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AMERICAN COLLEGE OF CHEST PHYSICIANS

Simulated Obesity-Related Changes in Lung Volume Increases Airway Responsiveness in Lean, Nonasthmatic Subjects*

Li-Ying Wang, PhD; Frank J. Cerny, PhD; Thomas J. Kufel, MD; and Brydon J. B. Grant, MD, FCCP

Study objective: To determine if obesity-related changes in lung volume might contribute to airway reactivity, we investigated the effects of simulated mild obesity-related lung volume reductions on airway responsiveness in lean, nonasthmatic subjects.

Participants and methods: We simulated the lung volume reductions of class 1 obesity in eight lean, nonasthmatic subjects by externally mass loading the chest wall and abdomen, and shifting blood volume into the lung with lower limb compression (LLC). Airway responsiveness was assessed by measuring FEV_1 before and after methacholine challenge tests (1, 2.5, 5, 10, and 25 mg/mL) with the following: (1) no intervention (control); (2) external chest loading (CL); (3) LLC; and (4) CL and LLC (COMB) on separate days. Lung function was measured before and after CL, LLC, and COMB were applied.

Results: The application of CL, LLC, and COMB decreased expiratory reserve volume, functional residual capacity, and total lung capacity compared with baseline. FVC and FEV_1 decreased significantly with CL and COMB, while FEV_1/FVC did not change compared to baseline. The maximal response to the methacholine challenge increased with CL, LLC, and COMB, with a mean maximal fall of FEV_1 of 9%, 11%, and 18%, respectively, compared to a 6% fall with control.

Conclusions: We conclude that decreases in lung volume increase airway responsiveness and may account for the increased propensity for increased airway responsiveness in the obese.

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Key words: asthma; bronchial provocation tests; lung volume reduction; obesity

Abbreviations: anti-G = antigravity; BMI = body mass index; CL = chest loading; CL_{32} = chest loading at body mass index of 32 kg/m^2; CL_{42} = chest loading at body mass index of 42 kg/m^2; COMB = combination of chest loading and lower limb compression; ERV = expiratory reserve volume; ΔFEV_1max = maximal percentage decrement of FEV_1; FRC = functional residual capacity; LLC = lower leg compression; PC_{20} = provocative concentration of methacholine causing a 20% fall in FEV_1; RV = residual volume; TLC = total lung capacity

Both obesity and asthma are on the rise in developed nations and pose a major public health challenge.[1,2] A positive association between obesity and asthma has been found in adults,[3,4] adolescents,

and children,[5,6] based on both cross-sectional and longitudinal cohort studies. Camargo et al[3] and Shaheen et al [4] showed that obesity (body mass index [BMI] $\geq$ 30 kg/m^2) is associated with an increased incidence of adult-onset asthma with a relative risk of

1.84 and 2.8, respectively, and suggested that obesity is an established risk factor for asthma in adults. However, the mechanisms of how obesity might lead to or exacerbate asthma have not yet been established.

Increased airway responsiveness to bronchoconstrictive stimulation is a universal hallmark of asthma[7] and a risk factor for the development of asthma.[8] Airway inflammation is a primary precursor to this hyperresponsiveness, and inflammatory mediators could individually or in concert induce changes in airway wall geometry and thus produce the symptoms of the disease. Therefore, any factor that changes the physical relationships among lung and airways could alter responsiveness. An enhanced bronchoconstrictor response to methacholine, a drug that directly stimulates the airway smooth muscle, was found when end-expiratory lung volume was decreased voluntarily[9] or when changing body posture from sitting to supine[10] in humans. These two studies[9,10] reasoned that the reduction in lung volume altered airway-parenchymal interdependence, decreasing the load that the airway smooth muscle has to overcome during contraction, thus enhancing the capacity of airway smooth muscle to respond to bronchoconstrictive stimuli.[11] These studies suggest that the decrease in lung volume associated with obesity may increase airway responsiveness.

Obesity is associated with an increased total blood volume, total plasma volume, and cardiac output roughly in proportion to the amount of excess body weight.[12] Clinical situations associated with increased pulmonary blood content such as left ventricular failure are associated with airway narrowing and increases in bronchial reactivity.[13] Regnard et al[14] found an increase in airway responsiveness to methacholine in healthy subjects with inflated anti-shock trousers at venous occlusion pressure, a maneuver known to induce acute pulmonary congestion. Pulmonary blood volume expansion might increase airway responsiveness through lung volume reduction, congestion, or edema of the airway wall (ie, increased airway wall thickness), release of humoral mediators such as prostaglandins,[15] and might stimulate pulmonary C-fiber and irritant receptors that can lead to vagally mediated reflex airway constriction.[13,14] In addition to lung volume changes, the shift in blood volume associated with obesity also may increase airway responsiveness.

In this study, obesity-related reductions in lung volume were simulated through externally mass loading the chest wall and abdomen (chest loading [CL]) and shifting blood volume into the lung with lower limb compression (LLC) in nonasthmatic, lean subjects. We hypothesized that compared to control,

airway responsiveness to methacholine would be greater with CL, LLC, and a combination of CL and LLC (COMB).

MATERIALS AND METHODS

Subjects

Eight subjects with a BMI ≤ 25 kg/m^2 (defined as lean) were studied. None of the subjects had history of asthma, smoking, cardiopulmonary disease, or abdominal injury or surgery. All subjects completed a questionnaire and underwent a physician interview as part of the screening process. Subjects were asked to refrain from ingesting caffeinated beverages on each of the 4 study days. Written informed consent was obtained from all subjects, and the study was approved by the Institutional Review Boards of the University at Buffalo, and the Veterans Affairs Western New York Healthcare System.

Pulmonary Function Tests

Spirometry was performed according to American Thoracic Society recommendations using a spirometer (Morgan Spiro 232; Morgan Scientific; Haverhill, MA). FEV$_1$, FVC, and FEV$_1$/FVC ratio were determined. Total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV) were measured using a volume-displacement pressure compensated body plethysmograph (Body Box 5500 Series; Morgan Scientific). Results were displayed as actual values and as percentage of predicted values. Normal predicted values were derived from the equations of Crapo et al.[16,17]

Methacholine Challenge Tests

Increased concentrations of inhaled methacholine (1, 2.5, 5, 10, and 25 mg/mL) were administered according to a published protocol.[18] The methacholine challenge test was performed using nebulizers (model 45; DeVilbiss; Somerset, PA) operated by compressed air at 50 pounds per square inch (0.345 kPa) and a flow rate of 5 L/min to give an output of 0.156 mL/min. A nose clip was worn, and the aerosol was inhaled through the mouth over a 2-min period. Spirometry was performed 1 min after each dose, and the higher of two acceptable measurements was selected to create dose-response curves. The challenge was stopped when there was a $\geq 20\%$ fall in FEV$_1$ from baseline, or after a concentration of 25 mg/mL had been administered. All subjects were administered β-agonists (albuterol) after completion of each methacholine challenge test, and remained in the laboratory until the FEV$_1$ returned to within 10% of the baseline value. No complications occurred during the challenges.

CL and LLC

The CL method is explained in detail in a previous article.[19] Briefly, a vest with pockets that could be filled with birdshot to attain a distribution of weight equivalent to that associated with moderate obesity was worn by each subject. A BMI of 32 kg/m^2 was used for the mass loading model to represent class 1 obesity (CL at BMI of 32 kg/m2 [CL$_{32}$].[20] The amount of weight that was added to each subject was calculated as follows:

$$(32b^2 - a) \times 0.355$$

where b = height in meters; a = weight in kilograms; 32 = BMI

in kilograms per meter squared; and 0.355 = mass of thorax and abdomen as percentage of total body mass.[21] To further substantiate whether the changes in airway responsiveness were dependent on the degree of simulated obesity, we tested five of the subjects using a CL that was equivalent to that of a BMI of 42 kg/m^2 (CL at BMI of 42 kg/m^2 [CL_{42}]).

Inflation of an antigravity (anti-G) suit was used to increase the pulmonary capillary blood volume.[22] The modified anti-G suit was constructed by disconnecting the abdominal bladder of a standard anti-G suit from the thigh and calf bladders. The bladders of the thigh and calf remained interconnected. The right and left thigh bladders had a joined inlet (3/8″ Tygon tubing [Saint-Gobain Performance Plastics; Taipei, Taiwan] and Swagelok 3/8″ connectors [Swagelok Company; Solon, OH]) that was connected with an aneroid pressure meter to monitor the pressure of the bladders. All limb bladders were inflated simultaneously to a pressure of 60 mm Hg, which was sufficient to cause venous compression. Pressure in the bladders was monitored continuously throughout the test and was readjusted if necessary.

Protocols

All subjects underwent methacholine challenge testing on the same time each day for four separate study visits with the following: (1) no intervention (control); (2) chest loading (CL_{32}); (3) LLC; and (4) COMB, with control conducted first and the order of the remaining tests randomized. The mean (range) time interval between tests were 2.2 days (range, 2.0 to 5.0).

PFTs were performed before and after CL_{32}, LLC, and COMB were applied and during the methacholine challenge test as described. All measurements were performed in the seated position.

Data and Statistical Analysis

The intrasubject coefficients of variation (SD/mean, %) were calculated for baseline pulmonary function parameters across the 4 study days. The maximal response to methacholine was the maximal percentage decrement of FEV_1 (ΔFEV_1max) in all cases as the values corresponding to the last step of the challenge. The generalized estimating equation regression was used with an exchangeable correlation matrix to take into account the repeated measurements of lung function by each subject before and during methacholine challenge (Splus 6.0; Insightful; Seattle, WA; and generalized estimating equation library available at: www.stats.ox.ac.uk/~ripley/).[23] The loading condition was coded for treatment contrasts so that LLC, CL_{32}, and COMB were compared with control. We determined the effects of loading condition on the influence of the methacholine concentration on the change of FEV_1 expressed as a proportion of prechallenge values. The logarithm (base 10) of the proportional changes in FEV_1 was related to the change in logarithm of the methacholine concentration for this analysis to obtain linear relations. The prechallenge FEV_1 values were omitted from the analysis because they were used to normalize the FEV_1 after methacholine challenge. The slope of this relation (S) is related to the clinical expression of methacholine challenge (concentration methacholine required to produce a 20% decrease in FEV_1 [PC_{20}]). PC_{20} can be obtained from $10^{-0.09691/S}$.

All values are expressed as mean ± SE. Analysis of variance with repeated measurements was used to test the significance of the mean differences between test conditions followed by the Bonferroni *t* test *post hoc* procedure to determine the specific differences among test conditions. Linear regression analysis was used to determine whether COMB-induced changes in expira-

tory reserve volume (ERV) and FRC were related to PC_{20} and ΔFEV_1max. The level used for statistical significance was $p < 0.05$.

RESULTS

All eight subjects completed the study. Mean age and BMI of the subjects were 30.88 ± 2.31 years and 24.55 ± 0.83 kg/m^2, respectively.

Baseline Pulmonary Function

Values of baseline pulmonary function were not different across the 4 study days ($p > 0.05$). Average intrasubject coefficients of variation were 7.3 ± 1.1% for FRC; 11.5 ± 3.2% for ERV; 14.6 ± 2.3% for RV; 4.9 ± 0.7% for TLC; 1.8 ± 0.3% for FVC; and 1.8 ± 0.3 for FEV_1.

Effects of CL_{32}, LLC, and COMB on Pulmonary Function

When CL_{32}, LLC, and COMB were applied, FRC ($p = 0.02$ for LLC and < 0.001 for CL and COMB); ERV ($p < 0.05$ for CL and LLC, and < 0.001 for COMB); RV ($p < 0.05$ for CL, LLC and COMB); and TLC ($p < 0.05$ for CL and LLC, and < 0.001 for COMB) were all decreased significantly (Fig 1). Although the mean decreases in lung volumes tended to be greater after COMB was applied than either CL or LLC were applied, these differences were statistically significant only for TLC ($p = 0.006$). When CL_{42} was applied (n = 5), a 13% fall in both FRC and ERV and a 5% fall in TLC was induced.

FVC and FEV_1 decreased significantly after CL_{32} and COMB were applied ($p < 0.05$), and FEV_1/FVC ratio remained unchanged after CL_{32}, LLC, and COMB were applied (Fig 1). The mean falls in FVC and FEV_1 were 4% and 3%, respectively, while CL_{42} was applied.

Airway Responsiveness to Methacholine

Mean dose-response curves to methacholine under different conditions are presented in Figure 2. With CL_{32}, LLC, and COMB, all subjects exhibited an augmentation of airway responsiveness to methacholine relative to that of control. The mean ΔFEV_1max of the methacholine challenge test was 5.68% (range, 3.11 to 8.14%) for control; 8.62% (range, 7.12 to 14.11%) with LLC; 10.5% (range, 5.12 to 11.89%) with CL_{32}; and 18.18% (range, 9.95 to 23.3%) with COMB. With CL_{42} (n = 5), the mean ΔFEV_1max of the methacholine challenge test was 15.6% (range, 16.21 to 21.22%). The largest dose of methacholine (25 mg/mL) did not induce a fall of $FEV_1 > 20\%$ in any of the subjects during control,
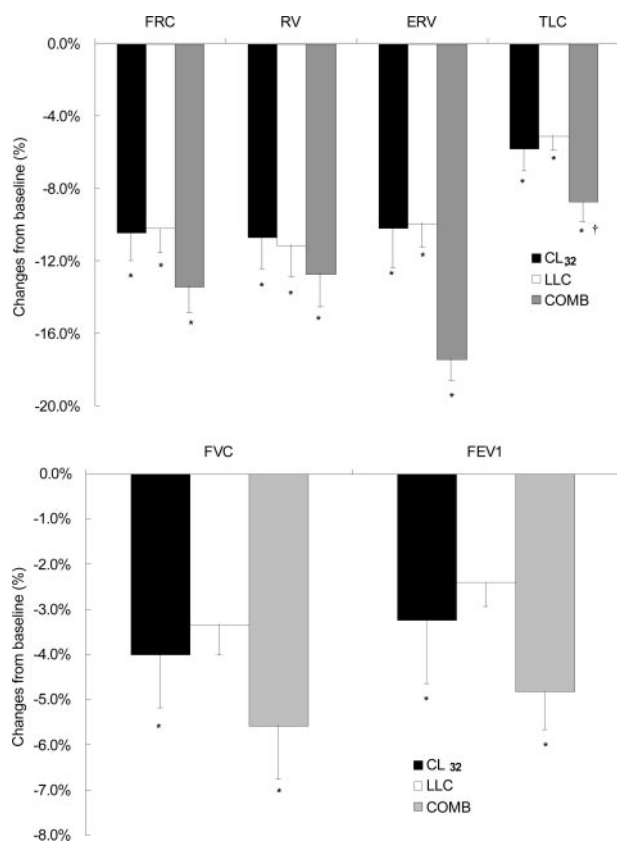
FIGURE 1. Mean (SD) changes of pulmonary function from baseline under different interventions. *Significantly different from baseline. †Significantly different from COMB.

CL$_{32}$, and LLC trials. In contrast, during the COMB trial, five of the eight subjects reached at least a 20% fall in FEV$_1$ in response to methacholine, with a mean PC$_{20}$ of 21.26 (range, 12 to 25 mg/mL). Figure 3 shows the regression coefficients for the response to methacholine challenge under four test condi-

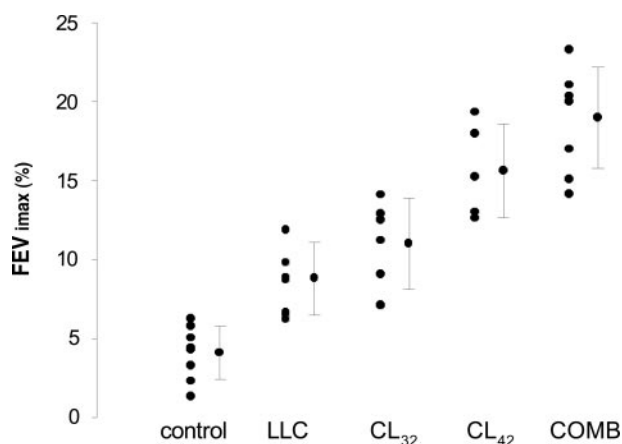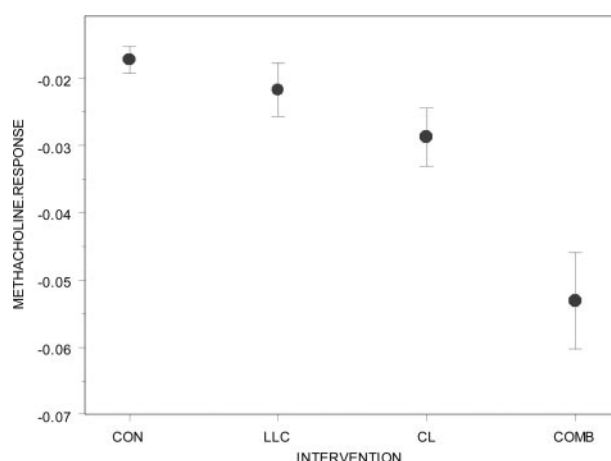FIGURE 2. Individual and mean ± SD values of ΔFEV$_1$max under different interventions.

FIGURE 3. Comparison of responses to methacholine challenge under different interventions.

tions. The intercept for control was not significantly different from zero, and the intercepts for CL, LLC, and COMB were not significantly different from control. In contrast, there was a significant (p < 0.001) decline in FEV$_1$ during control with methacholine, and the declines were significantly greater with CL (p = 0.002) and COMB (p < 0.001) compared with control, but the decline with LLC was not different than that of control (p = 0.184). To determine if there was a dose response, the regression coefficients for the response to methacholine challenge at the two levels of CL (BMI of 32 kg/m^2 and 42 kg/m^2) were determined. The decline in FEV$_1$ was significantly greater (p < 0.001) in response to methacholine with a CL of simulated BMI of 42 kg/m^2 compared with a simulated BMI of 32 kg/m^2 (p < 0.001).

Relations between COMB-induced changes in lung volume and measures of airway responsiveness (ΔFEV$_1$max) are shown in Figure 4. The ΔFEV$_1$max to methacholine was significantly (p < 0.05) correlated with percentage of COMB-induced changes of FRC (r = 0.77) and ERV (r = 0.88).

DISCUSSION

The results of the study showed that simulating the effects of obesity-related changes in lung volume with CL$_{32}$ and LLC alone and in combination increased airway responsiveness to methacholine. COMB increased airway responsiveness to a greater extent than with CL$_{32}$ or LLC alone. Finally, we showed a dose-response relationship exists between the degree of simulated obesity and airway responsiveness.

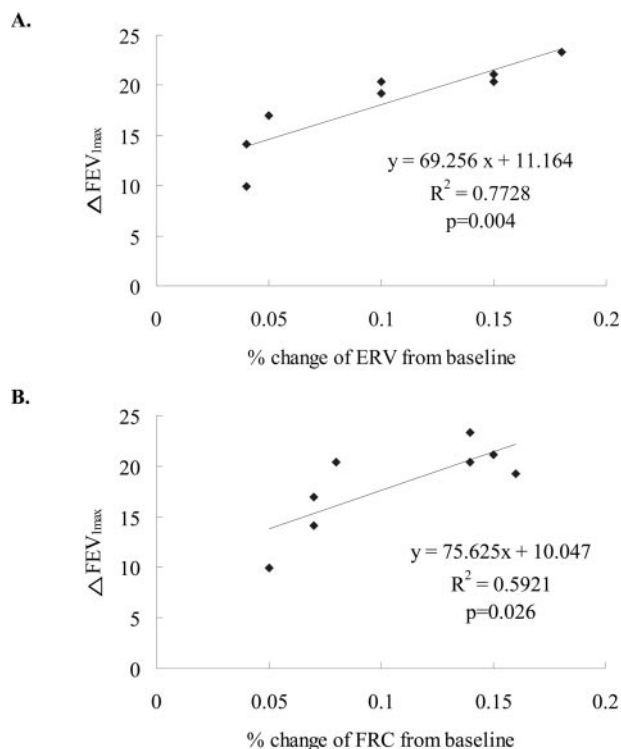Some limitations of the present study should be

A.

B.

FIGURE 4. Relationship between percentage change of ERV (*top*, A) and FRC (*bottom*, B) with COMB and ΔFEV_1max for eight subjects. Linear regression equation for all points is also shown.

acknowledged. First, although CL and LLC models have been used to induce lung volume reductions, the distribution of extra weight used in this study was not exactly the same as actual obesity, and the short-term nature of these effects on airway responsiveness may not match the long-term effects of obesity. A longitudinal study is needed to determine whether enhanced airway responsiveness persists or worsens with long-term CL or LLC. Although no subject had any complications during or after 30 min of anti-G garment inflation, this maneuver has shown to alter hemodynamics, and the safety issue for longer duration of application is a concern. Second, the possibility of tachyphylaxis (a reduced response with repeated stimulation) due to repeated methacholine tests must be considered.[24,25] Various durations (1.5 h to 3 days) of methacholine tachyphylaxis have been reported in healthy nonasthmatic subjects[25,26]; however, the doses used in these studies were much greater than what was used in our study (*eg*, 256 mg/mL vs 25 mg/mL), and thus we believe this adaptation was not a major concern in the present study. In addition, administering methacholine tests with at least 48 h between tests in our study decreased the chance for this adaptation to affect our results. Finally, the models used in this study are limited to the changes in mechanical properties of

the respiratory system associated with obesity on airway responsiveness and other mechanisms such as obesity-related inflammatory mechanisms that are found to be an independent risk factor for the development of asthma are not addressed in this simulation.[27]

Obesity alters lung volumes. We hypothesized that the reduction in lung volume, reflected in RV, ERV, FRC, and TLC, with CL_{32}, LLC, and COMB would be the primary cause for the observed increased airway responsiveness. The degree of lung volume reduction tended to greater with COMB than with CL_{32} or LLC alone. Decreases in ERV and TLC achieved with CL_{32}, LLC, and COMB were within the range reported in moderate obesity.[28–30] CL_{32} and COMB induced slight but significant decreases in FVC (3% and 4%, respectively) and FEV_1 (5% and 6%, respectively), and LLC induced a comparable reduction in FEV_1 (2%) but greater reduction in FVC as reported by Regnard et al[14] (9% vs 5%) using a similar model. The discrepancies might be due to different methods used to measure lung volume (plethysmography vs helium-dilution technique) and an additional abdominal compartment inflation used in the study of Regnard et al.[14] Compared to CL_{32}, decreases in lung volumes were greater with CL_{42}, but the changes in FVC and FEV_1 were not affected by the degree of mass loading.

Several mechanisms could explain increased airway responsiveness when lung volume is reduced: (1) decreasing the loads imposed on the airway smooth muscle; (2) decreasing baseline airway caliber; or (3) diminishing tidal stress on the airway smooth muscle. Decreased lung volume unloads the airway smooth muscle through lessening longitudinal stretching of the airway wall and decreasing both the parenchymal shear modulus and tethering forces.[31] As a result, the airways become more deformable, accounting for augmented airway responsiveness observed at lower lung volumes. In addition, lung volume is a major determinant of airway caliber. In normal subjects, airway responsiveness to a contracting stimulus is dependent, in part, on initial airway size with decreased caliber associated with increased responsiveness.[32] Although relatively small (*ie*, 2 to 6%), the reductions in FEV_1 and FVC with the application of CL, LLC, and COMB suggest a reduction in baseline airway caliber. According to the Poiseuille law,[33] a given degree of airway smooth muscle shortening causes a greater narrowing if the airway caliber is smaller. Both of these mechanisms concerning the static component of the airway behavior may have contributed to the observed increased responsiveness of the airways to methacholine under the conditions of CL, LLC, and COMB.

The dynamic behaviors of the airways and lung

parenchyma are affected by dynamic events such as tidal breathing. Fredberg et al[34] have proposed a model showing that the tidal action of spontaneous breathing imposes tidal strains on airway smooth muscle, and these tidal strains are the most potent bronchodilating agency. In the present study, subjects were breathing at lower lung volumes with CL, LLC, and COMB; therefore, this potent bronchodilating mechanism might have been compromised and caused airway smooth muscle to attain a more static or a stiff latch state, which then increases the airway response to contractile stimuli.

The application of lower-body positive pressure has been shown to induce acute pulmonary vascular engorgement.[14] Pulmonary vascular engorgement can lead to reflex airway constriction through increasing vagal, pulmonary C-fiber, and irritant receptor discharge activities.[35,36] While we do not know how much blood volume was displaced during LLC, it is likely that at least a part of the increased airway responsiveness observed could be due to this shift. The magnitude of lung volume reductions and airway responsiveness with LLC are comparable to that of CL_{32}. If a reflexive component was involved, one would expect that LLC would increase airway responsiveness more, but the result of this study failed to support this inference.

There is increasing evidence that the diagnosis of asthma is associated with increased body weight. Epidemiologic studies[3–5] have reported a consistent relation between asthma and obesity. The relation between obesity and asthma appears to be independent of atopy and exercise.[25] Celedon et al[37] reported a relation between BMI and physician-diagnosed asthma and airway hyperresponsiveness measured with methacholine challenges in > 7,000 adults. Methacholine acts directly on the smooth muscle of the airway, such that changes in methacholine responsiveness reflect airway remodeling[38] and possibly mechanical changes in the airway. As such, responses to methacholine may not reflect changes in airway responsiveness due to the inflammatory process associated with asthma. The implication of our study is that, at least in some persons, the changes in airway hyperresponsiveness associated with obesity may not be asthma, characterized by chronic airway inflammation, but may simply be a reflection of structural changes in the lung. If this hypothesis is verified, the treatment of obesity-related "asthma" may require weight loss. Further studies are required to better define this relation.

Of interest, we found a dose-response relationship between airway responsiveness and the degree of lung volume reductions. A greater degree of reduction in lung volume leads to a greater airway smooth muscle unloading, a smaller baseline airway caliber, and a greater perturbation of airway smooth muscle tidal stresses and consequently higher airway responsiveness compared to those with smaller degree of reduction in lung volume. These mechanisms could explain both our observations as well as the observations showing a close relationship between obesity and asthma. As the severity of obesity advances, the degree of lung volume reduction also increases. Since the relation between lung volume and airway responsiveness is proportional and we observed an increased responsiveness with an increase in the degree of simulated obesity, we can assume that the risk of airway hyperresponsiveness increases as obesity becomes more marked.

In conclusion, using the CL and LLC models, this study has provided evidence that lung volume reduction, as observed in the mildly obese, increases airway responsiveness to methacholine and may account for the high incidence of adult-onset asthma in this population. Reducing obesity may be important in the treatment of the obese with asthma symptoms.

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