was required for a power of 90% to reach a correlation coefficient at least of 0.5 between airway responsiveness and BMI with a type I error of 0.05. The relationship between variables was assessed by single-regression analysis and stepwise multiple linear regression analyses. Values of P < 0.05 were considered statistically significant. Data are presented as means ± SD.

RESULTS

BMI was significantly correlated with ESS in both men (r² = 0.388, P < 0.05) and women (r² = 0.455, P < 0.001) but not with GERD score.

Obesity and Airway Responsiveness

Per cents of predicted FRC and TLC were significantly and inversely correlated with BMI (Fig. 2). PD50MCh was significantly correlated with BMI (Fig. 3; r² = 0.32, P < 0.001) and waist circumference (r² = 0.25, P < 0.001), thus suggesting a link between obesity and airway responsiveness. This was confirmed in both men (r² = 0.48, P < 0.001 for BMI and r² = 0.31, P < 0.01 for waist circumference) and women (r² = 0.19 and 0.21, respectively; P < 0.05 for both). In addition, BMI was also related to the magnitude of airway narrowing induced by MCh, as suggested by the significant correlations with Rrs (r² = 0.19, P < 0.001) and Xrs (r² = 0.40, P < 0.001) (Fig. 4).

Airway Responsiveness and Lung Volumes

PD50MCh was positively correlated with percent of predicted FRC (r² = 0.56, P < 0.001) and TLC (r² = 0.59, P < 0.001 for both) in men (Fig. 5), but not in women (r² < 0.1 and P > 0.80 for both). When submitted to stepwise multiple linear regression analysis, both lung volumes were retained in the analysis for men (r² = 0.67, P < 0.001).

Airway Responsiveness and DB

The acute effects of DB on Rrs and Xrs during the bronchial challenge and subsequent recovery are reported in Table 2. The DB was associated with significant reductions in Rrs (P < 0.0001) and Xrs (P = 0.004) though the effects on the latter were significantly larger than on the former (P < 0.0001). Both RrsInt/Rrspre-DB and XrsInt/Xrspre-DB were positively correlated with BMI (r² = 0.13, P < 0.01 and r² = 0.10, P < 0.05, respectively) and negatively with PD50MCh (r² = 0.14, P < 0.01 and r² = 0.10, P < 0.05, respectively). This suggests that the greater the BMI and airway responsiveness, then the lower the decrease of Rrs or Xrs with the DB. The recovery rates of Rrs and Xrs after the DB were not significantly related to PD50MCh or BMI. No significant differences were observed for sex.

Obesity, Breathing Pattern, and Airway Responsiveness

Neither at rest nor during walking was the number of sighs correlated with BMI (Fig. 6). Analysis of breathing pattern at rest or during walking did not reveal significant correlations between number of sighs, BF, or V˙E on one side and PD50MCh, BMI or FRC on the other side, with the exception of a significant negative correlation between BF and PD50MCh in men only (r² = 0.50, P < 0.001). The number of sighs was

![Fig. 2. Functional residual capacity (FRC) (left) and total lung capacity (TLC) (right) as percentage of predicted plotted value against body mass index (BMI). Solid and open circles identify men and women, respectively.](http://jap.physiology.org/)

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significantly greater during walk than at rest independent of BMI ($P < 0.001$).

**DISCUSSION**

The main results of this study may be summarized as follows: 1) airway responsiveness was significantly correlated with BMI in nonasthmatic subjects; 2) this increase was significantly related to lung volume restriction (decrease in FRC and TLC) and to an increase of BF in men but not in women; and 3) the number of sighs at rest or during walking was similar in obese and lean subjects despite the reduction of lung volumes in the former.

**Obesity and Airway Responsiveness**

The results of the present study show that the increasing obesity was associated with a significant increase in airway responsiveness of about 25–40% as reflected in Figs. 3 and 4. The present findings contrast with a recent study by Salome et al. (34) reporting no significant differences between healthy obese and nonobese subjects in terms of maximal response to MCh or dose causing 50% of maximal response (34). Apart from differences in methodology (population sample, Chai’s score vs. tidal breath method to deliver MCh, times of measurements) and statistical analysis (differences between groups vs. correlation), a critical difference was our use of maximum flow corrected for thoracic gas compression volume instead of the FEV\(_1\). As demonstrated by Sharafkhaneh et al. (37, 38), differences in the volume of thoracic gas compressed can explain a substantial part of the changes in the FEV\(_1\) following interventions that modify bronchial tone or lung volume. That is, the FEV\(_1\) decreases more in subjects with larger lungs. In Salome’s study, TLC was smaller in obese than lean subjects by about 25% of predicted. This difference was likely associated with less gas compression volume and less FEV\(_1\) decrease for any given dose of MCh, tending to reduce the differences in airway responsiveness between groups. To test this possibility, we analyzed our data after dividing the subjects at a BMI cutoff of 30 as done in Salome’s study. The differences in the dose of MCh causing a decrease of FEV\(_1\) of 20% did not reach statistical significance ($P = 0.091$). However, the differences of PD\(_{50}\)MCh remained highly significant ($P = 0.0025$). We suggest that the effects of gas compression explain the difference between the two studies.

**Potential Mechanisms Linking Airway Hyperresponsiveness to Lung Restriction**

In a recent review, Shore (40) suggested that obesity and asthma may be linked by a series of biological and functional mechanisms. Among the latter were the effects of decreasing lung volumes within tidal breathing range and the reduced effects of volume history on airway caliber. Our results lend support to this hypothesis in that, at least in males, airway hyperresponsiveness is associated with the decrease of lung volumes.

In two recent studies by our group in healthy volunteers, interventions causing a decrease in lung volumes, i.e., chest wall strapping or shifting from the seated to the supine posture, were associated with a marked increase in response to MCh (28, 44). Because the only substantial changes obtained with these interventions were decrements in FRC, \(V_T\), and TLC, it was postulated that the increase in airway responsiveness could have been the result of several underlying mechanisms. First, by decreasing the operational lung volumes, the airways and thus the airway smooth muscle would accommodate to smaller dimensions by virtue of their interdependence with the surrounding lung parenchyma. As...
reported in vitro (18), airway smooth muscle recomposes its internal contractile machinery when kept at a short length in a way that its force generation is maintained. This results in further contraction when the myocyte is stimulated at this length and in reduction of the ability to distend with stretching (3). Secondly, the exaggerated response to MCh with decreased lung volumes could be due to the decrease in ventilation and/or depth of breathing. The stretching imposed by tidal breathing and/or large breaths on constricted airways relaxes airway smooth muscle, as slowly cycling cross bridges are progressively converted into rapidly cycling cross bridges (14). Reducing the extent of stretching or abolishing DBs has the opposite effect. Similar interpretations were offered by McClean et al. (27) to explain the observed increase in the rate of stress generation in response to carbachol of the intraparenchymal airways of adolescent and adult sheep subjected to chest wall strapping for 4 wk. The amount and activity of myosin light chain kinase were not increased with breathing at low lung volume, presumably ruling out an increase of shortening velocity as the cause of the augmented stress generation. Thirdly, as reported by Boulet et al. (2), the response to MCh in obese, in contrast to nonobese, individuals was independent of the large breaths taken before inhalation of a constrictor agent suggesting an intrinsic alteration of the airways. If this is the case, the loss of the bronchoprotective effects of DB could contribute to the increase in airway responsiveness in obesity.

In contrast to our previous studies on chest wall strapping and supine posture (28, 44), the present study did not show a significant relationship between BMI and recovery of reactance over time after the DB. On the basis of the present study and the data of McClean et al. (27), we now believe that the increase in the recovery rate of dynamic elastance after DB when airways were constricted in supine posture was presumably caused by a decrease of the external load with DB rather than a primary increase in the shortening velocity of airway smooth muscle.

Sex Differences

This is the first observation that, in contrast to males, airway responsiveness is not correlated with lung volumes in females. This unexpected finding cannot be explained by differences in BMI, waist or hip circumferences, magnitude of lung restriction, or degree of airway responsiveness between sexes. The only significant difference between males and females was in vital capacity, but this appears to be of negligible importance as the values were within the normal range in both men and women. The effects of sex hormones do not appear to be a cause because studies in postmenopausal women and women with early menarche seem to suggest the opposite (45, 46). We wonder whether intrinsic biological differences of fat tissue between sexes could be a factor. Adiponectin, for instance, has been shown to attenuate the airway hyperresponsiveness induced by ovalbumin in mice, as well as the number of eosinophils in the bronchoalveolar lavage, and the expression of Th2 cytokines in the lung (40, 42). Further studies are needed to address this issue.

Obesity, Breathing Pattern, Sighs, and Airway Responsiveness

Table 2. Percent changes and recovery over time of respiratory resistance and reactance after the deep breath under methacholine conditions

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All Subjects</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rrsna/RrspDBC, %</td>
<td>85±29</td>
<td>78±20</td>
<td>91±34</td>
</tr>
<tr>
<td>RrsSlope, cm H2O/lO2</td>
<td>0.024±0.038</td>
<td>0.019±0.017</td>
<td>0.028±0.049</td>
</tr>
<tr>
<td>Xrsna/XrspreDBC, %</td>
<td>55±33</td>
<td>48±34</td>
<td>60±32</td>
</tr>
<tr>
<td>XrsSlope, cm H2O/lO2</td>
<td>-0.023±0.037</td>
<td>-0.019±0.022</td>
<td>-0.026±0.046</td>
</tr>
</tbody>
</table>

Data are means ± SD. Rrsna/RrspDBC and Xrsna/XrspreDBC, percent changes in respiratory resistance and reactance after the deep breath, respectively; RrsSlope and XrsSlope, recovery of respiratory resistance and reactance over time after the deep breath, respectively.

The physiological response to reduction in lung volumes is rapid shallow breathing with a decrease in VT and increase in...
BF (32). In addition, in animals, lung deflation has been shown to be associated with an increase in number of sighs that could serve to restore lung compliance and reinflate poorly ventilated lung regions, thus improving gas exchange (10). As airway caliber varies directly with lung volume, the effects of the sighs may also help reduce the increase in airway smooth muscle tone associated with breathing at low lung volume. However, the increase in number in sighs occurred only when lung volume was acutely reduced (10), whereas, in sheep corseted for 4 wk (27), the decrease in FRC was not associated with any increase in number or size of sighs. Our findings mimic this pattern in sheep (27) in that the increase in BMI in our study was not correlated with the number of sighs during a 60-min rest period (Fig. 6, left). We speculate that long-standing breathing at low lung volumes may not contribute to modulate the response to MCh in obese subjects, presumably as a result of a chronic desensitization of the neural receptors.

A crucial point in measuring ventilation over time is the technique used. We chose a pneumotachograph positioned at the outlet of a tiny mask after attempts with an inductive plethysmograph were associated with many artifacts in obese subjects. The mask-pneumotachograph system provided signals void of artifacts and was well tolerated by all subjects during both 60-min rest and 30-min walking. There was no evidence of hyperventilation. The wireless connection to a small portable transmitter allowed the online transmission of the data to a PC so that the operator could detect the quality of the tracings in real time. Also the calibration check performed before and at the end of each test guaranteed the quality of the data.

There was a significant positive correlation between PD_{50}MCh and BF in obese men. Whether this represents an attempt of the respiratory system to compensate for an increase in airway responsiveness with a higher oscillation frequency applied to the airway smooth muscle is a matter of speculation. However, a study in mechanically ventilated rabbits documented a suppression of bronchoconstriction with increasing BF (39).

Finally, we found that, during walking, obese individuals were capable of increasing the number of sighs by about 20 times, similar to the nonobese, indicating that the obese individuals were capable of increasing ventilation during physical activity.

Comparison of the Present Findings With Epidemiological Trials and Clinical Implications for Asthma

Longitudinal and cross-sectional studies have documented that obesity is linked to an increase in airway responsiveness (9, 25). In the European Community Respiratory Health Survey study of 11,277 participants, the average data were in favor of the hypothesis that BMI and bronchial reactivity are significantly related. Surprisingly, however, in almost 30% of the centers, there was no relationship (9). In the Normative Aging Study of 305 men followed for a period of 4 years, a high BMI was associated with airway hyperresponsiveness with an odds ratio near 10 (25). Cross-sectional studies may be more subject to the thoracic gas compression artifacts in the FEV₁ measurement in subjects with different size and lungs. In longitudinal trials, in contrast, the thoracic gas volume should remain fairly stable over time, thus minimizing compression artifacts.

Airway hyperresponsiveness is a key feature of bronchial asthma (16). Whether conditions associated with airway hyperresponsiveness, such as obesity, are a risk factor for bronchial asthma is uncertain. Epidemiological studies provided discrepant results. In contrast to studies documenting a relationship between obesity and asthma (5, 9, 12, 15, 25, 30, 36), a recent study reached an opposite conclusion (30), and two others found that this was true only for females (6, 7). Among the confounding factors between studies are the self-reported...
diagnosis of the disease and anthropometric data (8), the association of obesity with only respiratory symptoms or use of medications (36), the different trends for obesity and asthma (50), the absence of synergistic effects of obesity and asthma on lung function (30), sex differences (6, 7, 15, 20, 25), and technical artifacts in lung function measurement as above discussed. Our findings do not settle this issue as none of our participants had bronchial asthma. However, we speculate than an obese male with asthma will be at risk for more severe attacks and more symptoms than a lean subject. We suggest that this is secondary to the decrease in lung volumes allowing greater airway smooth muscle shortening and/or increased proinflammatory cytokine release from adipose tissue. If correct, then programs that improve lung volumes through weight control and also reduce the amount of fat tissue in asthmatic patients should help with symptom control. Whether such speculation can also be extended to females remains a matter of debate because our findings cannot elucidate the role of reduced lung volumes in airway responsiveness.

Conclusions

Our study suggests that obesity and airway responsiveness are associated. This is true in both sexes. In men, the relationship appears to be linked to the effects of obesity on lung volumes and control of breathing. In women, the relationship is presumably more complex and possibly involves additional biological/biochemical mechanisms other than breathing control. Our results do not answer the question whether a causal relationship does exist between obesity and asthma. Nevertheless, they show that obesity by itself is associated with airway hyperresponsiveness, which is a key feature of bronchial asthma. Therefore, they might help explain why obese asthmatics may have worse disease that their lean counterparts.


REFERENCES

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