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Early Detection of Changes in Lung Mechanics with Oscillometry Following Bariatric Surgery in Severe Obesity

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Abstract

Background: Obesity is associated with respiratory symptoms that are reported to improve with weight loss; but this is poorly reflected in spirometry and few studies have measured respiratory mechanics with oscillometry. We investigated whether early changes in lung mechanics following weight loss is detectable with oscillometry. Furthermore, we investigated whether the changes in lung mechanics measured in the supine position following weight loss is associated with changes in sleep quality.

Methods: Nineteen severely obese female subjects (mean body mass index: $47.2 \pm 6.6 \text{ kg/m}^2$) were evaluated using spirometry, oscillometry, plethysmography and the Pittsburgh Sleep Quality Index before and 5 weeks after bariatric surgery. These tests were conducted in both upright and supine positions, and pre- and post-bronchodilation with 200mcg of salbutamol.

Results: Five weeks after surgery, weight loss of $11.5 \pm 2.5 \text{ kg}$ was not associated with changes in spirometry and plethysmography, except for functional residual capacity. There was also no change in upright respiratory system resistance (Rrs) or reactance following weight loss. Importantly, however, in the supine position, weight loss substantially reduced Rrs. In addition, sleep quality significantly improved and was highly correlated with the reduction in supine Rrs. Prior to weight loss, subjects did not respond to bronchodilator when assessed in the upright position with either spirometry or oscillometry, but with modest weight loss, bronchodilator response was regained to the normal range.

Conclusions: Improvements in lung mechanics occur very early following weight loss but mostly in the supine position, resulting in improved sleep quality. These improvements are detectable with oscillometry but not with spirometry.

Keywords: Oscillometry (Forced oscillation technique); Obesity; Body mass index; Lung function; Lung mechanics; Bronchial reversibility.

Background

The worldwide prevalence of obesity has nearly doubled over the past three decades, now exceeding 10 % of the adult population (World Health Organization, 2013). Obesity is associated with impaired lung function and respiratory conditions including asthma (Sideleva and Dixon 2014) and obstructive sleep apnea (Romero-Corral et al. 2010), and increased risk of respiratory symptoms such as wheeze (Schachter et al. 2001), dyspnea (Sin et al. 2002), and orthopnea (Ferretti et al. 2001).

Increasingly, bariatric surgery is used successfully to achieve and maintain weight loss, and this is accompanied by significant improvements in morbidity (Shah et al. 2010; Spivak et al. 2005), sleep quality (Toor et al. 2012), and lung function (Hasegawa et al. 2015; Thomas et al. 1989). While several studies have examined the effects of surgically induced weight loss on lung function in obese subjects with asthma, there is a paucity of data on the effects of bariatric surgery on obese individuals without asthma or other concomitant lung disease. The most significant lung function changes with weight loss in individuals without asthma are improvements in expiratory reserve volume (ERV) and functional residual capacity (FRC), with modest changes in total lung capacity (TLC) and residual volume (RV), accompanied by minor improvements in forced expiratory volume in one second (FEV₁) (Littleton 2012). Expiratory reserve volume and FRC were shown to increase by as much as 54 % and 37 % respectively, following a 34.2 kg weight loss (Thomas et al. 1989).

Dyspnea and wheeze in obesity are thought to arise largely from compression of the lungs by visceral fat around the mediastinum and in the abdominal and thoracic cavities which leads to decreased lung volumes (Babb et al. 2008; Sharp et al. 1964; Watson et al. 2010). While the reduced lung volumes alter airway-parenchymal interdependence (Mead et al. 1970), there is little apparent effect on airway obstruction, at least as reflected in FEV₁, despite the reductions in airway diameters (Zerah et al. 1993). This has led to the notion that obesity predominantly affects small airways, and is therefore not likely to be fully reflected in spirometry (Littleton 2012). However, evaluation of lung mechanics by oscillometry,

also known as the forced oscillation technique, in obesity has revealed an increase in respiratory system resistance (Rrs) (Salome et al. 2008; Yap et al. 1995; Zerah et al. 1993) and a decrease in respiratory system reactance (Xrs), primarily at low frequencies (Salome et al. 2008; Yap et al. 1995). Rrs is sensitive to central airway caliber, while low frequency Xrs can be used to determine respiratory system elastance (Ers), which is the inverse of respiratory system compliance (MacLeod and Birch 2001). In obesity, Xrs is thought to be significantly decreased due to closure of small airways in the lung periphery (Salome et al. 2008). Indeed, low frequency Xrs is sensitive to peripheral small airway closure (Dellaca et al. 2009; Goldman et al. 2005; King et al. 2005) making it a suitable tool for assessment of small airways (McNulty and Usmani 2014), which is considered a silent zone to spirometry (Konstantinos Katsoulis et al. 2013).

There have been very few studies of changes in lung mechanics with weight loss (Al-Alwan et al. 2014; Chapman et al. 2014; Oppenheimer et al. 2012; Zerah-Lancner et al. 2011). Moreover, there are no studies of how weight loss affects lung mechanics in the supine position, despite reports of increased severity of dyspnea and poor sleep quality in obesity (Ferretti et al. 2001; Toor et al. 2012). While the reduced lung volumes in obesity alters airway-parenchymal interdependence by decreasing tethering forces and shifting the pressure-volume relationship of the respiratory system (Mead et al. 1970; Zerah et al. 1993), it is not well understood how the reduced tethering forces in obesity might affect the responsiveness to bronchodilator (BD). Indeed, responsiveness to long acting bronchodilators and inhaled corticosteroids is impaired in obese subjects with asthma (Boulet and Franssen 2007; Camargo et al. 2010; Peters-Golden et al. 2006; Rodrigo and Plaza 2007), but the effect of obesity and weight loss on responsiveness to short-acting beta₂-adrenergic agonists has not been studied.

We hypothesized that oscillometry is more sensitive than spirometry and plethysmography to early changes in lung mechanics measured at 5 weeks following weight loss surgery and this may be associated with improvements in sleep quality reported by the patients. We assessed the mechanics of moving air into and out of the lungs in both upright and supine positions and recorded the changes that occurred with

weight loss by measuring Rrs and Xrs with oscillometry and comparing these assessments with results from spirometry and plethysmography. Furthermore, we hypothesized that changes in lung mechanics measured in the supine position following weight loss is associated with the changes in sleep quality. Finally, to probe the role of obesity and weight loss on bronchodilator response, we measured lung mechanics before and after salbutamol inhalation and compared the changes in lung mechanics to changes in spirometry values.

Methods

Selection of study participants and consent

Nineteen severely obese individuals without a diagnosis of asthma or other lung diseases were recruited from the Bariatric Surgery Clinic at the Queen Elizabeth II Health Sciences Center. This study was approved by the Nova Scotia Health Authority Research Ethics Board (reference number: CDHA-RS/2012-109). All participants provided written informed consent to participate in the study and also consented to have their data published.

Inclusion and exclusion criteria

All participants in the study had a body mass index (BMI) greater than 40 kg/m^2 and were scheduled for bariatric surgery within a few days of the baseline assessments described here. Subjects were excluded from the study if their BMI was less than 40 kg/m^2 , or if they presented with a physician-diagnosis of chronic lung disease (including asthma and chronic obstructive pulmonary disease). Other exclusion criteria included: a greater than 10 pack year smoking history, cognitive impairments that prevented accurate completion of study questionnaires or unacceptable performance of pulmonary function tests. Subjects were also excluded if they were unable to lie on their back for up to 10 minutes.

Study design

We assessed lung mechanics pre- and post-bronchodilator (BD) in the upright and supine postures, prior to and 5 weeks after bariatric surgery. We define all measurements before surgery to be baseline. At each assessment, oscillometry, whole body plethysmography and spirometry were performed as described below. The testing sequence is outlined in Figure 1.

Sleep quality questionnaire

Participants were asked to complete the Pittsburgh Sleep Quality Index (PSQI) before lung function assessments at baseline and 5 weeks after bariatric surgery. The PSQI was analyzed using previously described methodology with permission from Buysse and coworkers (Buysse et al. 1989). Briefly, the PSQI is a 19-item questionnaire that provides validated measurements of sleep disturbance and usual sleep habits in the previous month. The questions are grouped into seven components that analyze various aspects of sleep quality such as: subjective sleep quality, sleep latency, sleep duration, habitual sleep quality, sleep disturbances, use of sleep medication and daytime dysfunction due to sleepiness.

Respondents rated their sleep quality as “very good,” “fairly good,” “fairly bad” or “very bad” and this represented a score of 0, 1, 2, or 3, respectively. The PSQI also assessed various factors that disrupt sleep including breathing discomfort, waking up to use the bathroom, coughing or snoring loudly, feeling too hot or cold, having bad dreams and experiencing pain. The global sleep score was calculated as the sum of the seven components that make up the PSQI. A score of ≤ 5 is associated with good sleep quality while a score > 5 is associated with poor sleep quality.

The effect of weight loss on dyspnea in obesity was specifically assessed with the PSQI by analyzing the response of participants to perceptions of breathing discomfort. A score of zero was assigned when no breathing discomfort was reported in the past month; a score of 1 was assigned when breathing discomfort occurred less than once a week, corresponding to mild discomfort; a score of 2 was assigned when breathing discomfort occurred once or twice a week, corresponding to moderate discomfort, while a

score of 3 was assigned when breathing discomfort occurred three or more times a week, corresponding to severe discomfort.

Weight, height and waist circumference measurements

Participant weight and height were measured without wearing shoes or heavy clothing; these parameters were used to calculate BMI. Waist circumference (WC) was measured as the circumferential distance around the midpoint between the lowest rib and the iliac crest.

Pulmonary function tests

Spirometry and whole body plethysmography were performed according to recommended international guidelines using a spirometer-equipped body box (SensorMedics Corporation, Yorba Linda, CA, USA) (Pellegrino et al. 2005; Wanger et al. 2005). Forced expiratory flows, including forced expiratory volume in one second (FEV₁) and expiratory flow at 50 % (FEF₅₀), 75 % (FEF₇₅), and 25 – 75 % (FEF_{25–75}) of forced vital capacity (FVC) were obtained. Lung volumes and capacities, including expiratory reserve volume (ERV), inspiratory capacity (IC), functional residual capacity (FRC) and vital capacity (VC) were also measured. The average ERV, FRC and IC; and the best VC and forced expiratory flows were selected as the final result from three technically acceptable measurements (Miller et al. 2005). TLC was calculated as the sum of IC and FRC while RV was calculated as the difference between TLC and VC. Results obtained from these lung function tests were expressed as percentages of predicted values from Crapo *et al* (Crapo et al. 1981).

Oscillometry

The mechanical properties of the respiratory system were measured according to recommended guidelines (Oostveen et al. 2003) using the tremoFlo™ Airwave Oscillometry System (Thorasy Thoracic Medical Systems Inc., Montreal, QC, Canada). During each measurement, subjects wore a nose-clip and firmly held their cheeks and mouth floor so as to minimize the upper airway shunt artefact (Oostveen et al.

2003). The Airwave Oscillometry System delivered a multi-frequency composite oscillatory pressure waveform of about 1-2 cm H₂O superimposed on a subject's spontaneous breathing at 6, 11 and 19 Hz for 16 seconds. Mechanical parameters of the respiratory system were then computed from the impedance of the respiratory system (Z_{rs}) to the resulting flow oscillations. The frequency range allowed us to examine the frequency-dependent mechanics of the respiratory system and how it changed with weight-loss.

Respiratory system impedance is the spectral ratio of the fast Fourier transform (FFT) of the pressure and flow measured at the subject's mouth, and was computed by averaging 1 second windows of the pressure and flow recordings multiplied by Hamming windows with 50% overlap. Z_{rs} is a complex quantity where the real part depicts the portion of the pressure that is in phase with flow and thus describes R_{rs} , while the imaginary part depicts the portion of the pressure that is in phase with volume and acceleration of volume and thus describes X_{rs} . R_{rs} is largely governed by airway caliber and some lung tissue properties, while X_{rs} is governed by the elasticity of the chest wall and lung tissues, and the inertia of the oscillating column of gas in the central airways. Furthermore, while the resistance of the two components of the chest wall – the rib cage and diaphragm-abdomen accounts for a small part of the R_{rs} , the contribution of these two components to the total R_{rs} may be increased in the supine position particularly in obesity.

Within each 16 second recording, the effects of artefacts were minimized by automatic rejection of any 1 second window containing negative R_{rs} or R_{rs} values greater than three standard deviations and using the mean R_{rs} and X_{rs} to minimize the effect of any outliers. Additionally, measurements were repeated four times with periodic breaks of about 30 seconds between measurements. The average from these measurements was computed as the final result.

At low frequencies X_{rs} is negative and is dominated by the elastance of the respiratory system while at high frequencies when X_{rs} is positive, it is dominated by the inertia of the oscillating air column. For all subjects, X_{rs} at 6 Hz was less than -1 cmH₂O/L/s indicating that X_{rs} was dominated by elastance and an

estimate of Ers was obtained (Kaczka and Dellacá 2011) as: $Ers = -\omega Xrs_6$ where, ω is the angular frequency and is mathematically expressed as: $\omega = 2\pi f$.

The coefficient of variation (COV) for Rrs was computed from the standard deviation of the four consecutive Rrs measurements normalized to the mean to determine the repeatability and variability of Rrs . Coherence ≥ 0.90 was used as an acceptance criteria for each 16 second measurement of Zrs at each frequency.

Bronchial reversibility test

Lung mechanics and function was assessed before, and 15 minutes after inhaling 200 mcg of the BD – salbutamol, administered with a metered-dose inhaler and valved-holding chamber spacer device (CareStream Medical Ltd., Pickering, ON, Canada). This assessment was performed before and 5 weeks after bariatric surgery.

Bariatric surgery

All subjects underwent a laparoscopic sleeve gastrectomy – a minimally invasive procedure that results in the complete removal of about 85% of the stomach. The surgery was performed under general anesthesia and patients were discharged home 48-72 hours post-surgery. The postoperative diet regimen consisted of 4-6 weeks of a high protein, semi-liquid diet followed by a return to normal diet.

Statistical analysis

Results are expressed as means $\pm$ standard deviations (SD). Weight, BMI, waist circumference, PSQI and plethysmography results obtained before and after bariatric surgery were analyzed using a one-way repeated measures analysis of variance (ANOVA) while the effects of position and bronchodilation on spirometry and oscillometry results obtained before and after bariatric surgery were analyzed using two-way repeated-measures ANOVA with surgery and condition (position plus bronchodilation) as factors. Surgery was divided into two levels (i.e. before and after surgery) while condition was divided into four

levels (i.e. upright pre-BD, supine pre-BD, upright post-BD and supine post-BD). Where significance was found, separate post hoc pairwise testing was then performed with Student's t-test to identify differences due to surgery, position, or BD and the Benjamini-Hochberg procedure was applied to control the effect of multiple comparisons (Benjamini and Hochberg 1995). Correlation analyses were performed using linear regression methods in MATLAB R2013b (Natick, MA, USA) while all other analyses were performed in IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY, USA). P -values < 0.05 were considered statistically significant.

Results

Demographics and obesity parameters

Table 1 shows the age distribution and anthropometric characteristics of the subjects before and 5 weeks after bariatric surgery. Following bariatric surgery, there was a significant reduction in weight, BMI and WC ($p < 0.001$). The ANOVA summary table of within-subjects effects for oscillometry is presented in Table 2. With the exception of Rrs,19, weight loss surgery did not have a significant effect on any of the oscillometric (Table 2) or spirometric measures (not shown). Furthermore, position and bronchodilation significantly changed all oscillometric measures (Table 2) while the only spirometric indices that significantly changed were FEV1, FEV1/FVC, FEF₂₅₋₇₅ and FEF₇₅ (not shown). Also, there was a significant cross interaction between surgery and conditions (position plus bronchodilation) in Xrs,6 and Ers (Table 2).

Changes in lung mechanics with weight loss: posture and bronchodilation

Although weight loss had no effect on upright pre-BD Rrs measured at all the frequencies, weight loss significantly reduced pre-BD Rrs,19 measured in the supine position by $13.1 \pm 3.8\%$, but not Rrs,6 and Rrs,11 (Table 2, Figures 2 and 3A). In addition, moving from an upright to supine position elicited

changes in lung mechanics that were further influenced by weight loss and by bronchodilation. For instance, prior to weight loss, moving to the supine position pre-BD resulted in a 23.7 ± 11 % increase in pre-BD Rrs,₆, but there was no change post-BD; however, after weight loss, the increase in Rrs,₆ was 24.4 ± 8 % post-BD (Figure 3A). Ers was consistently sensitive to changes in posture increasing by similar amounts on moving from upright to supine position, both pre- and post-BD, and before and after weight loss (Figure 3B).

Weight loss and bronchodilator responsiveness

Figure 4 shows the effects of BD at each frequency. Prior to weight loss, BD only had a modest effect on Rrs,₁₁ measured in the upright position (Figure 4A); however, following weight loss, BD had a substantial effect by decreasing Rrs at all frequencies (Figure 4C). In contrast to measurements in the upright position, in the supine position, BD significantly decreased Rrs at all frequencies before weight loss but following weight loss, BD response was only observed in Rrs,₆ (Figure 3A) and not in Rrs,₁₁ and Rrs,₁₉ (not shown). There was also no BD response measured with Ers before surgery in both the upright and supine positions; however, significant response to BD was measured following weight loss in both the upright and supine positions (Figure 3B). Unlike Ers, Xrs measured at 11 and 19 Hz was consistently increased in response to BD in the upright (Figure 4B and 4D) and supine (not shown) positions both before and after weight loss.

Examining the responses due to BD in Rrs again, and evaluating the percent changes in Rrs to compare to the percent changes in Ers in Figure 5, we saw that at baseline, the percent change in upright Rrs at all frequencies in response to BD was negligible; however after surgery, the response was significant and significantly greater than before surgery at all frequencies, increasing on average by 17.6 ± 4.0 % (Figure 5A). By comparison, prior to surgery, BD induced only a modest 7.1 ± 10 % decrease in Ers measured in the upright position, but after surgery a larger reduction in Ers of 33 ± 8 % was seen (Figure 5A).

Similarly in the supine position, the BD-induced reduction in Ers after weight loss was much larger than before weight loss and larger than the change in Rrs, which was only significant at 11 Hz (Figure 5B).

Table 3 demonstrates results from spirometry measured in the upright position. Prior to bariatric surgery, only FEF₂₅₋₇₅, changed significantly in response to BD. After surgery, FEV₁, FEV₁/FVC, FEF₂₅₋₇₅ and FEF₇₅ all increased significantly in response to BD. FEF₇₅ and FEF₂₅₋₇₅ increased by $28.2 \pm 7.0 \%$ and $18.8 \pm 5.4 \%$ respectively, while FEV₁ increased by only $5 \pm 2 \%$ post-BD. In the supine position, BD induced a $4.0 \pm 2 \%$ increase in FEV1 before surgery and a $5.1 \pm 1.7 \%$ increase after surgery (not shown).

Weight loss and lung volumes

There was a $9.5 \pm 2.5 \%$ increase in FRC with weight loss following bariatric surgery but no change in other lung volume measurements (Table 4). There was a significant correlation between the change in FRC, expressed as a percent of predicted, and the percent weight loss following surgery ($r = 0.56$, $p = 0.019$).

Variability and repeatability of respiratory resistance

The variability and repeatability of respiratory system resistance was determined from the percent COV (Table 5) obtained from multiple measurements at each time and in each test condition (e.g. before and after bariatric surgery, in the upright and supine position, and pre- and post-bronchodilation). The variability in Rrs measurements obtained from oscillometry was less than 10 % in all tests indicating that the measurement was highly repeatable. Measures of variation in Xrs were estimated from the standard deviation of Xrs (SDXrs) and was found to be less than 0.5 cmH₂O/L/s in all tests. For example, at baseline, SDXrs was 0.46 cmH₂O/L/s; however, 5 weeks after surgery, the variation in Pre-BD Xrs dropped to 0.31 cmH₂O/L/s.

Sleep quality

Weight loss was associated with significant improvements in sleep quality as measured by the PSQI. Table 6 shows the component scores from the PSQI collected before and 5 weeks following bariatric surgery. Improvements in subjective sleep quality, sleep disturbances and daytime dysfunction due to sleepiness led to an improvement in the global sleep score. The overall improvement in sleep quality with weight loss was highly correlated with the reduction in Pre-BD Rrs,19 measured in the supine position ($r = 0.71$, $p = 0.009$) but not with any reductions in Pre-BD Rrs,6 ($r = 0.53$, $p = 0.075$) or Rrs,11 ($r = 0.43$, $p = 0.163$). We did not find any correlation between the reduction in waist circumference and improvement in sleep quality.

Prior to bariatric surgery, 8 of the 19 participants reported mild to severe breathing discomfort on the PSQI in the month prior to examination. Four respondents reported mild breathing discomfort (score of 1); 1 respondent reported moderate breathing discomfort (score of 2), while 3 respondents reported severe breathing discomfort (score of 3). Significant improvements were noted after bariatric surgery as follows: 16 respondents reported no breathing discomfort at all; 2 respondents reported mild breathing discomfort, while 1 respondent reported moderate breathing discomfort in the month prior to re-examination.

Discussion

We investigated the early changes in lung mechanics and lung function associated with weight loss in severely obese subjects at 5 weeks following bariatric surgery. Our principle finding was that despite normal spirometry and no changes in lung mechanics in the upright position, lung mechanics assessed by oscillometry significantly improved in the supine position with weight loss. Secondly, these changes were accompanied by a significant increase in BD responsiveness in the upright position; thirdly, these changes were accompanied by improvements in sleep quality.

This is the first study to examine changes in lung mechanics induced by weight loss in both the upright and supine positions. Although weight loss had no effect on Rrs measured in the upright position, it

significantly reduced Rrs measured supine (Figures 2 and 3A). Previous studies have consistently reported significant reductions in Rrs measured in the upright position following weight-loss surgery, but those assessments were conducted 12-24 months after surgery (Al-Alwan et al. 2014; Oppenheimer et al. 2012; Zerah-Lancner et al. 2011). Thus, the amount of weight loss achieved by the participants only a few weeks after bariatric surgery in our study was likely insufficient to induce a decrease in Rrs measured in the upright position. However, the modest weight loss was sufficient to reduce the Rrs measured in the supine position likely because moving to the supine position augments lung compression associated with obesity (Navajas et al. 1988; Yap et al. 1995) and that could amplify the changes in mechanics with weight loss. Compression reduces lung volume and lung elastic recoil (Pellegrino et al. 2014), resulting in weaker airway-parenchymal tethering and the collapse of dependent airways (Salome et al. 2010). Thus, the modest weight loss present at 5 weeks after surgery, which was accompanied by a decrease in waist circumference (Table 1), was sufficient to reduce lung compression in the supine position. Indeed, prior to weight loss, moving from an upright to supine position increased Rrs,6 by $23.7 \pm 11\%$, while after surgery, the increase in Rrs was not significant (Figure 3A).

The reduction in supine Rrs with weight loss measured at 19 Hz (Figure 2) may be due to a greater increase in the caliber of the central airways. This is because Rrs at higher oscillometry frequencies (Rrs,19) is usually dominated by the upper and central airways while the effect of small peripheral airways on Rrs is normally undetectable unless there is sufficient heterogeneous peripheral airway obstruction present (Bates et al. 2011). It is possible that with further weight loss larger changes in peripheral airway caliber might be detectable, leading to improvements in Rrs at lower frequencies as well. In some severely obese patients improvements in Rrs with weight loss might occur with resolution of upper airway obstruction associated with obstructive sleep apnea (Schwartz et al. 1991). Since the prevalence of obstructive sleep apnea in severely obese patients presenting for weight loss surgery is about 74 % (Lopez et al. 2008), it is quite likely that some of our study participants may have had

undiagnosed sleep apnea that could possibly have improved with weight loss resulting in improved sleep quality (Table 6).

The fact that we did not find any changes in spirometry but did with oscillometry may be because oscillometry measures lung mechanics near FRC, and particularly in the supine position, the effects may be greater than might occur during the forced exhalation manoeuvres performed during spirometry. Surprisingly, even at 18-24 months, spirometry appeared to be insensitive to weight-loss-induced improvements in upright lung function as reported previously (Oppenheimer et al. 2012; Zerah-Lancner et al. 2011), although Al-alwan *et al* (Al-Alwan et al. 2014) reported slight improvements in FEV₁ and FVC at 12 months.

Weight loss affected the response to BD in our study participants. Prior to bariatric surgery, inhalation of salbutamol did not result in significant reduction in Rrs measured in the upright position or in spirometry values. This is consistent with the results of other studies in obese individuals with asthma who demonstrated little or no change in spirometry values following BD (Dixon et al. 2006; Sutherland et al. 2009). In a study of obese subjects without respiratory disease, less than 15 % of subjects demonstrated a positive BD response and examining mean values, post BD FEV₁% was only 0.25 % higher than pre BD FEV₁% (Machado et al. 2008). We are the first group to publish data on the effect of weight reduction on BD responsiveness in obese adults without asthma. Our results demonstrate that weight loss is associated with an increased BD response in both oscillometric and spirometric indices (Figure 5A and Table 3). Although the BD response in Rrs was increased to 17 %, it was still within the normal range which is reported as an 11 % drop in Rrs (Oostveen et al. 2013). This response was also below traditional thresholds for reporting acute reversibility in both spirometry (<12%) (Pellegrino et al. 2005) and oscillometry (<33%) (Oostveen et al. 2013).

The lack of BD responsiveness before weight loss could be due to decreased airway-parenchymal tethering forces with obesity (Mead et al. 1970). Reduced tethering uncouples the airway smooth muscle

from the parenchyma and as a consequence, the airways fail to dilate with BD. This same mechanism has been suggested in nocturnal asthma where the airway is uncoupled from the parenchyma during sleep resulting in increased resistance that persisted throughout sleep (Ballard et al. 1990; Irvin et al. 2000). Weight loss reduces lung compression and accounts for the increase in FRC that we measured 5 weeks following bariatric surgery (Table 4). This effect could partially restore airway-parenchymal coupling, resulting in greater airway wall tension that would be responsive to bronchodilation. This may explain the increased BD response recorded in the upright position as an increased percent drop in post-BD Rrs following weight loss (Figure 5A), suggesting an increase in central airway caliber.

Another explanation for the reduced BD responsiveness measured in the upright position prior to weight loss surgery is that some of the bronchodilator may have been deposited within the oropharynx despite the use of a metered dose inhaler and valved-holding chamber in the administration of the drug. With weight loss, it is possible that there was a reduction in the amount of redundant supraglottic oropharyngeal tissue which increased BD deposition within the lung. However, this effect was likely modest since we found that BD reduced Rrs and FEV1 in the supine position indicating successful BD delivery to the lung. Regardless of the cause, reduced BD responsiveness is an important problem for severely obese subjects with asthma since they are usually prescribed short acting bronchial agonists for sudden symptoms. It is also possible that changes in systemic inflammation with weight loss may have led to physiological changes in the airways. Inflammation is associated with obesity and, in particular, increased secretion of pro-inflammatory adipokines by the visceral adipose tissue is suggested to lead to airway remodeling and bronchial hyperreactivity (Sideleva et al. 2012). However, changes in inflammatory status with weight loss is particularly associated with obese subjects who also have asthma (Sideleva et al. 2012), whereas our study focused on subjects without asthma. Furthermore, progesterone has been shown to potentiate BD-stimulated ASM relaxation (Foster et al. 1983), and it is down-regulated in obesity (Hernández García et al. 1999), suggesting a possible mechanism for the reduced BD responsiveness at baseline, since our study was limited to only female participants. Thus perhaps, even with modest weight-loss, these

hormonal and inflammatory mediators could have a functional effect on lung mechanics. Nevertheless, our subjects were severely obese before bariatric surgery and remained severely obese after surgery, despite significant weight loss.

In contrast to the upright position, supine Rrs was significantly reduced post-BD at all frequencies before weight loss; however, only Rrs,6 was reduced post-BD after weight loss (Figures 5B and 3A). Before weight loss, Rrs was highest in the supine position, indicating narrowed airways that may be attributed largely to the central airways, as we did not observe any frequency dependence indicative of small airways heterogeneity (King et al. 2005). Due to the inverse power relationship between radius and resistance, Rrs is exquisitely sensitive to airway diameter. Thus, small changes in airway caliber can cause large effects on Rrs. It is possible that despite diminished airway-parenchymal tethering in obesity, the BD was able to induce central airway dilation in the supine position before weight loss because of the reduced airway caliber. However, following weight loss, the beta-agonist had little effect in dilating the airways in the supine position (Figure 5B), since weight loss had already induced significant airway dilation in this position as shown in Rrs,19 (Figure 2). Moving from upright to supine position can cause significant changes in upper, and central airway geometries as well as changes to the lung periphery (Lorino et al. 1992; Navajas et al. 1988; Yap et al. 1995). Xrs is thought to be an indicator of airway closure (Dellaca et al. 2009; Goldman et al. 2005; Salome et al. 2008) and is decreased in the supine position (Lorino et al. 1992; Navajas et al. 1988; Yap et al. 1995) consistent with our findings. Xrs may also reflect changes in chest wall elastance that may occur with changes in posture (Hantos et al. 1986). Interestingly, we found that the BD was very effective at reducing upright and supine Ers after weight loss likely due to recruitment of small airways (Figures 3B and 5B). The larger relative change in Ers compared to Rrs following weight loss may mean a greater improvement in lung function due to recruitment of small airways with weight loss.

The biggest effect of weight loss at baseline was the improvement in supine lung mechanics which may help explain the improvements observed in sleep quality (Table 6). Eight (42%) out of the 19 subjects

interviewed in this study reported mild to severe breathing discomfort at baseline. However, after weight loss, only three (16%) of the respondents reported any breathing difficulty in the month prior to examination. This is in agreement with the findings of Oppenheimer *et al* where they reported that the prevalence of respiratory symptoms such as dyspnea, wheeze and cough was greatly reduced after weight loss (Oppenheimer *et al.* 2012). A PSQI of 8.4 ± 3.5 was measured at baseline in our cohort and this is quite similar to the findings of Toor *et al* (Toor *et al.* 2012) who reported a PSQI of 8.8 in their cohort. A global sleep score of ≤ 5 is associated with good sleep quality while a global sleep score > 5 is associated with poor sleep quality (Buysse *et al.* 1989). The PSQI reduced to 6.5 ± 3.7 following weight loss surgery (Table 6), unlike the findings of Toor *et al* (Toor *et al.* 2012) where global sleep score reduced to ≤ 5 , although their follow-up assessment was conducted after much greater weight loss was achieved at 3-6 months after bariatric surgery. Nevertheless, even with modest weight loss at 5 weeks, there were significant improvements in PSQI that was highly correlated with the reduction in Rrs,19 measured in the supine position. In fact, about 51% of the variance in the improvement in sleep quality was accounted for by the reduction in supine Rrs,19 suggesting that breathing discomfort due to narrowing of upper and central airways in the supine position may contribute more to poor sleep quality than previously thought.

We have shown that the assessment of lung mechanics with oscillometry in the supine position or with BD was sensitive to early changes in lung function associated with modest weight loss following bariatric surgery while spirometry and plethysmography, except for FRC, was not. Weight loss likely improved lung mechanics by restoring the airway-parenchymal tethering forces in the supine position and likely helps explain improvements in sleep quality. In addition, the tethering forces were likely sufficiently restored to allow the BD to dilate the airways even after weight loss. These findings demonstrate the sensitivity of oscillometry and that improvements in lung mechanics occur early after weight loss surgery improving sleep quality.

Conflict of interest

Dr. Geoffrey Maksym has a US patent, “Method of assessment of airway variability in airway hyperresponsiveness.” Dr. Maksym is co-founder and Chief Scientific Advisor and holds some shares in Thoracic Medical Systems THORASYS Inc. The authors declare that they have no other conflict of interest, financial or otherwise, related to this study.

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Table 1. Age distribution and anthropometric characteristics of study participants.

	Before Surgery	After Surgery	<i>p</i> -value
Number of participants	19	19	
Sex (Females, Males)	19, 0		
Age (years)	48.3 ± 7.6		
Mean weight (kg)	123.4 ± 19.0	111.9 ± 18.1	< 0.001
Mean BMI (kg/m ²)	47.2 ± 6.6	42.8 ± 6.6	< 0.001
Mean Waist Circumference	1.30 ± 0.04 m (134 ± 4 cm)	1.20 ± 0.03 m (121 ± 3 cm)	< 0.001
Average weight loss (kg)	N/A	11.5 ± 2.5	
Percent of initial weight lost (%)	N/A	9.4 ± 2.1	

Note: Weight, BMI and waist circumference significantly reduced after bariatric surgery. Data are expressed here as mean ± standard deviation.

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Table 2. Analysis of Variance for Oscillometry

	Surgery		Conditions (Position + Bronchodilation)		Interactions (Surgery*Conditions)	
	F-value	<i>p</i> -value	F-value	<i>p</i> -value	F-value	<i>p</i> -value
Rrs6	.562	.463	7.873	< .001	2.355	.082
Rrs11	3.251	.088	8.783	.001	2.053	.117
Rrs19	5.627	.029	4.421	.017	2.353	.082
Xrs6	.214	.650	26.415	< .001	1.207	.029
Xrs11	1.331	.264	25.551	< .001	.717	.546
Xrs19	.011	.919	24.687	< .001	.266	.850
Ers	.214	.650	26.415	< .001	1.207	.029

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Table 3 Pre- and Post-BD spirometric data obtained before and 5 weeks after bariatric surgery (n = 17).

	Before weight loss			After weight loss		
	Pre-BD	Post-BD	<i>p</i> -value	Pre-BD	Post-BD	<i>p</i> -value
FVC	102 ± 3	101 ± 3	0.397	102 ± 3	102 ± 4	0.926
FEV ₁	95 ± 3	96 ± 4	0.490	94 ± 4	98 ± 4	0.031
FEV ₁ /FVC	94 ± 2	96 ± 3	0.056	93 ± 3	97 ± 3	0.002
PEF	104 ± 6	103 ± 6	0.649	103 ± 6	103 ± 6	0.850
FEF ₂₅₋₇₅	85 ± 7	92 ± 8	0.005	84 ± 9	97 ± 9	<0.001
FEF ₅₀	105 ± 8	112 ± 10	0.068	102 ± 11	110 ± 10	0.124
FEF ₇₅	72 ± 11	82 ± 12	0.108	69 ± 9	86 ± 12	<0.001

Note: Values are expressed as % predicted mean ± standard deviation. FVC: forced vital capacity, FEV₁: forced expiratory volume in 1 sec, FEV₁/FVC: ratio of forced expiratory volume in 1 sec to forced vital capacity, PEF: peak expired flow, FEF₂₅₋₇₅: forced expiratory flow between 25% and 75% of FVC, FEF₅₀: forced expiratory flow at 50% of FVC, FEF₇₅: forced expiratory flow at 75% of FVC.

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Table 4. Lung Volumes obtained before and five weeks after bariatric surgery (n = 17).

LUNG VOLUMES	PRE-SURGERY	POST-SURGERY	<i>p</i> -value
TLC	90 ± 9	91 ± 10	0.223
FRC	69 ± 8	75 ± 12	0.003
RV	61 ± 17	65 ± 18	0.356
VC	104 ± 12	104 ± 14	0.950
IC	115 ± 17	112 ± 16	0.326
ERV	72 ± 16	83 ± 25	0.143

Note: Values are expressed as % predicted mean ± standard deviation. TLC: total lung capacity, FRC: functional residual capacity, RV: residual volume, VC: vital capacity, IC: inspiratory capacity, ERV: expiratory reserve volume.

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Table 5. Percent Coefficient of Variation (COV) for oscillometric Rrs obtained under various test conditions.

	Pre-Surgery	Post-Surgery	<i>p</i> -value
Upright Pre-BD	7.3 ± 2.9	5.2 ± 2.2	0.010
Supine Pre-BD	7.0 ± 1.8	6.5 ± 1.7	0.181
Upright Post-BD	5.5 ± 1.7	5.4 ± 2.2	0.362
Supine Post-BD	6.4 ± 2.3	7.0 ± 2.5	0.230

Note: Values are expressed as % mean ± standard deviation.

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Table 6. Component scores of the PSQI collected before and 5 weeks after bariatric surgery.

Components of the PSQI	Before surgery	After surgery	<i>p</i>-value
Subjective Sleep Quality	1.2 ± 0.8	0.7 ± 0.8	0.025
Sleep Latency	1.6 ± 1.1	1.4 ± 1.1	0.297
Sleep Duration	1.0 ± 1.2	0.7 ± 1.0	0.297
Habitual Sleep Efficiency	1.2 ± 1.0	1.2 ± 1.2	1.00
Sleep Disturbances	1.8 ± 0.5	1.4 ± 0.5	0.007
Use of Sleeping Medication	0.3 ± 0.8	0.2 ± 0.5	0.506
Daytime Dysfunction	1.2 ± 0.9	0.8 ± 0.6	0.042
Global score	8.4 ± 3.5	6.5 ± 3.7	0.049

Note: Values are expressed as mean ± standard deviation

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Figure 1. Testing sequence for assessment of the effect of weight loss on lung mechanics.

Figure 2. Effect of weight loss on pre-BD resistance measured in the supine position. Error bars indicate standard error of the mean.

Figure 3. Effect of moving from an upright to supine position on Pre- and Post-BD Rrs,6 (**A**) and Ers (**B**) measured before and after bariatric surgery. In Panel B, moving to the supine position significantly increased Ers for all conditions ($p < 0.001$). Error bars indicate standard error of the mean.

Figure 4. The effect of BD on Rrs and Xrs measured in the upright posture before (**A & B**) and five weeks after bariatric surgery (**C & D**). (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). Error bars indicate standard error of the mean.

Figure 5. Percent drop in Rrs and Ers in the upright (**A**) and supine position (**B**) measured in response to BD before and after surgery. (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). The effect of BD on upright Rrs measured before and after surgery is shown in Figure 4A and 4C. Prior to surgery, BD significantly lowered supine Rrs at all frequencies, however after surgery, only Rrs,6 reduced following inhalation of BD. Error bars indicate standard error of the mean.

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