Raising end-expiratory volume relieves air hunger in mechanically ventilated healthy adults

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Vovk A. Binks AP. Raising end-expiratory volume relieves air hunger in mechanically ventilated healthy adults. J Appl Physiol 103: 779–786, 2007. First published May 17, 2007; doi:10.1152/japplphysiol.01185.2006.—Air hunger is an unpleasant urge to breathe and a distressing respiratory symptom of cardiopulmonary patients. An increase in tidal volume relieves air hunger, possibly by increasing pulmonary stretch receptor cycle amplitude. The purpose of this study was to determine whether increasing end-expiratory volume (EEV) also relieves air hunger. Six healthy volunteers (3 women, 31 ± 4 yr old) were mechanically ventilated via a mouthpiece (12 breaths/min, constant end-tidal PCO₂) at high minute ventilation (Ve; 12 ± 2 l/min, control) and low Ve (6 ± 1 l/min, air hunger). EEV was raised to ~150, 400, 725, and 1,000 ml by increasing positive end-expiratory pressure (PEEP) to 2, 4, 6, and 8 cmH₂O, respectively, for 1 min during high and low Ve. The protocol was repeated with the subjects in the seated and supine positions to test for the effect of shifting baseline EEV. Air hunger intensity was rated at the end of each breath on a visual analog scale. The increase in EEV was the same in the seated and supine positions; however, air hunger was reduced to a greater extent in the seated position (13, 30, 31, and 44% seated vs. 3, 9, 23, and 27% supine at 2, 4, 6, and 8 cmH₂O PEEP, respectively, P < 0.05). Removing PEEP produced a slight increase in air hunger that was greater than pre-PEEP levels (P < 0.05). Air hunger is relieved by increases in EEV and tidal volume (presumably via an increase in mean pulmonary stretch receptor activity and cycle amplitude, respectively).

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Physiological Measures

Forced vital capacity (FVC) and forced expiratory volume (FEV) were assessed (Steal-Wells spirometer), and the percentage of predicted FEV/FVC was calculated for each subject (12). During mechanical ventilation, VT, breathing frequency, and airway pressure were measured by pressure transducers integral to the ventilator (model 900C, Siemens). Changes in EEV were measured with Respirotrace bands that were placed around the rib cage and abdomen, secured with Coban (3M), and calibrated by a previously described method (6). End-tidal PCO2 (PETCO2) was sampled at the mouth continuously (Cardiovap II CG-2GS, Datex). Arterial O2 saturation was monitored using an infrared pulse oximeter probe placed on the index finger (Biox 3740, Ohmeda). Heart rate was measured using a three-lead ECG (Cardiovap II CG-2GS, Datex). Blood pressure was monitored every 2 min via a cuff placed around the upper arm. All analog signals (except blood pressure) were digitized (Powerlab, ADInstruments, Colorado Springs, CO) for computer storage and analysis.

Mechanical Ventilator

Subjects were mechanically ventilated (model 900C, Siemens) in volume control mode through a mouthpiece while wearing nose clips. Before the experiment, subjects practiced relaxation and tried to avoid activating their respiratory muscles during mechanical ventilation. Within 15–30 min, all but two subjects were comfortable during mechanical ventilation. Comfort was assessed on the basis of visual inspection of the air pressure and flow traces and subjects’ verbal reports. Subjects who reported difficulty relaxing or demonstrated unstable inspiratory air pressure and flow traces at ventilator settings that should have provided the most comfort (i.e., high VT and low PETCO2) were dismissed from the study. On the basis of our experience, subjects who are unable to relax at the most comfortable ventilator settings are unlikely to relax during air hunger and PEEP. Minute ventilation (Ve) was initially set to 0.16 l·min⁻¹·kg body wt⁻¹, and breathing frequency was set to 12 breaths/min. Once the subject was comfortable, inspired PCO2 was raised to bring PETCO2 to ~41 Torr. Inspired O2 was maintained at 30%. Airway pressure during inspiration and flow during expiration were used to determine whether subjects were relaxed and letting the ventilator breathe for them.

Air hunger. Sensations of air hunger were induced by reducing VT by approximately half of control levels (i.e., VT = 0.08 l·min⁻¹·kg body wt⁻¹) while maintaining breathing frequency at 12 breaths/min and PETCO2 at ~41 Torr (by concurrent reduction of inspired PCO2). EEV. EEV was increased to four different levels by raising PEEP to 2, 4, 6, and 8 cmH2O while maintaining PETCO2.

Protocol

Practice session. After they were trained in mechanical ventilation, the subjects performed an initial test that familiarized them with the sensation of air hunger. During mechanical ventilation, PETCO2 was increased in a stepwise fashion (1-min steps) while VT was kept constant at 0.16 l·min⁻¹·kg body wt⁻¹. Subjects were asked to use the VAS to rate their general breathing discomfort at the end of each breath. All subjects reported experiencing “air hunger.” PETCO2 was increased until subjects rated the sensation “extreme.” Subjects then were debriefed (see above).

Experimental sessions. The protocol design is illustrated in Fig. 2. Each trial consisted of two 3-min segments of low VT (air hunger) separated by two 3-min segments of high VT (control). Within each 3-min segment, PEEP was 0 for the 1st min, raised to 2, 4, 6, or 8 cmH2O for the 2nd min, and returned to 0 for the 3rd min. The four PEEP levels were presented in a randomized order. Subjects completed two trials, so that all combinations of VT and PEEP were covered. The experiments were performed in the seated and supine positions (thorax at 80° and 0° from the horizontal, respectively).

Data Analysis

Descriptors. The three descriptors most commonly selected by the subjects after each debriefing were tabulated for each subject and expressed as a percentage of occurrence. Percentages were averaged for the group for the seated and supine positions.

Lung volume. Changes in EEV were determined by calculating the difference in the Respirotrace signal from pre-PEEP levels (calculated as the average of 10 breaths before PEEP was increased) to PEEP levels for each breath (i.e., ∆EEV). Breath-by-breath changes in EEV were plotted over time for each subject and averaged to generate a group response. EEV was plotted vs. time for each PEEP modification and each body position, and data were fitted with a two-component exponential equation (Sigma Plot 9.0).
EEV values from the last five breaths of the EEV vs. time curve were averaged and used to represent the maximal increase in EEV at each PEEP (i.e., $\Delta EEV_{max}$). By the last five breaths, EEV reached a “steady state” at all PEEP levels. For determination of the average increase in EEV at each of the four PEEP levels in the seated and supine positions, maximum $\Delta EEV$ was plotted against the corresponding PEEP and fitted with a linear regression equation.

$V_t$. Average $V_t$ values were calculated from the last 10 breaths of each stepwise change (high and low $V_t$). The change in $V_t$ between high and low $V_t$ was calculated from the difference between these two means for each subject in each body position.

Air hunger. Changes in air hunger were calculated as the difference in pre-PEEP air hunger ratings (calculated as the average of 10 breaths before PEEP was increased) from those at elevated PEEP levels for each breath and plotted vs. time for each subject. Air hunger changes associated with changes in $V_t$ were calculated by subtraction of air hunger ratings during high $V_t$ (control) from those during low $V_t$ (air hunger). The maximal decrease in air hunger was calculated in the same manner as EEV; air hunger ratings associated with the last five breaths from the air hunger vs. time curve were used to represent the maximal decrease in air hunger at each PEEP.

Statistics. Multiple means from multiple conditions (i.e., PEEP, $V_t$, and position) and differences in response frequency of phrase descriptions between body positions were compared using ANOVA and Tukey’s test when significance was achieved ($P < 0.05$). Values are means ± SE unless otherwise stated.

RESULTS

Perceptual Measures

The descriptor phrases most commonly selected by the subjects in the present study were as follows: “air hunger,” “starved for air,” “urge to breathe,” and “size of breaths felt too small.” These phrases have previously been associated with the sensation of air hunger (4). There was no difference in the type of respiratory sensation between the seated and supine positions (Fig. 1).

Physiological Measures

Subjects’ physical and ventilator parameters are listed in Tables 1 and 2, respectively. Pulmonary function of all subjects fell within the normal range. Visual inspection of the air pressure and flow traces during inspiration and expiration indicated that subjects were relaxed during high-$V_t$ (control). Traces were slightly more variable during low $V_t$ (air hunger) and high PEEP (i.e., 6 and 8 cmH2O) while some subjects were in the seated position. This was not observed when subjects were in the supine position, suggesting that they were more relaxed. Blood pressure did not change with mechanical ventilation, air hunger, or PEEP (data not shown).

Table 1. Physical parameters and pulmonary lung function

<table>
<thead>
<tr>
<th>Subj No.</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>BMI, kg/m²</th>
<th>FVC, liters</th>
<th>FEV₁, liters</th>
<th>FEV₁/FVC, %predicted</th>
</tr>
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<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>168</td>
<td>64</td>
<td>22.7</td>
<td>3.20</td>
<td>2.65</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>165</td>
<td>68</td>
<td>25.0</td>
<td>4.10</td>
<td>3.20</td>
<td>90</td>
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<tr>
<td>3</td>
<td>35</td>
<td>170</td>
<td>60</td>
<td>20.8</td>
<td>3.20</td>
<td>2.80</td>
<td>104</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>196</td>
<td>91</td>
<td>23.7</td>
<td>6.00</td>
<td>4.60</td>
<td>100</td>
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<td>5</td>
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<td>188</td>
<td>93</td>
<td>26.5</td>
<td>4.65</td>
<td>4.00</td>
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<td>29</td>
<td>180</td>
<td>65</td>
<td>20.1</td>
<td>4.95</td>
<td>3.80</td>
<td>100</td>
</tr>
<tr>
<td>Mean</td>
<td>30</td>
<td>178</td>
<td>73</td>
<td>23.1</td>
<td>4.35</td>
<td>3.51</td>
<td>100</td>
</tr>
<tr>
<td>SD</td>
<td>4</td>
<td>12</td>
<td>15</td>
<td>2.4</td>
<td>1.08</td>
<td>0.76</td>
<td>8</td>
</tr>
</tbody>
</table>

BMI, body mass index; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s.

Table 2. Physiological parameters of mechanically ventilated subjects

<table>
<thead>
<tr>
<th>Subj No.</th>
<th>End-Tidal $P_{CO_2}$, Torr</th>
<th>Frequency, breaths/min</th>
<th>Resting $V_t$, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41.0</td>
<td>12</td>
<td>10.2</td>
</tr>
<tr>
<td>2</td>
<td>40.8</td>
<td>12</td>
<td>10.9</td>
</tr>
<tr>
<td>3</td>
<td>40.1</td>
<td>12</td>
<td>9.6</td>
</tr>
<tr>
<td>4</td>
<td>40.7</td>
<td>12</td>
<td>14.5</td>
</tr>
<tr>
<td>5</td>
<td>40.9</td>
<td>12</td>
<td>14.9</td>
</tr>
<tr>
<td>6</td>
<td>43.6</td>
<td>12</td>
<td>10.4</td>
</tr>
<tr>
<td>Mean</td>
<td>41.2</td>
<td>12</td>
<td>11.7</td>
</tr>
<tr>
<td>SD</td>
<td>1.2</td>
<td>0</td>
<td>2.3</td>
</tr>
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</table>

$V_t$, minute ventilation.
End-Expiratory Lung Volume

A representative raw trace of induced PEEP is shown in Fig. 3. EEV reached steady state after two to five breaths, depending on PEEP. Slightly more time was required to attain steady-state EEV at higher PEEP, and more time was required overall in the supine position (Fig. 4). The rate of increase in EEV in response to increasing PEEP and the related $r^2$ values are reported in Table 3.

Increasing PEEP produced a significant increase in EEV that was different from baseline ($P < 0.01$) and varied between PEEP levels ($P < 0.05$ by ANOVA). There was no difference in EEV during high $V_e$ (i.e., control) and low $V_e$ (i.e., air hunger); thus these values were averaged at each PEEP. PEEP increases of 2, 4, 6, and 8 cmH$_2$O increased EEV by 225 ± 24, 472 ± 26, 696 ± 25, and 1,085 ± 280 ml in the seated position and 140 ± 32, 427 ± 16, 738 ± 17, and 1,150 ± 16 ml in the supine position. EEV increased at a rate of 155 and 168 ml/cmH$_2$O PEEP ($P < 0.05$) in the seated and supine positions, respectively. There were no differences in $\Delta$EEV between body positions.

Tidal Volume

The change in $V_t$ between high and low $V_e$ was 284 ± 38 and 347 ± 42 ml in the seated and supine positions, respectively. There was no significant effect of body position on $V_t$ ($P > 0.05$).

Air Hunger

The relief from air hunger for each PEEP is illustrated in Fig. 5 for the seated and supine positions. Air hunger relief was related to the magnitude of the increase in EEV: larger increases in EEV produced faster and greater air hunger relief (Table 4). In Fig. 5, the air hunger relief response is calculated for the increase in $V_t$ (i.e., transition to the high $V_e$; since breathing frequency was constant, changes in $V_t$ reflect changes in $V_e$). The rate of air hunger decline in response to

### Table 3. Effect of rising PEEP on rate of EEV increase

<table>
<thead>
<tr>
<th>PEEP, cmH$_2$O</th>
<th>Seated $V_t$, l/s</th>
<th>$r^2$</th>
<th>Seated $V_t$, l/s</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.010 ± 0.001</td>
<td>0.92</td>
<td>0.003 ± 0.001</td>
<td>0.97</td>
</tr>
<tr>
<td>4</td>
<td>0.062 ± 0.002</td>
<td>0.94</td>
<td>0.035 ± 0.001</td>
<td>0.93</td>
</tr>
<tr>
<td>6</td>
<td>0.122 ± 0.002</td>
<td>0.94</td>
<td>0.059 ± 0.001</td>
<td>0.97</td>
</tr>
<tr>
<td>8</td>
<td>0.130 ± 0.001</td>
<td>0.97</td>
<td>0.106 ± 0.001</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Values are means ± SE. PEEP, positive end-expiratory pressure. Rate of end-expiratory volume (EEV) increase was significantly different between PEEP levels in seated and supine positions ($P < 0.05$). For all $r^2$ values, $P < 0.001$. 

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Fig. 3. Raw traces of airflow, airway pressure, air hunger, end-tidal PCO$_2$ (PETCO$_2$), and lung volume from 1 trial during the low-$V_e$ step maneuver. Raising the PEEP setting on the mechanical ventilator raised end-expiratory volume (EEV) and reduced air hunger.

Fig. 4. Group average of breath-by-breath changes in EEV ($\Delta$EEV) in seated (top) and supine (bottom) positions. Data were fitted with a 2-component exponential equation. Curves represent rise in $\Delta$EEV during 2 cmH$_2$O (●), 4 cmH$_2$O (▲), 6 cmH$_2$O (●), and 8 cmH$_2$O (●●) PEEP.
The sensation of air hunger is believed to be generated by a gated collateral discharge of respiratory-related neurons from the brain stem to higher brain centers, such as the insular cortex (7, 18, 40). Any mechanism that reduces the respiratory-related brain stem activity, therefore, has the potential to reduce air hunger. It is likely that the relief reported with large VT (22, 29, 39) is due to an increased inhibitory effect of PSR on inspiratory neurons in the brain stem or a direct effect on higher brain centers involved with air hunger generation. Conversely, reducing VT, as in this and previous studies (11, 18, 29),
increases air hunger by reducing the inhibitory effect of the PSRs. Thus it is reasonable to conclude that the degree of air hunger relief is directly related to the magnitude of the increase in PSR activity.

We have shown that air hunger relief was more effective with greater increases in EEV. With the assumption that relief induced by raising lung volume is directly related to PSR activity, raising EEV could have augmented air hunger relief in at least two ways: 1) by producing a greater overall increase in PSR activity (1 and 2) by modifying the PSR recruitment pattern and response characteristics (1, 35, 47). For instance, “high-threshold” PSRs are phasically active during inspiration at rest but become tonically active throughout the duty cycle at larger lung volumes (34). Furthermore, high-threshold PSRs are activated only with large increases in lung volume (small volume increases activate “low-threshold” PSRs). Therefore, raising EEV can increase the activity of already active PSRs and can recruit previously silent high-threshold PSRs to produce an overall increase in vagal afferent traffic to the brain stem and higher brain centers.

In the present study, increasing VT (when the subjects transitioned from low to high V̇e) relieved air hunger at a faster rate and to a greater extent than similar increases in EEV. Bishop et al. (10) report that increases in EEV preferentially activate low-threshold receptors, whereas increases in airflow (the result of increased Vr) additionally activate high-threshold receptors. Thus the difference in air hunger relief between static (EEV) and dynamic (VT) lung volume increases may be partly due to the type of PSR recruited.

Increasing lung volume activates other thoracic receptors, such as the rapidly adapting PRSs in the lower airways (44) and pressure receptors in the mouth and upper airways (37, 43). Their role in air hunger generation and relief is unknown. Although mechanoreceptors in the chest wall are also activated by increases in lung volume, they do not appear to play a role in air hunger relief per se (9, 11, 29). They have been associated with generating other forms of respiratory sensations, such as the “work” and “effort” of breathing (27). Indeed, our subjects reported that they felt a “resistance to exhale” and that they “couldn’t exhale enough,” which was “at times uncomfortable,” particularly at higher lung volumes. These anecdotes can be interpreted as work and effort respiratory sensations due to lung hyperinflation. Thus there is a limit to the level to which EEV can be raised to compensate for air hunger without inducing other uncomfortable respiratory-related sensations, such as work and effort of breathing. This is an important consideration for pulmonologists and respiratory therapists when making adjustments for the comfort of their patients on ventilators, in particular, those without airway obstruction.

**Air Hunger Relief and PSR Adaptation**

One important consideration in the relationship of static increases in lung volume (i.e., EEV) to air hunger relief is the adaptation of PSR activity to sustained lung volume changes. Immediately after EEV is elevated, extrapulmonary PSR activity rapidly decreases as much as 50% (13) but then remains constant for up to 1 h (31, 47). A decrease in PSR activity due to adaptation would presumably reduce the degree and duration of air hunger relief. We did not observe a rise in air hunger during the 1 min of elevated EEV. If EEV were sustained for >1 min, we may have seen a dissipation of air hunger relief.

The duration of lung volume increases is particularly relevant for pulmonologists and respiratory therapists, who use PEEP to provide respiratory comfort to nonobstructed patients on the ventilator, because it suggests that the relief in this mode may only be temporary. A regimen that maximizes PSR activity, which would include moderate and intermittent increases in PEEP, may be more beneficial for ventilated nonobstructed patients experiencing air hunger.

**Body Position**

Although raising EEV relieved air hunger in the seated and supine positions, the effect was more pronounced in the seated position. Differences in initial lung volume and regional ventilation between body positions may explain this observation. Absolute EEV was not measured in this study (Respitrace can only measure relative changes in EEV), but we can assume that the initial lung volume was greater in the seated position because of the effect of gravity on the diaphragm and abdominal contents (42). Even though the relative increase in EEV (i.e., ΔEEV) at a given PEEP was the same between body positions, a higher initial lung volume would result in a greater absolute EEV and, consequently, greater PSR activity (14), which may account for the greater relief from air hunger in the seated position. In support of this view, the air hunger relief curve for the seated position in Fig. 5 is shifted rightward by ~500 ml compared with that for the supine position. The 580-ml decrease in functional residual capacity in humans shifting from the upright to the supine position reported by Bettinelli et al. (8) approximates this difference (32). Therefore, air hunger relief is dependent on lung volume: it is augmented with larger increases in PEEP and in the seated position, where initial lung volume is presumably greater.

Changing body position will also produce regional changes in lung ventilation. The base of the lung is better ventilated in the seated than in the supine position. Because PSRs are more highly concentrated at the base of the lung (34), greater expansion at the base of the lung will activate a greater proportion of high-threshold PSRs. The significance of this lies in the fact that, in contrast to their low-threshold counterparts, high-threshold PSRs do not plateau at high lung volumes (33, 38). Therefore, activation of a greater number of high-threshold PSRs may contribute to the greater air hunger relief in the seated position.

**Post-PEEP Rise in Air Hunger**

Removing PEEP caused an increase in air hunger that was greater than pre-PEEP levels in high V̇e (control) and low V̇e (air hunger). This is unlikely to be due to a direct effect of lung volume, since the degree to which air hunger increased was not related to the magnitude of ΔEEV. It is more probable that the slight rise in air hunger is an effect of temporary “silencing” of the PSRs when EEV was reduced. Several animal studies have shown that, after a sustained increase of EEV, there was a transient inhibition of PSR activity for up to 20 s when EEV was returned to baseline (23, 47, 50) and that up to 90 s of breathing at normal EEV was required to return PSR activity to baseline levels (47). The reason for this “resetting” is unknown, but it may be due to the viscous properties of the

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airway smooth muscle (13), slow posthyperpolarization of the PSRs (30), or inhibition of PSR activity via the phrenic nerve input (47).

Clinical Implications

Increasing EEV is a method to alleviate the sensation of air hunger in ventilated and nonventilated patients. However, there are caveats to these results when applied to the clinical setting. Since PEEP can impose a threshold load on the inspiratory muscles, only limited benefit might be expected in patients on assisted ventilation. Also, benefit may be limited in patients with intrinsic PEEP, such as those with chronic obstructive pulmonary disease.

Summary

The results from the present study demonstrate that an increase in EEV relieves the sensation of air hunger and that this effect is more pronounced with higher EEV and in the increase in EEV relieves the sensation of air hunger and that this effect is more pronounced with higher EEV and in the seated than in the supine position. Furthermore, relief is not as effective as that achieved by dynamic lung volumes (i.e., increased Vt). The differences in air hunger relief between body positions (seated vs. supine) and methods (static vs. dynamic lung volume increases) are likely due to the degree and type of PSRs recruited. In addition, removing PEEP produced an unexpected increase in air hunger, which may be related to changes in the mechanical and electrical properties of the PSRs.

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GRANTS

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