Effect of Increased Lung Volume on Sleep Disordered Breathing in Sleep Apnoea Patients

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Key words: Sleep apnea, lung volume, upper airway, continuous positive airway pressure, airflow limitation

Running head: Effect of Lung volume on obstructive sleep apnoea
Abstract

Background: Previous studies have demonstrated that changes in lung volume influence upper airway size and resistance, particularly in obstructive sleep apnoea (OSA) patients, and that continuous positive airway pressure (CPAP) requirements decrease when the lung volume is increased. We sought to determine the effect of a constant lung volume increase on sleep disordered breathing during non REM sleep. Methods: Twelve OSA subjects were studied during non REM sleep in a rigid head-out shell equipped with a positive/negative pressure attachment for manipulation of extrathoracic pressure. The increase in lung volume due to CPAP (at therapeutic level) was determined with four magnetometer coils placed on the chest wall and abdomen. CPAP was then stopped and the subjects were studied for 1 hour in three conditions (in random order): 1) with no treatment (Baseline); 2) at the “CPAP lung volume”, with the increased lung volume being reproduced by negative extrathoracic pressure alone (Lung Volume 1), and 3) 500 ml above the “CPAP lung volume”(Lung Volume 2). Results: respectively for baseline, Lung Volume 1, and Lung Volume 2 the mean AHI (SE) was 62.3 (10.2), 37.2 (5.0), and 31.2 (6.7) events per hour (p = 0.009); the 3% oxygen desaturation index was 43.0 (10.1), 16.1 (5.4), and 12.3 (5.3) events per hour (p =0.002) and the mean oxygen saturation was 95.4 (0.3) %, 96.0 (0.2) %, 96.3 (0.3) % (p =0.001). Conclusion: An increase in lung volume yields a substantial decrease in sleep disordered breathing in OSA patients during NREM sleep.

Introduction

Obstructive sleep apnoea syndrome (OSA) is a common disorder occurring in approximately 4% of middle-aged men and 2% of women (1). OSA is characterized by repetitive pharyngeal collapse during sleep leading to sleep disruption, arousals and arterial oxygen desaturation. However, the mechanisms leading to pharyngeal collapse are not completely understood. Previous investigators have suggested that this airway collapse involves the combination of an anatomically compromised pharyngeal airway and sleep-induced decrements in pharyngeal dilator muscle activity (2-5).

During sleep, in normal subjects, upper airway resistance increases and functional residual capacity decreases (6-8). This sleep-induced decrement in lung volume is believed to result in increased upper airway collapsibility and contribute to inspiratory flow limitation, although the exact mechanisms have not been delineated. Animal data, using mongrel dogs, have suggested that thoracic inflation increases upper airway pharyngeal size and stiffness through caudal traction on the trachea independently of upper airway muscle activity (9, 10).

Our group recently demonstrated that in OSA patients, increased end expiratory lung volume (EELV) decreased the CPAP level required to prevent upper airway flow...
limitation (11). Similarly when EELV is decreased the required CPAP level to prevent flow limitation increased. This suggests that increments in lung volume have a stabilizing effect on the upper airway during sleep in OSA patients. We therefore sought to determine the influence of a stable increase in EELV on sleep disordered breathing and sleep architecture in OSA patients during NREM sleep.

Methods

Subjects

We calculated that we needed 12 subjects to have 80% power to detect 4 events (apneas plus hypopneas) per hour difference with a SD of 3 events per hour and an alpha of 0.05. We recruited sleep apnoea patients with moderate to severe OSA determined by overnight diagnostic polysomnogram, using AASM defined criteria (12). The subjects were currently treated with continuous positive airway pressure (CPAP). The protocol was approved by the Human Subjects Committee at Brigham and Women’s Hospital. All subjects provided informed written consent prior to participation in the study. Subjects with medical disorders potentially affecting chest compliance or the upper or lower airway (other than obstructive sleep apnoea and obesity) were excluded.

Equipment and Measurements.

Airway pressure was recorded at the level of the epiglottis with a pressure-tipped catheter (Millar instruments inc, Houston). Prior to insertion of the catheter, both nostrils were decongested with 0.05% oxymetazoline hydrochloride and one nostril was anesthetized with 1-2 ml of 4% lidocaine topical spray. Subjects breathed through a nasal mask (Respironics, Murraysville, PA) with airflow measured with a pneumotachograph (Hans Rudolph, Kansas City, MO) and pressure transducer (Validyne corp. Northridge, CA). End-tidal CO2 was sampled at the mask using a calibrated infrared CO2 analyzer (BCI corp, Waukesha).

Wake/sleep states were determined using standard electroencephalography (EEG), chin electromyogram (EMG) and electrooculogram (EOG). Lung volume was manipulated with the subject lying supine in a head-out rigid shell (Porta-lung inc, Murraysville, PA) adapted with a vacuum/blower attachment (ShopVac, Williamsport, PA) to increase or decrease extrathoracic pressure. Changes in EELV were measured with two pairs of magnetometers (EOL Eberhard, Oberwil, Switzerland) placed in the antero-posterior axis of the chest and abdomen using a standardized formula previously validated by Kono and Mead(13). Calibration was performed during quiet breathing supine: the changes in chest wall and abdomen anterioposterior diameter were averaged over twelve breaths and combined with the pneumotachograph data. Each change in AP diameter values was entered into the following equation describing the relationship between tidal volume and chest/abdominal excursion: TV = X (4 RC + AB). Tidal volume (TV) is determined using X, a coefficient determined in the calibration procedure for a given individual. All calibration maneuvers were performed with subjects instrumented, lying supine in the rigid shell. This posture was maintained throughout the study.
Protocol

The CPAP was initially set at the patient’s prescribed level. After achieving stable non-rapid eye movement (NREM) sleep, the CPAP level was adjusted to the minimum required to prevent flow limitation. This was accomplished by adjusting the CPAP until the flow signal (pneumotachograph) and the pressure signal at the epiglottis consistently demonstrated similar inspiratory curves. Flow limitation was defined as at least a 1 cm H2O decrement in epiglottic pressure without an associated increase in inspiratory flow (14).

The increase in lung volume above the baseline EELV associated with this level of CPAP (defined as “CPAP lung volume”) was determined with the four magnetometer coils during NREM sleep. CPAP was then stopped and the subjects were studied for 1 hour in each of three conditions (in random order): 1) without any treatment (baseline); 2) at the “CPAP lung volume”, with the increased lung volume being reproduced by negative extrathoracic pressure alone, without CPAP (Lung Volume 1); and 3) 500 ml above the “CPAP lung volume” (Lung Volume 2).

Data Analysis

The above-mentioned signals were recorded on both a 16 channel polygraph (Grass model 78) and a personal computer. Each signal (EEG, EOG, EMG, EKG, etCO2, abdominal and rib cage magnetometers, flow, tidal volume, mask and epiglottic pressure) was analyzed using signal-processing software (Spike 2, CED Ldt. Cambridge, UK).

The recording of each lung volume condition (baseline, LV1 and LV2) was analyzed in a blinded fashion. Blinding was achieved by splitting the recording into 1 hour segments for each condition. The 1 hour segments were given a unique name and the extrathoracic pressure channel was removed to prevent recognition of the condition. The segments were staged for sleep and breathing disturbances. The specific variables measured were: apnoea / hypopnoea index (AHI), 3% oxygen desaturation index, arousal index, mean oxygen saturation and sleep stage distribution. Apnoeas and hypopnoeas were scored according to the Chicago criteria (15) with the respiratory effort being determined with the abdominal and thoracic magnetometers instead of bands. An arousal was defined as an abrupt shift in EEG frequency which includes theta, alpha, and/or a frequency higher than 16 Hz (but not spindles) of 3 seconds or greater in duration. Arousals longer than five minutes and REM periods were not included in the recording time used to determine the indexes. A spectral analysis was also performed on the C3 A2 EEG channel which was digitized at 128 Hz frequency. The time in apnoea was estimated by the time spent with an inspiratory flow lower than or equal to 0.1 l/s. The time spent with a SaO2 < 90% was also determined for each condition using a custom script (Spike 2 CED Ldt, Cambridge, UK).

All data are reported as means and standard error of the mean (SE). A p value < 0.05 was considered significant. A repeated measure ANOVA (or an ANOVA on the ranks when data were not normally distributed) was performed to compare the AHI, arousal index,
oxygen desaturation index, mean saturation, power spectrum, time spent in the different sleep stages and the time spent in apnoea or under 90% SaO2. The p for each ANOVA represents the p value for heterogeneity. We used a post hoc Tukey test to determine if there was a significant difference between baseline, lung volume 1 and lung volume 2 for the main outcomes (AHI and 3% desaturation index).

Results:

Sixteen patients were recruited for this study. Three patients couldn’t complete the protocol because they couldn’t sleep inside the iron lung and one patient because she couldn’t sleep without her CPAP. Twelve patients completed the protocol (5 females, 7 males), age 47.5 (2.8) (range 32-63) years (table 1). The mean AHI from the diagnostic polysomnogram was 41.5 (7.9) events/hour of sleep. The mean CPAP level required to prevent upper airway flow limitation was 12.9 (4.0) cm H2O. At this CPAP level, the mean EELV increase was 770 (165) ml above the baseline EELV during sleep (without CPAP). The mean negative extrathoracic pressure required to induce the same EELV increase (lung volume 1) was -8.9 (2.2) cm H2O. The mean negative extrathoracic pressure required to induce “lung volume 2” (EELV increase of 529 (30) ml above lung volume 1 or ~ 1300 ml above baseline) was –14.0 (3.2) cmH2O.

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SE</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>47.5</td>
<td>2.8</td>
<td>32 – 63</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>34.9</td>
<td>2.2</td>
<td>25.6- 46.8</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>41.5</td>
<td>7.9</td>
<td>15-99</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7/5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The results of the main outcomes are reported for each condition in table 2. With increased EELV there was a significant decrease in AHI (figure 1), arousal index, and 3% oxygen desaturation index (figure 2) as well as a significant increase in the mean SaO2. The AHI and the type of respiratory events that occurred in each condition are depicted in figure 1. For AHI and 3% oxygen desaturation index we also performed a post hoc Tukey test: For both the difference was significant between baseline and lung volume 1 (p<0.05) and between baseline and lung volume 2 (p<0.05); however the difference between lung volume 1 and lung volume 2 was not significant.
Table 2. Main results: mean (95% Confidence Interval)

<table>
<thead>
<tr>
<th></th>
<th>Baseline Supine</th>
<th>Lung volume 1</th>
<th>Lung volume 2</th>
<th>p value for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AH1 (events/h)</td>
<td>62.3 (42.3 - 82.3)</td>
<td>37.2 (27.4 - 47.0)</td>
<td>31.2 (18.1 - 44.3)</td>
<td>p=0.009</td>
</tr>
<tr>
<td>Arousal (events/h)</td>
<td>63.8 (46.2 - 81.4)</td>
<td>43.5 (31.2 - 55.8)</td>
<td>38.2 (27.2 - 49.2)</td>
<td>p=0.039</td>
</tr>
<tr>
<td>3% Desat (events/h)</td>
<td>43.0 (23.2 - 62.8)</td>
<td>16.1 (5.5 - 26.7)</td>
<td>12.3 (1.9 -22.7)</td>
<td>p=0.002</td>
</tr>
<tr>
<td>Mean O2 sat (%)</td>
<td>95.4 (94.8 - 96.0)</td>
<td>96.0 (95.6 - 96.4)</td>
<td>96.3 (95.7 - 96.9)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>% Wake</td>
<td>17.4 (10.1 - 24.7)</td>
<td>10.1 (6.0 - 14.2)</td>
<td>8.6 (4.1 - 13.1)</td>
<td>p=0.071</td>
</tr>
<tr>
<td>% Stage 1</td>
<td>27.8 (20.9-34.7)</td>
<td>13.5 (9.6-17.4)</td>
<td>14.1 (5.7-22.5)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>% Stage 2</td>
<td>54.8 (41.1 - 68.5)</td>
<td>66.5 (54.0 - 79.0)</td>
<td>77.2 (67.0 - 87.4)</td>
<td>p=0.009</td>
</tr>
<tr>
<td>Beta Power</td>
<td>11.5 (8.4 - 14.6)</td>
<td>8.6 (6.6 - 10.6)</td>
<td>7.9 (5.7 - 10.1)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Alpha Power</td>
<td></td>
<td>7.1 (4.9 - 9.3)</td>
<td>7.2 (4.8 - 9.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Theta Power</td>
<td>10.9 (7.8 - 14.0)</td>
<td>14.9 (10.6 - 19.2)</td>
<td>14.7 (12.2 - 17.2)</td>
<td>p=0.004</td>
</tr>
<tr>
<td>DeltaPower</td>
<td>46.4 (33.7 - 59.1)</td>
<td>55.7 (35.5 - 75.9)</td>
<td>48.8 (35.1 - 62.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

For baseline, lung volume 1 and lung volume 2 conditions respectively, the percentage of time spent with an inspiratory flow lower or equal to 0.1 l/s was 22.9 (3.9) %, 15.3 (3.8) % and 13.2 (3.8) % (p=0.018). The percentage of time spent with a SaO2 < 90% was respectively 4.7 (2.0) %, 0.8 (0.4) % and 0.3 (0.3) % (p =0.012).

When EELV was increased there was a significant decrease in the percentage of stage 1 NREM sleep, as well as an increase in the percentage of stage 2 NREM sleep (table 2). There was also a trend toward a reduction in the percentage of time awake (p value for heterogeneity = 0.071). Only four subjects had slow wave sleep (stage III/IV) during the recordings, which only occurred when lung volume was increased and never at baseline. The power density (µV^2/Hz) of Beta waves decreased (p=0.001) and the power density of theta waves increased (p=0.004) when EELV was increased. Delta power tended to increase and alpha power to decrease but these differences did not reach statistical significance.
Discussion:

These results demonstrate the influence of lung volume changes on apnoea severity and sleep architecture in OSA patients during NREM sleep. When EELV was increased, the AHI, the arousal index and the oxygen desaturation index all decreased significantly. Moreover, “light sleep”, as measured by the percentage of stage 1 and beta power, decreased when EELV was increased.

Previous animal and human studies suggest that the mechanism underlying these results is probably an increase in upper airway stiffness and size with increased lung volume due to caudal traction on the pharyngeal airway. Studies in normal adult humans (without obstructive sleep apnoea) have shown that, during wakefulness and sleep, changes in lung volume result in important variations in upper airway mechanics (16-19). Moreover pharyngeal airway size, as measure by CT scan (20, 21) or acoustic reflection (22), increases with lung inflation and decreases at lower lung volume. Lastly it has been shown that OSA patients exhibit greater lung volume related dependence of upper airway size than non apnoeic individuals both in men (21) and women (22).

Because the subjects we studied were overweight or obese (like most sleep apnoea patients), we suspect that their diaphragm was pushed upwards (cranially) when lying on their back. The negative extrathoracic pressure applied almost certainly pulled the diaphragm and trachea to a more caudal position, thereby increasing the traction on the upper airway making it less collapsible. Other authors have found that the AHI can be considerably reduced when obese OSA patients sleep in a semi recumbant position (24), which likely corroborates this hypothesis. In the present study, there was also a trend toward a correlation between the extent of the reduction in AHI between baseline and lung volume 2 and the BMI (correlation coefficient = 0.53, p=0.077). This could suggest that the more obese patients tend to have a bigger effect of lung volume increase.

Another possibility is that an increase in EELV led to an overall increase in the SaO2 due to improved ventilation/perfusion matching that could lead to decreased SaO2 fluctuations. This reduction in chemical stimuli fluctuations may have stabilized respiratory control, decreasing the risk of cyclic breathing.

A previous study from our group demonstrated an important effect of lung volume on the CPAP level required to prevent upper airway flow limitation, suggesting that increments in lung volume may be one of the mechanisms by which CPAP eliminates disordered breathing during sleep. In the present study, we demonstrated that an increase in lung volume alone (without CPAP) is able to significantly decrease the apnoea and hypopnoea frequency, which supports this hypothesis. The rest of the effect of CPAP is likely due to a splinting effect of positive airway pressure on the upper airway, maintaining a positive transmural pressure throughout the respiratory cycle.

Series et al previously conducted a study where the EELV was increased by 500 cc during sleep in OSA subjects (25, 26). They observed a decrease in the severity of oxygen desaturations, which is confirmed by our results. However, in contrast to our
results, they found no effect on sleep structure and a non-significant decrease in AHI when EELV was increased, despite studying their subjects for a longer period of time in each condition. There are several possible explanations: First we induced a larger increase in lung volume (770 and 1300 ml compared to 500 ml), which probably achieved a greater traction on the trachea and on the upper airway. Second, we didn’t use the same technique to measure the lung volume changes: Series et al. determined during wakefulness the negative pressure required to induce a 500 ml increase in lung volume and then applied this negative pressure during the night. It is possible that there were behavioural influences during the awake manoeuvre. In our study, we constantly monitored the lung volume during sleep to be sure that the lung volume increase was maintained during the night. It is possible that our technique allowed us to achieve a more precise and constant lung volume increase. Third, the population we studied had 90.7% obstructive apnoeas at baseline (7.9% mixed and 1.4% central apnoea), whereas the subjects studied by Series et al had only 56.3% obstructive apnoeas (36.8% mixed and 6.9% central apnoea), even though the definition of central and mixed apnoea may have evolved between 1989 and 2005. It is therefore possible that upper airway mechanics was the main cause of sleep apnoea in our population, and that respiratory control instability made a greater contribution to apnoea in the population studied by Series et al. Indeed, one of our subjects who had 14% central sleep apnoeas at baseline had an increase in time spent in apnoea when EELV was increased, despite the fact that the AHI decreased and SaO2 improved. It is possible that for a subset of sleep apnoea patients with a high increased ventilatory instability, an increase in lung volume could trigger a “Hering Breuer” reflex inhibiting inspiration and thus extending the time in apnoea.

Finally our population was probably more obese (mean BMI 34.9) than the Series population (124% of ideal body weight). This could have induced a more important effect of increased lung volume in our study because the diaphragm of obese patients is pushed more rostrally by abdominal fat compared to less obese patients. However, further work will be needed to define which subgroups of sleep apnea patients respond best to manipulations in lung volume.

As mentioned in the results, there was a significant decrease in AHI between baseline and both lung volume 1 and 2. However the decrease in AHI between lung volume 1 and 2 did not reach significance and some patients even had a higher AHI at lung volume 2 compared with lung volume 1. This may be due either to a ceiling effect of increasing EELV on AHI or to arousals secondary to the discomfort of higher negative pressure in the iron lung, which could have induced some respiratory instability in these patients.

There are several limitations to this study. First, because the subjects were studied during supine NREM sleep only, these results may not apply to other body positions or REM sleep. The supine posture is usually the position in which the greatest respiratory disturbances are recorded, possibly in part due to abdominal fat applying pressure on the diaphragm leading to decreased lung volume and decreasing the traction on the upper airway by the trachea. If this assumption is correct, it is possible that, when subjects lay on their side or prone, the effect of negative extrathoracic pressure would be smaller.
Second, while Series et al studied their subjects for the whole night in each of the two conditions (baseline, + 500 ml EELV), we studied our subjects for one hour in each of the three different conditions (baseline, + 770 ml, + 1300 ml). However with our sample size (12 subjects) we had 80% power to detect a difference of 4±3 events per hour between the three conditions using an ANOVA. Moreover this design gave us homogeneous data, collected in the exact same conditions during the same night. In addition, the randomization of the order of the conditions prevented a “time of the night” bias. Thus, although this is a potential problem, we doubt it influenced our results.

Finally, a direct effect of the iron lung negative pressure on the neck and upper airway cannot be completely excluded. A decrease in the pressure around the neck when lung volume was increased could have “unloaded” the upper airway making it less collapsible. However, when the pressure in the iron lung was decreased, the webbing making the seal around the neck was shifted inside the chamber, which would only further decrease the neck area potentially exposed to the negative pressure in the lung. Thus we doubt this contributed to the reduction in sleep disordered breathing.

In summary, these results show that an increase in lung volume yields a decrease in sleep disordered breathing and improves sleep architecture in sleep apnoea patients during NREM sleep. Although an iron lung may well be more cumbersome than nasal CPAP therapy, our data do suggest that increments in lung volume may be one of the mechanisms by which sleep disordered breathing is improved by CPAP. Thus, increased lung volume could be a direct therapeutic target for sleep apnoea patients using, for example, an expiratory resistance as suggested by Mahadevia et al (27).
References:


Legends:

Table 1: Demographic data on the twelve subjects included in the study

Table 2: Main results: Mean (SE). AHI=Apnoea + Hypopnea Index, Arousal = nb of arousal per hour, Desat 3% = nb of 3% oxygen saturation drop per hour, Mean sat = mean oxygen saturation, Beta, Alpha, Theta and Delta power are defined in the text.

Figure 1: Type and number of respiratory event per hour at each lung volume

Figure 2: Mean (SE) number of respiratory events per hour (AHI), arousals per hour and number of 3% oxygen drops per hour at each lung volume
Figure 1.

![Bar chart showing number of events per hour across baseline, Lung Vol 1, and Lung Vol 2. The chart indicates specific statistical comparisons with P<0.05 and NS.](image)

Figure 2

![Line graph showing events per hour versus lung volume increase (ml). The graph includes AHI, 3% Desat Index, and Arousal Index.](image)
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