The effect of diaphragm contraction on upper airway collapsibility

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LUNG VOLUME IS AN IMPORTANT determinant of upper airway collapsibility. Increasing lung volume increases upper airway caliber (2, 11) and reduces its resistance and tendency to collapse (1, 21, 23–25). Conversely, the decrease in end-expiratory lung volume with sleep and anesthesia contributes to increased upper airway collapsibility in each state (6, 24).

Potential mechanisms by which an increase in lung volume may increase upper airway patency include 1) an increase in transmural distending pressure induced by thoracic expansion and associated mediastinal traction effects should be apparent immediately stimulation is applied, whereas lung volume changes may follow slowly, particularly where airway resistance is high.

Apart from addressing questions relating to pathogenesis, the method could have therapeutic potential providing it proved to be efficacious in decreasing upper airway collapsibility. While diaphragm activation by intermittent (phasic) phrenic nerve stimulation has been in use for many years as a therapy for upper motor neuron lesions affecting respiratory motor output (e.g., high spinal cord injuries), continuous (tonic) phrenic nerve stimulation remains largely unexplored as a potential therapy to prevent or treat upper airway obstruction. Such possibilities provide the rationale for this study. We hypothesized that sustained diaphragmatic contraction achieved by tonic phrenic stimulation would decrease upper airway collapsibility and that the technique would allow the effects of thoracic expansion and diaphragm descent to be differentiated. Our aims were to determine the mechanisms by which lung volume and upper airway collapsibility are related and whether phrenic nerve stimulation has therapeutic potential in preventing or treating upper airway obstruction.

METHODS

Subjects

After approval from our institutional ethics committee and obtaining written informed consent we enrolled 10 healthy subjects [8 men; age 40.6 ± 9.4 yr (means ± SD)] of normal build (body mass index 23.6 ± 2.6 kg/m²). None were known to have obstructive sleep apnea (OSA).

Techniques

All measurements were obtained during intravenous Propofol anesthesia with infusion rate adjusted (50–200 μg·kg⁻¹·min⁻¹) to
maintain a bispectral index score (BIS) below 40 units, indicative of deep (unconscious) sedation (10). Subjects were supine with head posture maintained in a neutral position (Frankfort plane perpendicular to the floor) throughout the study. Routine anesthetic monitors were applied including ECG, oximetry, blood pressure, and end-tidal CO2.

Prior to induction of anesthesia, subjects were fitted with respiratory inductance pneumography belts (Respiract, Ambulatory Monitoring, Ardsley, NY) around the abdomen and rib cage, calibrated using an isovolume maneuver so that their outputs were equivalent in volumetric terms. The sum of these signals was calibrated against respired volumes. A multipressure transducer catheter (Gaeltec model CTO-4; Gaeltec, Dunvegan, Scotland, UK) was inserted via the nose, and pressure transducers positioned in the naso-, oro-, and hypopharynx and midesophagus (Pes). Submental fine wire electrodes were positioned percutaneously into the genioglossus muscle to monitor its activity electromyographically (3). Subjects were fitted with a nasal mask via which positive or negative airway pressure could be administered. The mask was equipped with a calibrated Fleisch pneumotachograph (Hewlett Packard, Waltham, MA) to allow respired volume changes to be measured from the integrated flow signal. A sample port in the mask was connected to a pressure transducer (model 143PC, Micro Switch; Honeywell, Morristown, NJ) for continuous measurement of mask pressure. The mouth was kept closed with occlusive tape.

A neck brace (Sternoc-Occipital Mandibular Immobilizing brace, model 8005; Camp International, Jackson, MI) was fitted to stabilize head, neck, and jaw posture and provide a rigid structure on which to clamp bipolar electrodes positioned to deliver bilateral percutaneous stimulation to the phrenic nerves as they traverse the anterior scalene muscle on their way to the thoracic inlet. The electrodes were positioned to produce diaphragm stimulation (outward abdominal displacement) with minimal coactivation of neck or brachial muscles. We have previously described these methods (4).

Once the subject was instrumented, airway pressure delivered via the nasal mask was adjusted to a “holding pressure” of 10 cm H2O to maintain airway patency (abolish inspiratory flow limitation) during anesthesia. Anesthesia was then induced. Holding pressure was adjusted further under anesthesia where necessary to maintain airway patency (abolish inspiratory flow limitation) during anesthesia. Anesthesia was then induced. Holding pressure was adjusted further under anesthesia where necessary to maintain airway patency between the pressure drops described below.

**Protocol**

Once stable anesthesia was established, nasal pressure was intermittently rapidly decreased in late expiration (a “pressure drop”) from the holding pressure to levels sufficient to produce varying degrees of inspiratory flow limitation for at least five breaths before restoring holding pressure. Inspiratory flow limitation was characterized by a decrease and plateauing of peak inspiratory flow despite Pes continuing to become more negative. In five of the nine subjects this required the application of negative pressure to the upper airway. Once unstimulated pressure drop data were obtained and stable breathing at holding pressure reestablished, tonic phrenic nerve stimulation was then variously applied before and during equivalent pressure drops to examine its effect in preventing or reducing the degree of flow limitation evident in the unstimulated pressure drop recordings.

The phrenic nerves were stimulated bilaterally at a frequency of 30 Hz. Stimulation was initiated in late expiration. Two stimulation procedures were used.

**Procedure 1:** stimulation applied before and through the pressure drop. Nine of the 10 subjects underwent this procedure. In this procedure stimulation was applied for 10 contiguous breaths astride the pressure drop: 5 breaths just prior to the drop and 5 beyond it. The purpose was to ensure the increment in lung volume achievable by phrenic stimulation was completed in the favorable nonflow limited circumstances of holding pressure and, therefore, in place by the time of the pressure drop. The influence of lung volume on airway patency could then be examined by comparing inspiratory flow rates between the different unstimulated and stimulated lung volumes following the pressure drop. Cessation of stimulation was followed by a further five breaths with pressure drop maintained before pressure was increased back to the holding pressure (see Fig. 1 to observe this sequence). Low and high stimulus intensities were applied during separate maneuvers to examine dose-response characteristics. The stimulus intensities applied varied from subject to subject depending on accuracy of placement of the stimulating probes, skin, and tissue impedance to the stimulating current and resultant magnitude of abdominal displacement with stimulation (low-intensity range 0.85–3.5 mA; high-intensity range 1.0–4.5 mA).

**Procedure 2:** stimulation applied after the pressure drop. A subset of five patients was studied for this procedure, four of whom were also
Procedure 1; the fifth subject underwent this procedure but not Procedure 1. The other five subjects who had undergone Procedure 1 were not subjects for this procedure. In this procedure, stimulation was applied for five breaths after the pressure drop had occurred and stable flow limitation had been established. The purpose was to provide a circumstance under which the effects of diaphragm shortening and associated caudal traction (which occur immediately after phrenic stimulation is applied) could be separated from the effects of volume change (which may evolve more slowly in these flow-limited circumstances; see Figs. 4, 5, and 6 to observe this sequence).

Data Analysis

 Procedure 1. mean peak inspiratory flow and end expiratory rib cage and abdominal volumes for breaths three to five of the five-breath stimulated and unstimulated sequences were measured. Lung volume was determined from the sum of rib cage and abdominal volumes.

 Procedure 2. Peak inspiratory flow and end expiratory rib cage, abdominal, and lung volumes were measured during the following pressure drops: 1) at the breath immediately prior to initiation of stimulation, 2) at the first inspiration or inspiratory effort after stimulation was applied, and 3) after lung volume stabilized during stimulation or at the final breath during stimulation in cases where stimulation was ceased prior to stabilization. Where a first inspiratory effort was delayed following onset of stimulation (e.g., see Fig. 5), the response “at first inspiration” after stimulation was assessed at the point where inspiration would have occurred had the preceding breathing frequency been unaffected by stimulation.

Statistical Analysis

 We tested the hypothesis that phrenic nerve stimulation would mitigate flow limitation induced by pressure drops by comparing peak inspiratory flow rates measured during stimulation with peak flows under comparable conditions without stimulation using ANOVA. The relationships between peak inspiratory flow rates and compartmental volume changes were examined by Pearson correlation coefficients. A P value of less than 0.05 was considered significant. Continuous variables were summarized using means and standard deviations.

RESULTS

 It was not possible to assess intramuscular EMG activity during periods of phrenic nerve stimulation due to stimulation-related recording artifacts. However, where there was no stimulation, intramuscular EMG activity was absent throughout these studies, consistent with findings from previous studies in humans at BIS levels <40 units (5, 10), and there was no suggestion that genioglossus EMG activity was increased by phrenic nerve stimulation. There was minimal coactivation of cervical or brachial muscles during stimulation. BIS did not change with stimulation, remaining <40 units throughout the measurements. There were no patient movements or changes in ventilatory or cardiovascular (heart rate, blood pressure) parameters with stimulation.

Procedure 1: Stimulation Applied Before and Through the Pressure Drop: The Effect of Lung Volume Increase on Pharyngeal Patency

When applied prior to a pressure drop sufficient to cause flow limitation in the unstimulated condition, phrenic nerve stimulation reduced the magnitude of lung volume decrease and abolished or reduced the degree of inspiratory flow limitation relative to the changes observed in these parameters during an equivalent pressure drop without stimulation. Increasing the intensity of stimulation magnified these mitigating effects on lung volume and inspiratory flow (Figs. 1 and 2; Table 1).

Analysis of the mean data from the final three breaths of the five-breath sequences obtained during the pressure drops (Table 1) illustrates the increase in lung volumes and peak inspiratory flow during the pressure drop with phrenic stimulation relative to the unstimulated condition in the nine subjects who underwent this procedure. These changes were greater with high- than with low-intensity stimulation.

Figure 3 illustrates the relationships between the stimulation-induced increments in lung volume and augmentation of peak inspiratory flow during pressure drops relative to values in the unstimulated condition for each individual. Analysis of all data points in Fig. 3 reveals a correlation coefficient between changes in lung volumes and peak flows of 0.65 (P < 0.01).

Procedure 2: Stimulation Applied After the Pressure Drop: Separating the Effects of Caudal Traction and Lung Volume Change on Pharyngeal Patency

Three patterns of response were observed where phrenic nerve stimulation was first applied after pressure was dropped to levels associated with flow limitation: 1) stimulation was associated with prompt outward displacement of the abdomen and either no or brief rib cage paradox followed by an increase in rib cage and abdominal volumes and their sum (i.e., lung volume) with continued tidal breathing and a relatively prompt reduction in or resolution of flow limitation as lung volume increased (Fig. 4); 2) stimulation was associated with prompt outward displacement of the abdomen and paradoxical (inward) motion of the rib cage. Sustained flow limited inspiratory flow followed, during which the rib cage and abdomen expanded and lung volume increased. When lung volume increase reached a threshold [which appeared to coincide with resolution of rib cage paradoxical displacement (i.e., return of rib cage volume to near that observed prior to application of stimulation)], the sustained inspiratory flow ceased, expiration followed, and regular tidal ventilation resumed with the next inspiratory effort associated with a lesser degree or abolition of flow limitation (Fig. 5); and 3) where the pressure drop was sufficient to produce complete upper airway obstruction (apnea) stimulation was associated with prompt outward movement of the abdomen and paradoxical (inward) rib cage movement, but no lung volume change (i.e., persisting apnea) (Fig. 6).

Figure 7 illustrates the relationship between changes in end-expiratory lung volume and peak inspiratory flow rate with stimulation applied after pressure drops in the subgroup of five subjects in which this procedure was applied. Figure 7 displays two runs for each subject as follows: 1) the “best” response in terms of incremental increase in peak inspiratory flow rate following stimulation and 2) a lesser flow response (because of lower stimulation amplitude and/or greater flow limitation at the time stimulation was applied). For each run data are provided for prestimulation, early during stimulation, and at the maximum change in lung volume, achieved later in the stimulation period, as defined in METHODS. Consistent increases in peak inspiratory flow rates were observed where phrenic stimulation had resulted in lung volume increases of greater
than 400 ml. Flow responses were variable with lesser volume changes. In one subject (Subject 3) a substantial increase in flow was observed without apparent volume change on sum Respitrace signal. However, this apparent absence of volume change may be artifactual, as end expiratory Pes became more negative with stimulation in this subject, consistent with an increase in transpulmonary pressure. In three of the examples where a positive flow response was seen at maximum lung volume change, this was not evident at the first inspiratory effort following stimulation [“early stimulation”; 5 (a), 9 (a), and 10 (a) in Fig. 7]. Examination of best responses from each subject demonstrated significant increases in mean peak flows and end expiratory lung volumes between prestimulation and maximum change during stimulation (93.2 ± 46.3 ml/s, P = 0.002, and 656 ± 462 ml, P = 0.005, respectively) but not between prestimulation and early stimulation (10.3 ± 5.3 ml/s and 164 ± 164 ml; one-way repeated measures ANOVA). In every case (not illustrated for all subjects, but see Figs. 4 – 6 for examples), there was prompt outward displacement of the

Table 1. Increases in peak inspiratory flow and volumes during pressure drops with high and low intensity phrenic nerve stimulation relative to unstimulated values in Procedure 1

<table>
<thead>
<tr>
<th></th>
<th>High-Intensity Stimulation</th>
<th>Low-Intensity Stimulation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Peak inspiratory flow (ml/s)</td>
<td>137 ± 108</td>
<td>69 ± 57</td>
<td>0.02</td>
</tr>
<tr>
<td>Δ Lung volume (liters)</td>
<td>0.76 ± 0.56</td>
<td>0.39 ± 0.27</td>
<td>0.02</td>
</tr>
<tr>
<td>Δ Abdominal volume (liters)</td>
<td>0.71 ± 0.53</td>
<td>0.35 ± 0.33</td>
<td>0.02</td>
</tr>
<tr>
<td>Δ Rib cage volume (liters)</td>
<td>0.05 ± 0.24</td>
<td>0.04 ± 0.17</td>
<td>0.28</td>
</tr>
</tbody>
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All values (means ± SD) are relative to the unstimulated condition; P values are for differences between the high- and low-intensity stimulation values, n = 9.
abdomen with initiation of phrenic stimulation, whether an increase in flow and/or lung volume was observed then or later in the course of stimulation.

DISCUSSION

The findings of this study demonstrate that tonic phrenic nerve stimulation can reduce upper airway collapsibility. Phrenic nerve stimulation applied prior to the pressure drops reduced the magnitude of lung volume decrease and flow limitation that developed during the pressure drop in its absence. This mitigating effect of phrenic stimulation was greater with high-intensity than low-intensity stimulation. There was a direct relationship between the degree to which lung volume was maintained by stimulation during the pressure drop and preservation of peak inspiratory flow rates. The effect on flow rates appeared more closely related to lung volume change than to caudad displacement of the diaphragm, because during maneuvers where phrenic stimulation was first applied after pressure drops, outward movement of the abdominal wall was not accompanied by increased inspiratory flow unless or until lung volume also increased. Indeed, a threshold increase in lung volume (>400 ml) appeared necessary before a reduction in flow limitation was consistently apparent, consistent with a previous suggestion made by Kairiatis et al. (13). A highly negative intrathoracic pressure produced by phrenic nerve stimulation was not, of itself, sufficient to resolve flow limitation; a lung inflation-associated increase in transpulmonary pressure was required.

This observation reflects behavior of a collapsible tube, as modeled by a Starling resistor. According to this model, during flow limitation, inspiratory flow rate is independent of downstream (intrathoracic) pressure, being dependent on the transmural pressure gradient across the flow-limited segment (and wall compliance of this segment). Of itself, a further decrease in intrathoracic pressure with, for example, more intense phrenic nerve stimulation would not be expected to be accompanied by an increase in flow, because the pressure within the airway lumen would be decreased to the same degree as that surrounding it. In this setting only an associated increase in lung volume (which would be slow under severely flow-limited circumstances) could change conditions to favor increased flow rates. It could do so by the following: 1) an associated increase in the transmural pressure gradient across the flow-limited pharyngeal segment, favoring distension. As lung volume increases so does transpulmonary pressure, the components of which are intrapleural pressure and intra-alveolar pressure. Intrapleural pressure appears readily transmitted to the thoracic inlet and peripharyngeal tissue (13), whereas intraluminal pressure will tend to equilibrate with alveolar pressure downstream of a site of substantial inspiratory flow limitation. Hence inflation-related increased transpulmonary pressure is likely to be reflected in increased pharyngeal transmural pressure gradients under flow limited circumstances; and 2) a decrease in pharyngeal wall compliance through an increase in stretching forces on it that relate to lung volume change rather than diaphragm descent.

Where the degree of flow limitation is modest, lung volumes would be expected to increase relatively promptly following phrenic nerve stimulation, with a prompt accompanying increase in flow rates. Where severe flow limitation is present, volume change will be slow, despite prompt diaphragm descent, with slow accompanying expression of volume-related effects on pharyngeal patency. Where total obstruction is present, then lung volume increase cannot take place with phrenic nerve stimulation, in turn precluding any change in patency. These patterns are observed in the examples given in our results.

The importance of lung volume as a determinant of upper airway collapsibility is also illustrated by its slow reduction over several breaths following each pressure drop (which, by
design, occurs instantaneously), with a parallel slow evolution of flow limitation. This is observed whether or not the pressure drop occurs in the presence of phrenic nerve stimulation (Figs. 1, 4, 5, and 6). The evolving flow limitation and increased duty cycle acts as a brake on the rate at which lung volume decreases (6, 20).

Rib cage paradoxical (inward) displacement with application of phrenic nerve stimulation was indicative of high airway impedance to inspiration, with consequent development of highly negative intrathoracic pressures (9). Where the airway was not completely occluded, this paradoxical displacement resolved as the lung inflated. This resolution appeared to be a precondition for the increased inspiratory flow observed after the lengthy periods of flow limitation seen in some subjects during Procedure 2, suggesting net thoracic expansion may be necessary for improvement in pharyngeal patency. The presence of paradoxical displacement reflects inspiratory inefficiency in two respects: first, it reflects high transthoracic

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**Fig. 5.** A: polygraph tracing showing flow, pressure, and compartmental volume responses to phrenic stimulation (shaded region) delivered during a pressure drop. Stimulation artifact is evident on the Pes channel. Compared with Fig. 4, more sustained rib cage paradox was evident with stimulation, and a prolonged flow-limited inspiration occurred during which rib cage volume returned to near prestimulation values. Thereafter, tidal breathing resumed with resolution of flow limitation. Flow limitation recurred with cessation of phrenic stimulation until mask pressure was restored at the end of the sequence. B: enlargement of the stimulation period.
pressure gradients and so is an indication of inspiratory force unrequited by lung volume increase; and, second, it reflects redistribution of volume between the abdominal and rib cage compartments, offsetting the inspiratory effect of abdominal compartment increase.

It is important to note that the responses to Procedures 1 and 2 are not directly comparable. During Procedure 1 stimulation is applied prior to pressure drop, and so its mitigating effects on airway collapse with deflation are observed. During Procedure 2, phrenic nerve stimulation is applied after the pressure drop, and its effects on airway opening with inflation are examined. As there is hysteresis in upper airway pressure-flow relationships, which appears based on surface forces (14), behavior during airway opening will be different to that during closure, with greater forces required to reopen the collapsed airway than to stabilize the patent airway. Thus in Procedure 2 it is quite possible that the potentially significant surface forces involved preclude reopening of the collapsed airway or expansion of the narrowed airway, despite a potential stabilizing effect of longitudinal tension on an already patent airway, the conditions pertaining to Procedure 1.

It was notable that the presence of paradoxical rib cage displacement during stimulation was accompanied by a prolonged flow-limited inspiratory flow with suppression of expiration (Fig. 5). It is possible that this unusual, but repeatedly observed, response represents delayed activation of inhibitory lung stretch receptors (i.e., the inspiratory Hering Breuer reflex) to terminate inspiratory flow (because of the slowness of lung volume increase under these flow-limited circumstances) or activation of a load/muscle length compensation reflex acting to augment inspiration because of imbalance between demanded and achieved changes in lung volume (8). It has been suggested that a primary function of “load-compensating” reflexes when inspiring against increased airflow obstruction is to provide rib cage stability, which may well be relevant given the degree of paradox observed in the present study (22). Where this pattern was observed, tidal breathing generally resumed once rib cage paradox had resolved to the point where end-expiratory rib cage volume had returned to near prestimulation values (Fig. 5).

The findings appear unlikely to be explained by reflex or arousal effects. Anesthesia depth was monitored by BIS, a parameter based on a processed electroencephalogram. The
BIS level was maintained at <40 units for the duration of the measurements, a level associated with consistent lack of awareness during anesthesia (16). The lack of body movement or of change in BIS, ventilatory pattern, heart rate, or blood pressure with stimulation also reflects the depth of sedation and likely reflex suppression. Collateral stimulation of adjacent nerves is also not a likely explanation for the changes we observed. We positioned our bipolar stimulating electrode to minimize this (Methods). Fatigue was also not a satisfactory explanation for our findings, as stimulation was maintained for relatively brief periods. The effectiveness of stimulation was reflected in the changes in lung volume induced by it, and the changes in upper airway collapsibility were, in turn, related to these changes.

These observations have therapeutic implications, which deserve consideration. Because of their unacceptability to many patients, there is interest in therapeutic alternatives to commonly used positive pressure therapies for OSA. One example of this is hypoglossal nerve stimulation by an implanted nerve stimulator (15, 19). Our findings suggest phrenic nerve stimulation is another potential neurostimulatory therapy for OSA. Sleeping in a negative chest wall pressure device (17) would be impractical, whereas an implantable stimulator, though invasive, potentially offers an attractive means of harnessing the beneficial effect of elevating lung volume to stabilize pharyngeal airway patency. The phrenic nerve is accessible for stimulation in the neck or intra-abdominally at its motor point, where it enters the diaphragm. Such possibilities have been actively considered (e.g., US Patent Application 8,140,164, issued 20 Mar 2012 in the name of Tehrani AJ et al., and related applications) and appear worthy of further pursuit. Our findings suggest that therapeutic responses would be enhanced by a stimulation mode that starts prior to the development of upper airway obstruction.

The study has several limitations. First, transcutaneous stimulation is an imperfect way to stimulate the phrenic nerves, because relatively small movement of the stimulating electrode relative to the nerves (for example, with changes in chest wall configuration with lung volume change) can lead to a loss of efficacy of stimulation. This limited the effectiveness of stimulation in several subjects and electrode repositioning was required from time to time. In general, in instances where small volume changes were seen, they were attributable to imperfect stimulation. It is also possible that imperfectly applied transcutaneous stimulation could stimulate adjacent neck musculature, increasing pharyngeal tissue pressure, potentially aggravating flow limitation where a lung volume increase was not attained. Second, chest wall motion was monitored by RespiTRACE. This is an imperfect guide to chest wall displacement in the presence of airway obstruction, because distortions in the chest wall mean that it may move with more than two degrees of freedom, breaching the conditions under which accurate estimates are most assured. Third, these studies have been conducted during anesthesia rather than sleep, allowing the mechanics to be examined in relative isolation (7) but, conversely, precluding study of the interplay of these with arousal responses. Fourth, the subjects were all normal individuals, not known to have OSA, so the responses observed may not precisely reflect the behavior of subjects with abnormally collapsible upper airways.

In conclusion, tonic phrenic nerve stimulation decreases upper airway collapsibility. Our findings suggest that the decrease in collapsibility is primarily mediated through lung volume increase related changes in airway wall compliance and/or airway transmural pressure gradients, rather than through mediastinal traction secondary to diaphragm descent. Phrenic nerve stimulation deserves further exploration as a therapy for OSA.

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DISCLOSURES


AUTHOR CONTRIBUTIONS


REFERENCES