

Letter to the Editor

Peripheral airways dysfunction in obesity reflects increased bronchomotor tone

To the Editor:

Asthma and obesity frequently coexist,^{1,2} and obesity has been established as a risk factor for subsequent development of asthma.³ Studying obesity independent of asthma may lead to increased understanding of the association. We have previously shown that obesity is characterized by peripheral airways dysfunction with increased small airways resistance and increased low frequency reactance area, a measure that reflects lung stiffness.⁴ The cause is unknown, but it may relate to altered respiratory mechanics or intrinsic airways dysfunction.^{1,5} We hypothesized that increased small airways bronchomotor tone is present in obesity, and we have tested this hypothesis by studying the effect of albuterol on forced oscillation and spirometric indices in obese and non-obese individuals without asthma.

We enrolled 12 obese (body mass index [BMI] ≥ 30 kg/m²) and 14 non-obese (BMI < 25 kg/m²) individuals in this study. Both groups met all inclusion criteria: age 18 to 60, < 5 pack-years smoking, no rhinitis or asthma symptoms or diagnosis, no symptoms in response to asthma triggers, no upper respiratory symptoms within 4 weeks of testing, ≤ 2 positive skin prick tests to common aeroallergens, no obstruction by spirometry, and normal diffusion capacity (DL_{CO}). Eight of the 12 obese participants had negative methacholine inhalation challenge (PC₂₀ ≥ 16 mg/mL). This study was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai, and informed, written consent was obtained from each subject.

Routine pulmonary function was performed using a Sensor-Medics 6200 body plethysmograph (Yorba Linda, Calif) and interpreted according to American Thoracic Society criteria.⁶ Measured parameters included FEV₁, forced vital capacity (FVC), FEV₁/FVC, total lung capacity (TLC), residual volume, functional residual capacity, expiratory reserve volume, inspiratory capacity, and DL_{CO}. Forced oscillation testing was employed using a Jaeger impulse oscillation system, as previously described.⁴ We measured: 1) resistance (R) at 5 Hz (R5), global index of airways resistance; 2) R at 20 Hz (R20), index of large airways resistance; 3) R5-R20, reflective of small airways resistance; and 4) integrated area of low frequency reactance (AX). The latter measurement includes all negative values of X (a measure of elastic load against which subjects breathe) between 5 Hz and the frequency at which X = 0. AX is an index of small airways obstruction complementary to frequency dependence of R (ie, R5-R20) and reflects lung stiffness.

Subjects underwent forced oscillation testing followed by spirometry and plethysmography. They then inhaled 2 puffs of albuterol via metered dose inhaler (90 μ g per puff) and waited 15 to 20 minutes before repeating forced oscillation and spirometric testing.

We analyzed differences between post- and pre-bronchodilator values for forced oscillation and for spirometric indices. The albuterol effect was defined as post- minus pre-bronchodilator value for each parameter. Crude contrasts (unadjusted for

TABLE I. Baseline patient characteristics

Parameter (all mean $\pm$ SEM except where stated otherwise)	Non-obese (n = 14)	Obese (n = 12)	P value (crude)
Age (y)	31 $\pm$ 2	36 $\pm$ 3	.151
n (%) Female	7 (50)	7 (58)	.713
Positive skin test ≥ 2 (n)	0	3	.015
n (%) Former smokers	1 (7)	0 (0)	1.000
FEV ₁ (% predicted)	96.7 $\pm$ 2.6	89.7 $\pm$ 3.1	.093
FVC (% predicted)	97.4 $\pm$ 2.5	92.7 $\pm$ 3.5	.678
FEV ₁ /FVC (%)	82.5 $\pm$ 1.9	79.6 $\pm$ 1.1	.218
TLC (% predicted)	100.2 $\pm$ 1.9	92.5 $\pm$ 5.1	.145
FRC (% predicted)	95.5 $\pm$ 3.6	97.9 $\pm$ 8.4	.783
ERV (% predicted)	99.9 $\pm$ 7.3	80.8 $\pm$ 12.6	.184
RV (% predicted)	90.8 $\pm$ 7.2	83.3 $\pm$ 10	.538
R5 (cm H ₂ O/L/sec)	3.04 $\pm$ 0.20	4.54 $\pm$ 0.25	.0001
R20 (cm H ₂ O/L/sec)	2.93 $\pm$ 0.19	3.60 $\pm$ 0.19	.0223
R5-20 (cm H ₂ O/L/sec)	0.11 $\pm$ 0.06	0.95 $\pm$ 0.14	$<.0005$
AX (cm H ₂ O/L/sec)	2.32 $\pm$ 0.33	8.05 $\pm$ 1.27	.0001
PC ₂₀ < 16 mg/mL (n)	0	4	.090

ERV, Expiratory reserve volume; FRC, functional residual capacity; RV, residual volume.

lung volumes) between obese and non-obese subjects were studied using the Student *t* test. Contrasts adjusted for TLC percent predicted used linear regression. Pearson correlations were used to analyze the association of BMI with the albuterol effect.

As shown in Table I, obese and non-obese groups were similar in terms of demographics and baseline spirometry and plethysmography, but resistance and reactance indices were significantly higher in the obese subjects. Fig 1 shows individual data for the (unadjusted) albuterol effect based on forced oscillation. The decrease in resistance and reactance measures following albuterol was significantly greater in the obese group for all forced oscillation parameters except R20. The significant effect persisted only in small airways parameters after adjusting for TLC percent predicted (Δ R5-R20: $P = .003$; Δ AX: $P = .014$). The albuterol effect was not significantly different between groups when spirometric indices were examined. We found significant correlations between BMI and albuterol effect on small airways indices (Δ R5-R20: $|r| = 0.67$, $P = .0002$; Δ AX: $|r| = 0.49$, $P = .01$), which persisted after adjustment for TLC percent predicted for R5-R20 ($P = .003$), indicating a continuous relationship of greater magnitude albuterol effect with increasing BMI. We also tested whether the presence of airways hyperresponsiveness noted in 4 obese participants influenced our findings by excluding these subjects. The albuterol effect on small airways remained significantly greater in the obese subjects both crudely and after adjustment for TLC percent predicted ($P \leq .01$).

Our results demonstrate greater albuterol response on small airways parameters in obese compared to non-obese individuals, in the absence of history or symptoms of asthma. These data support our hypothesis that peripheral airways dysfunction in obesity reflects exaggerated bronchomotor tone. Our adjusted analysis showed that these findings cannot be attributed to reduced TLC in the obese. It is possible that with a larger sample

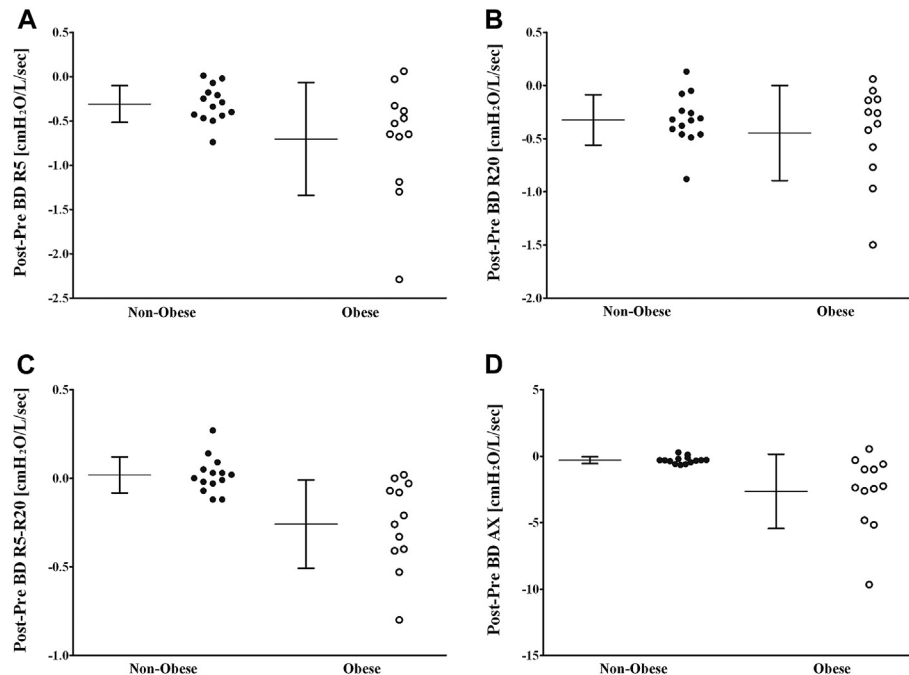


FIG 1. A-D, Crude albuterol effect on forced oscillation indices in obese (*open circles*) and non-obese (*closed circles*) subjects (mean $\pm$ SEM). The albuterol effect on R5, R5-R20, and AX was significantly greater in the obese than in the non-obese subjects ($P = .038$, $.0008$, and $.005$). The albuterol effect on R20 (**B**) was not significantly different between groups ($P = .380$). BD, Bronchodilator.

size we would have been able to detect large airways parameters differences between obese and non-obese subjects, but the important finding is that, even with our modest sample size, small airways parameters were affected by obesity. The presence of asymptomatic airways hyperresponsiveness in one-third of obese subjects does not drive our findings, because re-analysis excluding their data did not alter the outcome. Airways hyperresponsiveness is not a surprising finding considering the known abnormal response to deep inspiration in obesity.⁴ Notably, we found concordance between hyperresponsiveness and atopy, in that 3 of 4 subjects with hyperresponsiveness had positive skin tests, and these 3 subjects represented 3 of the 4 with positive skin tests. This raises the possibility that, despite the lack of upper or lower airway symptoms, this subgroup of obese individuals may represent a distinct phenotype with increased diathesis for development of asthma.

The mechanism for increased bronchomotor tone in obesity is unknown, but several hypotheses are possible. Obese subjects may have decreased breathing amplitude leading to stiffer small airways, which, in turn, would reduce the bronchodilatory effects of sighing and lead to increased bronchomotor tone. However, we did not measure tidal volumes in this study to support this explanation. It is also possible that adipokines (ie, leptin), which are increased in obesity,⁵ may have direct effects on bronchial diameter, independent of airway inflammation.⁷ Leptin dysfunction in obesity may increase parasympathetic signaling, leading to increased bronchomotor tone.⁷ More recent evidence suggests that this may be modulated by insulin.⁸

Our findings suggest that the frequent co-existence of obesity and asthma may be partially explained by peripheral airways dysfunction in obesity that could synergize with asthma-related abnormalities. We believe that further

investigation will offer major insight into the relationship of asthma and obesity, but it may also benefit individuals with obesity alone, whose increased small airways resistance may influence their functionality.

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