Changes in lung volume and diaphragm muscle activity at sleep onset in obese obstructive sleep apnea patients vs. healthy-weight controls

Daniel L. Stadler,1,2 R. Doug McEvoy,1,2,3 Jana Bradley,1 Denzil Paul,1 and Peter G. Catcheside1,2,3
1Adelaide Institute for Sleep Health, Repatriation General Hospital, Daw Park; 2School of Medical Sciences, Discipline of Physiology, University of Adelaide, Adelaide; and 3Department of Medicine, Flinders University, Bedford Park, South Australia, Australia

Submitted 15 December 2009; accepted in final form 11 August 2010

OBSTRUCTIVE SLEEP APNEA (OSA) is a common sleep disorder characterized by repetitive periods of upper airway (UA) collapse during sleep. Male sex and obesity are two key predictors of OSA (4, 38), but the mechanisms via which these factors contribute to OSA remain unclear. In addition to an anatomically smaller airway (15) and an abrupt fall in UA dilator muscle activity following sleep onset (6, 16, 25), reduced lung volume is also likely to contribute to poor UA function in obese OSA patients (11, 27). A decrease in lung volume potentially reduces the degree of axial tension (caudal traction) exerted on the UA and, therefore, the propensity for UA collapse. Our laboratory recently demonstrated increased UA collapsibility with experimental abdominal compression during sleep in OSA patients (26), strongly supporting mechanical effects of abdominal obesity on UA function. These effects are likely to be most evident in the supine posture and during sleep, particularly at the wake-sleep transition when other compensatory mechanisms become diminished, and may at least partly explain sex and obesity influences in OSA.

Stanchina et al. (27) demonstrated important effects of changes in lung volume on UA function, with a decrease in lung volume during sleep resulting in marked increases in UA collapsibility and pharyngeal resistance. Data from animal studies suggest that changing lung volume may alter UA stiffness by modulating tracheal traction on the UA (21, 31). End-expiratory lung volume (EELV) decreases when healthy-weight individuals move from upright to the supine posture (33, 36), largely due to cranial displacement of the diaphragm (32). Despite increased thoracoabdominal mass loading and intra-abdominal pressure (23), there is little change in EELV following a similar postural transition in obese individuals (33, 36). One possible explanation is that obese individuals may actively defend against a fall in lung volume via increased minimum expiratory (tonic) diaphragm muscle activity (eEMGdia). Muller (17) identified augmented tonic diaphragmatic activity with external abdominal compression (17), consistent with active defense of lung volume, at least during wakefulness. Consequently, obese OSA patients may have augmented tonic diaphragm activity to help preserve lung volume and UA tension, such that transient reductions in diaphragm activity at sleep onset could lead to exaggerated lung volume changes and propensity for UA collapse.

Data concerning the magnitude of lung volume and trans-diaphragmatic pressure changes at sleep onset in obese OSA patients vs. healthy-weight controls are currently lacking. In healthy-weight individuals, EELV has been shown to fall by ~15% during sleep (2, 14) and is profoundly reduced following induction of general anesthesia in the obese (18). Consequently, a fall in EELV at sleep onset, particularly in obese OSA individuals, could importantly contribute to an acute increase in the propensity for UA collapse at sleep onset. While it is difficult to separate effects of obesity per se from other potential pathogenic factors operating in OSA patients, lung volume and tracheal traction effects are likely dominated by thoracoabdominal mass loading effects of obesity itself. Consequently, we elected to first establish if diaphragm muscle activity and lung volume changes occurring in the immediate sleep-onset period are any different in obese OSA patients vs. healthy-weight controls before further separate studies de-
signed to separate obesity from other potential contributory effects in OSA.

The aims of this study were, therefore, to compare eEMGdia during wakefulness between obese OSA patients and age-matched, healthy-weight controls and to compare changes in inspiratory diaphragm muscle activity (iEMGdia), eEMGdia, end-expiratory gastric (Pga) and transdiaphragmatic pressure (Pdi), and EELV following sleep onset between these two groups. Given sleep onset is frequently associated with respiratory events in OSA patients, we also aimed to investigate if the magnitude of lung volume, iEMGdia, eEMGdia and end-expiratory Pga, and Pdi changes differ according to the degree of UA collapse following sleep onset. We hypothesized that eEMGdia would be higher during wakefulness in obese OSA patients and that there would be a greater fall in lung volume, iEMGdia, eEMGdia and end-expiratory Pga, and Pdi following sleep onset in obese OSA patients compared with healthy-weight controls, with a greater reduction at sleep onset shortly followed by respiratory events.

METHODS

Participant Selection

Obese [body mass index (BMI) 30–40 kg/m²] male OSA patients with moderate-to-severe OSA, aged between 18 and 65 yr, and healthy-weight (BMI ≤ 25 kg/m²), age-matched male subjects without sleep-disordered breathing participated. Nasal pressure recordings of airflow were undertaken, and OSA diagnosis and severity was assessed using a thin air-perfused nasal catheter [see Hilditch et al. (13) for further detail]. This catheter was advanced 1–2 cm below the base of the tongue under direct visualization, taped at the nose, and connected to another pressure transducer (MP45; Validyne Engineering, Northridge, CA).

Participants were fitted with a nasal mask (ComfortGel Nasal Mask, Philips Respironics, Murrysville, PA) attached to a non-re-breathing valve (Series 2600, Hans Rudolph, Kansas City, MO), equipped with sealable luer ports to accommodate each catheter. Inspiratory nasal flow and volume were measured by a pneumotachograph (PT16, Jaeger, Germany) attached to the inspiratory port of the mask. End-tidal Pco₂ (Capstar-100, CWE) and mask pressure (MP45; Validyne Engineering, Northridge, CA) were also measured. Pdi was determined as Pga-Pes at end-expiration.

Intraesophageal EMGdia activity. EMGdia was recorded via a series of nine equally spaced (1-cm interelectrode distance) stainless steel rings situated between the Pga and Pes balloons of the multilumen catheter. Electrodes were connected in sequentially adjacent pairs [electrodes 1 (most proximal) and 2, 2 and 3, etc.] to an amplifier (model 15LT, Grass Instruments, Quincy, MA) and band-pass filtered (0.3–1 kHz). To provide eight bipolar EMG channels with an interpair distance of 1 cm. Once connected, catheter position was further adjusted to achieve maximal iEMGdia activity near the center of the electrode array, while maintaining positive Pga and negative Pes swings during inspiration. The catheter was then secured at the mask using a tight-sealing stainless steel luer (SSA1380, S4J Manufacturing Services, Cape Coral, FL).

Changes in lung volume. Abdominal and thoracic excursions were measured continuously using two pairs of magnetometer coils (Polhemus Liberty, Colchester, VT) placed in the anterior-posterior axis of the chest and abdomen (26). See the online supplement for further details on lung volume measurements.

Data acquisition. All conventional sleep-related signals were recorded on a Compumedics data-acquisition system (E-series, Compumedics, Melbourne, Australia). X, Y, and Z coordinates for each of the four magnetometer sensors were acquired on a second computer at a sample rate of 120 Hz (Polhemus Liberty). The remaining signals were recorded on a 32-channel data-acquisition system at 200 Hz, except for EMGdia channels, which were sampled at 1 kHz (DI-720 DATAQ Instruments). To facilitate accurate time matching (within ~100 ms) between the three recording system, a computer-actuated event mark signal was simultaneously placed on all three acquisition systems approximately every hour.

Protocol

Following instrumentation and while supine, participants underwent a 5-min baseline period in which they were instructed to remain relaxed, with their eyes open, breathing solely through their nose. For recording maximal iEMGdia activity, participants then performed a minimum of three maximal Mueller maneuvers by maximally inspirating against a closed glottis at end-expiration until plateaus in both iEMGdia and Pes activity were reached. The mouth was then taped to ensure nasal breathing, the lights switched off, and the participant allowed to fall asleep in the supine position (confirmed by a position sensor and video camera monitoring). Following approximately five sleep-disordered breathing events in the obese OSA patients or a similar time period (~5 min) in control subjects, participants were fully awoken by a researcher and asked to keep their eyes open for at least 1 min before a subsequent sleep onset opportunity. This cycle was continued throughout the remainder of the night. If the participant was unable to sleep due to discomfort, they were allowed to briefly change postures for a short period of time (~15 min), then awoken if necessary and asked to return to the supine posture to continue the experiment. Nonsupine periods were excluded from analysis.

Data Analysis

Sleep recordings were analyzed by an accredited sleep technologist using 30-s epochs and Rechtschaffen and Kales criteria for staging.
sleep (20). Arousals and respiratory events were scored according to standard criteria (1, 5). Sleep onset was defined as an EEG activity followed by ≥10 s of θ EEG activity. Each sleep onset was then categorized according to the absence or presence of scored respiratory events within the 30-s period immediately following sleep onset as either 1) stable breathing; 2) hypopnea (a ≥10-s event defined by either >50% decrease in flow compared with the previous 2 min of breathing, or a discernable decrease in effort followed by an arousal or a ≥3% desaturation); or 3) apnea sleep onsets (a ≥10-s event defined by complete cessation of inspiratory airflow followed by an arousal or ≥3% desaturation). Wake-sleep transitions were only included for data analysis if there was at least 30 s of wakefulness before sleep onset and at least three inspiratory efforts (breaths with or without obstruction) of continuing sleep following sleep onset. Transitions were excluded from analysis if any one of the following occurred: 1) a respiratory event (hypopnea, apnea, central, mixed) or ≥3% oxygen desaturation was scored within 30 s before sleep onset; 2) if a swallow was present within the 30 s before sleep onset; or 3) mask leaks or mouth breathing was evident before or following the wake-sleep transition.

For each wake-sleep transition meeting the inclusion criteria for analysis, breaths either side of the transition were numbered relative to the transition from −5 to +3. Inspiratory minute ventilation (VI), iEMGdia, and eEMGdia were calculated for each breath (see online supplement for calculation of iEMGdia and eEMGdia data) and expressed as a percentage of the mean of breaths −5 to −2, excluding breath −1 to avoid potential confounding by α-θ EEG changes within this breath. Several control subjects showed near zero end-expiratory Pdi and Pga at baseline. Consequently, changes in end-expiratory Pdi and Pga across the wake-sleep transition were evaluated as absolute changes from the mean of breaths −5 to −2, rather than percentage change from baseline pressures. EELV changes were assessed as previously described (26) (see online supplement for further information for EELV measurements).

Respiratory variables, including VI, tidal volume, breathing frequency, end-tidal PCO2, UA airflow resistance (RUA), iEMGdia, eEMGdia (% maximum), iEMGdia, eEMGdia (μV), and end-expiratory Pga and Pdi were calculated on a breath-by-breath basis and averaged across breaths −5 to −2 before sleep onset, providing average presleep onset data for each variable.

For hypopnea and apnea transitions, breath-by-breath changes in VI, EELV, iEMGdia, and eEMGdia were also examined in the last two breaths leading into respiratory events and the first two breaths/inspiratory efforts during events.

Statistical Analysis

Anthropometric data were compared between groups with two-sample Student’s t-tests. Presleep onset group differences were examined using linear mixed-model analysis (SPSS 16.0, SPSS, Chicago, IL). In addition, for VI [% change (Δ) from baseline], EELV (ml Δ from baseline), iEMGdia and eEMGdia (%Δ from baseline), end-expiratory Pga and Pdi (%Δ from baseline) variables, effects of group and group × postsleep onset breath number interaction were examined using linear mixed-model analysis, with breath number and sleep onset number as repeated factors with an autoregressive covariance structure and subject as a random effect each with a separate intercept. Subgroup analyses were conducted to further examine respiratory event severity effects within each group separately. Linear mixed models were also used to examine differences in VI (%Δ from baseline), EELV (ml Δ from baseline), and iEMGdia and eEMGdia (%Δ from baseline) variables for the period leading into hypopneas and apneas. Custom contrasts within each mixed model were also undertaken to calculate VI, EELV, and muscle activity differences between average wakefulness (breaths −5 to −2) and postsleep onset breaths, and the first breath/inspiratory effort in hypopneas and apneas. Relationships between changes in EELV vs. changes in eEMGdia, and changes in EELV vs. changes in peak inspiratory flow (PIF) between baseline and the third postsleep onset breath for each sleep onset transition type were examined using Pearson correlation. All data are expressed as means ± SE. P < 0.05 was considered significant.

RESULTS

Anthropometric and Presleep Onset Data

A total of nine obese OSA patients and eight control subjects were recruited. Data from one obese OSA patient were excluded due to significant mask leaks. Complete presleep measurements of breath-by-breath ventilatory data were obtained in eight patients and eight controls. One control subject could not tolerate the multilumen catheter, and RUA measurements could not be assessed in one obese OSA patient and one control subject due to catheter blockage. Thus end-expiratory Pga and Pdi measurements were obtained in eight obese OSA patients and seven control subjects, while RUA measurements were obtained in seven obese OSA patients and seven control subjects. Two obese OSA patients and one control subject could not reliably perform Mueller maneuvers. Consequently, between-group comparisons in iEMGdia and eEMGdia (% maximum) data are represented by six obese OSA and six control individuals.

Anthropometric variables in each group are presented in Table 1. Both groups were matched for age and had healthy lung function, while OSA patients were significantly heavier than controls and had severe OSA by design. Maximal EEMGdia was not significantly different between groups (OSA vs. controls, 29.7 ± 4.0 vs. 23.6 ± 4.3 μV, P = 0.27).

Average presleep onset (sleep onset categories combined) data are shown in Table 2. VI, RUA, end-expiratory Pga, Pdi, iEMGdia (% maximum), and iEMG (μV) were all significantly higher in the obese OSA group before sleep onset [VI, P = 0.007; RUA, P < 0.001; Pga, P = 0.001; Pdi, P = 0.008; iEMGdia (% maximum), P = 0.019; and iEMG (μV), P = 0.006]. There was a trend for increased eEMGdia (μV) in the OSA group (P = 0.063).

Changes at Sleep Onset

There were, on average, 20.9 ± 2.9 (range 13–33) and 22.9 ± 2.6 (range 14–35) sleep onsets in obese OSA patients and control participants respectively, that met the inclusion criteria for analysis. Sleep onsets with respiratory events were significantly more frequent in obese OSA patients than controls with 78/167 (46.7%), 48/167 (28.7%), and 41/167 (24.6%) of sleep

| Table 1. Anthropometric data of obese OSA patients and controls |
|-----------------------------|-----------------------------|
|                             | OSA                        | Controls                    |
| Age, yr                     | 47.4 ± 3.4                 | 48.3 ± 3.9                  |
| BMI, kg/m²                  | 35.0 ± 1.4*                | 23.8 ± 0.5                  |
| FEV1, % predicted           | 94.9 ± 5.6                 | 104.8 ± 3.6                 |
| FVC, % predicted            | 90.9 ± 6.7                 | 102.0 ± 5.1                 |
| AHl events/h                | 73.5 ± 9.2*                | 10.0 ± 1.6                  |

Values are means ± SE; N = 8 obese obstructive sleep apnea (OSA) patients and 8 controls. Age, body mass index (BMI), forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and apnea-hypopnea index (AHI) values are shown. *P < 0.05, obese OSA patients vs. controls.
Table 2. Average presleep onset (breaths −5 to −2) data in obese OSA patients and controls

<table>
<thead>
<tr>
<th></th>
<th>OSA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vt, l/min</td>
<td>8.1 ± 0.5§</td>
<td>6.4 ± 0.2</td>
</tr>
<tr>
<td>Vt, liter</td>
<td>0.53 ± 0.04</td>
<td>0.46 ± 0.03</td>
</tr>
<tr>
<td>Fsb, breaths/min</td>
<td>16.0 ± 1.0</td>
<td>14.4 ± 0.3</td>
</tr>
<tr>
<td>PrCO2, Torr</td>
<td>41.9 ± 0.6</td>
<td>44.1 ± 1.3</td>
</tr>
<tr>
<td>Rl, cmH2O·L−1·s−1</td>
<td>15.3 ± 1.0§</td>
<td>9.0 ± 0.6</td>
</tr>
<tr>
<td>Pga, cmH2O†</td>
<td>12.3 ± 0.8§</td>
<td>6.6 ± 1.5</td>
</tr>
<tr>
<td>Pdi, cmH2O†</td>
<td>5.3 ± 0.5§</td>
<td>0.2 ± 1.8</td>
</tr>
<tr>
<td>iEMGdia, %maximum‡</td>
<td>20.6 ± 1.6§</td>
<td>14.6 ± 1.7</td>
</tr>
<tr>
<td>eEMGdia, %maximum‡</td>
<td>10.1 ± 0.6</td>
<td>9.2 ± 0.8</td>
</tr>
<tr>
<td>iEMGdia, µV‡</td>
<td>5.9 ± 0.5§</td>
<td>3.3 ± 0.5</td>
</tr>
<tr>
<td>eEMGdia, µV‡</td>
<td>2.9 ± 0.3</td>
<td>2.0 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE; N = 8 obese OSA patients and 8 controls, †N = 7 obese OSA patients and 7 controls, ‡N = 6 obese OSA patients and 6 controls. Minute ventilation (Vt), tidal volume (Vt), breathing frequency (Fsb), end-tidal PCO2 (PrCO2), upper airway resistance (Rl), end-expiratory gastric (Pga), and average inspiratory (iEMGdia) and tonic expiratory diaphragm activity (eEMGdia) are shown. §P < 0.05, obese OSA patients vs. controls.

onsets classified as stable, hypopnea, and apnea wake-sleep transitions, respectively, in the obese OSA patients vs. 149/179 (83.2%), 30/179 (16.8%), and 0/179 in the control participants (χ², P < 0.001).

Figure 1 shows changes in Vt across the wake-sleep transition in the obese OSA patients and control subjects for all sleep onsets combined (Fig. 1A) and with stable sleep, hypopnea, and apnea transitions shown separately for the obese OSA patients (Fig. 1C) and stable sleep and hypopnea transitions in the control subjects (Fig. 1E). There was a significantly greater and more rapid reduction in Vt in obese OSA patients (Fig. 1A, group, P = 0.009; group × breath, P < 0.001). By analytic design, the fall in Vt following sleep onset was dependent on the degree of subsequent airway obstruction (Fig. 1, C and E, category, P < 0.001).

EELV significantly decreased by 61.4 ± 8.0 and 34.0 ± 4.2 ml by the third sleep onset breath from wakefulness in obese OSA patients and control subjects, respectively (Fig. 1B, wake vs. postsleep onset breath 3, P < 0.001). While there were no between-group differences in the overall reduction in EELV following sleep onset (P = 0.528), there was a greater decline in EELV over time following sleep onset in the obese OSA patients (Fig. 1B, group × breath, P = 0.007), with this group experiencing greater decrements in EELV over time in apnea and hypopnea transitions (Fig. 1D, category × breath, P < 0.001). While there was no category × breath interaction effect in the control group, the overall decrease in EELV was significantly greater in hypopnea compared with stable breathing transitions (Fig. 1F, category, P = 0.01). By the third breath following sleep onset in the obese OSA group, EELV had statistically significantly fallen in each transition category (stable, 25.9 ± 10.8 ml, P = 0.017; hypopnea, 84.7 ± 16.3 ml, P < 0.001, and apnea, 118.9 ± 16.4 ml, P < 0.001, Fig. 1D). Similar decrements in lung volume by the third postsleep onset breath were evident for each transition category in the controls (stable, 34.2 ± 4.3 ml, P < 0.001; hypopnea, 41.0 ± 13.1 ml, P = 0.002, Fig. 1F).

Changes in iEMGdia and eEMGdia activity following sleep onset are shown in Fig. 2. iEMGdia and eEMGdia showed significantly greater (Fig. 2A, P = 0.02, and Fig. 2B, P = 0.017, respectively) and more rapid (Fig. 2A, group × breath, P < 0.001, and Fig. 2B, group × breath, P < 0.001, respectively) reductions following sleep onset in the obese OSA group.
group, with activity significantly decreasing by a maximum of 14.5 ± 1.6% of baseline (P < 0.001) and 8.3 ± 1.2% of baseline (P < 0.001) from wakefulness, respectively. In the obese OSA group, decreases in iEMGdia and eEMGdia were significantly greater and more rapid when accompanied by respiratory events (Fig. 2, C and D, category, P < 0.001, category × breath, P < 0.001). iEMGdia and eEMGdia decreased by a maximum of 28.3 ± 2.7% of baseline (P < 0.001) and by 13.2 ± 2.6% of baseline (P < 0.001), respectively, for apnea transitions. In contrast, the control group showed no significant sleep onset category or sleep onset category × breath-dependent effects.

Relationships between changes in EELV and eEMGdia and changes in EELV and PIF from baseline to the third postsleep onset breath within each patient and category of sleep onset response are shown in Fig. 3. A and B, respectively. There was no significant relationship between eEMGdia and EELV when data from OSA patients and controls were combined (Fig. 3A; $r^2 = 0.06, P = 0.19$). Similarly, there was no significant relationship in either the obese OSA group (Fig. 3A; $r^2 = 0.06, P = 0.3$) or the control group (Fig. 3A; $r^2 = 0.04, P = 0.5$). Greater falls in EELV were associated with larger decrements in PIF for all group data combined (Fig. 3B; $r^2 = 0.27, P = 0.005$). While not statistically significant, there was a trend for a relationship in the obese OSA group (Fig. 3B; $r^2 = 0.18, P = 0.07$). A strong relationship was evident in the control group (Fig. 3B; $r^2 = 0.78, P < 0.001$).

Changes in end-expiratory Pga and Pdi following sleep onset are shown in Fig. 4. There were no group or interaction effects in changes in end-expiratory Pga following sleep onset (Fig. 4A). Similarly, there were no sleep onset category or sleep onset category × breath-dependent effects in changes in end-expiratory Pga in either the obese OSA group or the control group (Fig. 4C and E). However, there was a greater increase in end-expiratory Pdi over time following the wake-sleep transition in the control group (Fig. 4B, group × breath, $P =$.
Changes Preceding Respiratory Events

Figure 5 shows changes in $V_I$ preceding the onset of hypopneas and apneas in obese OSA patients (Fig. 5A) and preceding the onset of hypopneas in the control group (Fig. 5B). $V_I$ significantly decreased preceding respiratory events in both groups (breath effect, all $P < 0.001$), with $V_I$ decreasing by 51.0 $\pm$ 4.2 and 35.7 $\pm$ 8.1% below wakefulness levels by the first hypopneic breath (both $P < 0.001$) in the obese OSA patients and control subjects, respectively. EELV significantly decreased by 29.4 $\pm$ 12.3 ml ($P = 0.018$) and 89.6 $\pm$ 14.2 ml ($P < 0.001$) below wake levels by the first hypopneic breath and apneic inspiratory effort, respectively, in the obese OSA group (Fig. 5C). However, there were no sleep onset category or sleep onset category $\times$ breath differences between the decrease in EELV leading into hypopneas and the decline leading into apneas in this group. EELV also significantly decreased by 51.1 $\pm$ 14.8 ml below baseline levels ($P = 0.001$) by the first hypopneic breath in the controls (Fig. 5D). $iEMG_{dia}$ significantly decreased leading into hypopneas and apneas in the obese OSA group (Fig. 5E, breath effect, $P < 0.001$), with activity significantly decreasing by 20.9 $\pm$ 2.7% ($P < 0.001$) and 30.7 $\pm$ 2.8% ($P < 0.001$) by the first hypopneic and apnic breath, respectively. $iEMG_{dia}$ was also significantly lower during the period leading into apneas compared with the level preceding the onset of hypopneas ($P = 0.002$). Similar results were evident in $eEMG_{dia}$ in the obese group (Fig. 5G). $eEMG_{dia}$ was significantly below wakefulness levels at the beginning of hypopneas and apneas (hypopneas, 11.0 $\pm$ 3.0% below awake levels, $P < 0.001$; apneas, 11.1 $\pm$ 2.9% below awake levels, $P < 0.001$). In the control group, $iEMG_{dia}$ was 7.7 $\pm$ 3.7% below awake levels at the onset of hypopneas (Fig. 5F, $P = 0.038$), whereas $eEMG_{dia}$ was not significantly different compared with baseline at the onset of hypopneas (Fig. 5H).

DISCUSSION

The key findings of this study were that acute decrements in EELV accompany sleep onset in both obese OSA patients and healthy-weight controls, and that greater decrements in EELV and end-expiratory Pdi occur during wake-sleep transitions accompanied by respiratory events. However, despite obesity and substantially raised intra-abdominal pressure, consistent with previous reports (23, 29), there was no evidence for a greater overall sleep onset-related reduction in lung volume, end-expiratory Pga, or end-expiratory Pdi in obese OSA patients compared with healthy-weight controls. While some caution is warranted, given the small sample size, we estimate that lung volume changes in the order of $\sim$145 ml could have been detected between groups with 80% power and a two-tailed significance level of 0.05. Given that significant lung volume changes of this magnitude were detected accompanying apnea events following sleep onset, it appears unlikely that a similar magnitude or larger systematic effects of obesity on average lung volume responses at sleep onset in OSA patients, compared with healthy-weight controls for the same event severity, would have been missed due to type II error. Given more frequent hypopnea and apnea events and greater lung...
volume decrements over time in OSA patients compared with controls, more substantial lung volume changes were, nevertheless, a more common outcome following sleep onset in OSA patients compared with healthy-weight controls.

EELV significantly decreased in the order of ~100 ml at the onset of complete UA obstruction in the obese OSA group. The contribution of this decrement to the development of obstruction in the immediate postsleep onset period is not clear and cannot be separated from other potential effects of reduced respiratory drive on UA function. Nevertheless, this finding highlights that systematic lung volume changes with a similar time course to decrements in ventilatory drive do accompany respiratory events. This study also demonstrated a significant relationship between changes in EELV and PIF, supporting previous reports demonstrating significant modulating effects of EELV on UA function (10, 11, 30). While these reports typically investigated the influence of EELV changes in the order of 500 ml above normal EELV, the effects of lung volume changes below EELV are unknown. Longitudinal traction effects on UA compliance could be nonlinear at the lower range of tension, rendering UA function more sensitive to lung volume changes below EELV, particularly in obese patients with already reduced lung volume (33, 36) and UA size during wakefulness (24). Consequently, modest lung volume changes at sleep onset in obese OSA patients, at least equivalent to those seen in normal-weight controls, may have greater effects on UA function. Further studies are needed to elucidate the impact of experimentally induced lung volume decrements in the order of 100–150 ml below EELV on UA function in obese vs. nonobese controls.

A similar pattern and time course of changes in Vt, iEMGdia, and eEMGdia activity at sleep onset support that ventilatory and lung volume decrements reflect an acute and widespread reduction in phasic and tonic respiratory muscle tone at the wake-sleep transition, with periods of greater reduction associated with more severe respiratory events. The greater decline in end-expiratory Pdi over time following sleep onsets accompanied by respiratory events in obese OSA patients is consistent with diaphragm relaxation and ascent. As reported by a previous study (28), iEMGdia was found to be significantly higher in the obese group during wakefulness, likely reflecting increased inspiratory work required to offset mass loading...
effects on the respiratory system. In contrast, we found little evidence of increased eEMGdia to support active defense of lung volume during wakefulness, although post-sleep onset falls in activity did appear to be greater and more rapid in obese OSA patients. While these findings do not support a diaphragm neurocompensatory reflex, caution is warranted, given the small sample size. We estimate that wakefulness eEMGdia in the order of −3% of maximal activity could have been detected between groups with 80% power and a two-tailed significance level of 0.05. Therefore, it appears unlikely that larger systematic effects of obesity on tonic diaphragm activity in OSA patients would have been missed due to type II error.

If the reduction in eEMGdia at sleep onset is a key factor contributing to a cranial displacement of the diaphragm and, consequently, fall in EELV, temporal relationships and associations between changes in eEMGdia, changes in EELV, and the degree of UA obstruction would be expected. While changes in eEMGdia, EELV, and ventilation occurred over a similar time course, and with greater changes in more severe obstructive events, eEMGdia decreases appeared more abrupt and to plateau while EELV continued to decrease. In addition, there was no correlation between the degree of change in eEMGdia and EELV by the third post-sleep onset breath. While cause-and-effect relationships cannot be discerned from these data, these findings are perhaps consistent with an abrupt reduction in muscle tone contributing to decrements in lung volume, but with further modulation by other factors, such as reduced drive to other muscles, abdominal muscle contraction (12), development of atelectasis, and potentially intrinsic positive end-expiratory pressure similar to that seen under general anesthesia (18) and greater expiratory vs. inspiratory tidal volume (37).

The larger decline in ventilation and iEMGdia following sleep onset in OSA patients supports previous findings (6). In addition to decrements in diaphragm muscle activity and EELV observed in this study, reduced ventilation in OSA patients is known to be importantly influenced by reduced UA dilator muscle activity at sleep onset (6, 16). In a follow-up protocol, Fogel et al. (6) found that the decline in diaphragm muscle activity at sleep onset was not significantly different between OSA patients and controls when RUA was matched between groups via application of continuous positive airway pressure. While continuous positive airway pressure led to a significant reduction in phasic activation of the genioglossus during wakefulness in obese OSA patients, activity remained substantially higher than in control individuals. These findings support the presence of a heightened centrally mediated respiratory drive output beyond the negative neurocompensatory reflex component of UA dilator muscle activation. Combined with the present findings, these data support that OSA patients exhibit an increased and widespread wakefulness-dependent drive to the respiratory system that is not limited to the UA. This may be an adaptation necessary to compensate for respiratory system mass loading effects.

Methodological Considerations

There are several methodological issues to consider in this study. Greater decreases in lung volume and diaphragm muscle activity with more severe respiratory events at sleep onset clearly do not establish that causal relationships with UA collapse necessarily exist. Nevertheless, these observations are consistent with, and do not discount, the presence of causal relationships and are in contrast to ruling out lung volume influences had we found no changes at sleep onset. That lung volume/caffeine changes with obesity per se contribute to increased UA collapse and the strength of such effects remain to be established.

We did not attempt to recruit an obese non-OSA comparator group for several reasons. The primary intent of the study was to investigate the impact of obesity, a known major factor in OSA risk, on ventilatory parameters potentially contributing to UA collapse in the context of OSA. Obese non-OSA individuals are difficult to recruit, may be skewed toward abnormally robust UA function, despite obesity effects, and/or exhibit a different pattern of obesity than captured by conventional BMI measurements. Consequently, we elected to first establish the nature and magnitude of lung volume changes at sleep onset before further studies designed to examine these mechanisms in more detail.

We used conventional criteria using manual scoring of sleep recordings (blinded to group allocation and independent from the respiratory analysis) to identify sleep onset as α EEG activity followed by three breaths or more of θ EEG activity. We did not employ a breath-by-breath α-to-θ criterion ratio as has been performed by others (6, 35). While it is not clear what impact this may have on the measured outcomes, we speculate that manually scored sleep onset periods would include fewer and more prolonged transitions into sleep, and potentially underestimate transitory effects identified from shorter episodes of sleep in closer proximity to prior respiratory and arousal events.

In contrast to previous studies in which diaphragm activity was assessed by surface electrodes (6, 35), the present study measured diaphragm activity via intraesophageal recordings over a larger area of the crural diaphragm (3). Surface recordings are likely to be highly influenced by changes in lung volume/diaphragm position (8) and must be interpreted with considerable caution, as apparent decreases in activity may reflect diaphragm movement away from the recording electrodes. Although intraesophageal recordings must also be interpreted with caution, by averaging across all electrode pairs over a wide distance, these measures are more robust to confounding by diaphragm movement with respiration and lung volume changes. Consequently, the apparent loss in diaphragm activity at sleep onset is unlikely a recording artifact and was consistent with simultaneous decrements in lung volume and ventilatory output. It is also unclear to what extent sleep onset-related changes in lung volume and potentially caudal tracheal traction are influenced by costal vs. caudal diaphragmatic displacement. Two studies have shown significant cranial movement of the most posterior regions of the diaphragm apportioned to the lung following the induction of anesthesia in patients in the supine position (7, 19). Given that −30% of the diaphragm muscle, i.e., the domes of the diaphragm, is lung apposed at functional residual capacity (9) and caudal traction forces are importantly modulated by the action of the diaphragm acting on mediastinal structures, we would suggest that the caudal diaphragm may have a greater effect (via caudal traction) on the UA than does the costal diaphragm.
Our method of quantifying diaphragm EMG activity is somewhat of a departure from more conventional methods (6, 34) and was chosen on the basis of superior signal-to-noise characteristics via integration over the full period of inspiration. In six subjects from a previous study undertaken in our laboratory, the coefficient of variation in eEMG_{dia} and iEMG_{dia} was 7.8 ± 0.5 and 6.2 ± 0.9% compared with 12.9 ± 2.4 and 6.4 ± 1.1% derived from conventional peak and tonic activity measurements, respectively.

**Summary and Conclusions**

Despite increased intragastric pressure and Pdi, we found no significant difference in eEMG_{dia} during wakefulness between obese OSA patients vs. healthy-weight controls. Sleep onset was accompanied by significant decrements in ventilation and both iEMG_{dia} and eEMG_{dia}, with the overall decreases greater in obese OSA patients vs. healthy-weight controls. Muscle activity and EELV significantly decreased below wakefulness levels at the onset of respiratory events, particularly in the obese OSA patients. This is consistent with a widespread acute decline in phasic and tonic respiratory muscle activity, with greater decrements potentially promoting more severe respiratory events. In the presence of an already more collapsible airway, both UA muscle activity and EELV changes potentially contribute to the increased propensity for UA collapse in OSA patients at sleep onset.

**ACKNOWLEDGMENTS**

The authors are very grateful to Amanda McKenna for valuable assistance in scoring arousals and respiratory events and staging the sleep studies, and to David Schembri and the Respiratory Function Unit staff, Repatriation General Hospital, who assisted with lung function measurements.

**GRANTS**

This study was supported by the National Health and Medical Research Council of Australia (Grant 480438).

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**REFERENCES**


