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Influence of pharyngeal muscle activity on inspiratory negative effort dependence in the human upper airway

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ABSTRACT

The upper airway is often modeled as a Starling resistor, which predicts that flow is independent of inspiratory effort during flow limitation. However, while some obstructive sleep apnea (OSA) patients exhibit flat, Starling resistor-like flow limitation, others demonstrate considerable negative effort dependence (NED), defined as the percent reduction in flow from peak to mid-inspiration. We hypothesized that the variability in NED could be due to differences in phasic pharyngeal muscle activation between individuals. Therefore, we induced topical pharyngeal anesthesia to reduce phasic pharyngeal muscle activation to see if it increased NED.

Twelve subjects aged 50 ± 10 years with a BMI of $35 \pm 6\,kg/m^2$ and severe OSA (apnea-hypopnea index = 52 ± 28 events/h) were studied. NED and phasic genioglossus muscle activity (EMG_{GG}) of flow limited breaths were determined before and after pharyngeal anesthesia with lidocaine. Pharyngeal anesthesia led to a 33% reduction in EMG_{GG} activity ($p < 0.001$), but NED worsened only by $3.6 \pm 5.8\%$ ($p = 0.056$).

In conclusion, phasic EMG_{GG} had little effect on NED. This finding suggests that individual differences in phasic EMG_{GG} activation do not likely explain the variability in NED found among OSA patients.

1. Introduction

The human pharynx during sleep exhibits substantial inspiratory narrowing as a result of the reduction in luminal pressure (Morrell and Badr, 1998). The upper airway is often modeled as a Starling resistor, which predicts that maximum flow is independent of inspiratory effort during flow limitation. That is, for increasing respiratory effort, flow should be constant (Gold and Schwartz, 1996). However, flow-limited breaths in obstructive sleep apnea (OSA) patients often exhibit negative effort dependence (NED), in which flow decreases as inspiratory effort increases. NED, as defined by the percentage reduction in flow from peak to mid-inspiration, can be marked (>50%) among OSA patients (Owens et al., 2014a). Using an experimental protocol in which the upper airway was passive (no muscle activity) we showed that all subjects had substantial NED (Owens et al., 2014b). During routine polysomnograms, however, NED can vary markedly between patients, with some exhibiting a very flat (no NED) Starling resistor-like flow limitation, whereas others demonstrate an almost 100% decrease in flow from early to mid-inspiration (Owens et al., 2014a). The mechanisms for this variability in NED are not known, but our prior work implies that muscle activity might be important.

Pharyngeal dilator muscle activity during sleep is determined by both central (i.e respiratory drive) and local (i.e. negative pressure reflex) inputs, and plays an essential role in the maintenance of pharyngeal patency (Eckert et al., 2013). During sleep, respiratory drive is primarily influenced by the chemoresponsiveness to PCO_2 and PO_2. When the central drive to the pharyngeal muscles was reduced via mechanical hyperventilation, we observed significant NED (Owens et al., 2014b). Such a finding suggests that the reduction

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of pharyngeal EMG activity may be responsible for the development of NED. However in our previous experiment, the relationship between the negative pressure reflex and the degree of NED was not assessed. The negative pressure reflex is induced by pharyngeal negative pressure and mediated by pharyngeal mechanoreceptors, resulting in phasic muscle activation, that mitigates the tendency for pharyngeal collapse during inspiration (Horner et al., 1991). However, pharyngeal muscle responsiveness to negative pressure varies considerably (Eckert et al., 2013). Therefore, we hypothesized that robust pharyngeal muscle responsiveness to negative pressure could potentially explain why some OSA patients do not exhibit major NED (i.e. fixed flow limitation—"Starling resistor like"), whereas ineffective muscle responsiveness could explain the appearance of NED. Recognizing the interaction of phasic muscle activation and NED is important for modeling/understanding the mechanisms of pharyngeal collapse in OSA. Specifically, we are interested in whether the pharynx is truly a Starling resistor, or rather if it simply appears to be like a Starling resistor because the phasic muscle activation offsets the underlying NED.

To test this hypothesis, topical pharyngeal anesthesia was used to blunt the negative pressure reflex and attenuate phasic muscle activation (Berry et al., 1997; Fogel et al., 2000; Horner et al., 1991). We then examined the relationship between muscle activation and NED before and after topical pharyngeal anesthesia.

2. Methods

Participants from both genders were recruited from the sleep laboratory at Brigham and Women's Hospital. All subjects had OSA and were being treated with CPAP. The age range was 21 to 70 years. Subjects were excluded if they had uncontrolled heart failure, diabetes or renal insufficiency, or if they were taking medications that could affect upper airway muscle function. The study was approved by the Hospital's Institutional Review Board and informed consent was obtained from each subject before the study began.

2.1. Instrumentation

Subjects arrived in the laboratory 2 h before their usual bedtime. They were instrumented with electrodes for electroencephalography (C3-A2, Oz-A2), left and right electrooculography and submental electromyography for sleep staging. A 5-French pressure catheter (Millar Instruments, Houston, TX) was inserted through one nostril to the level of the epiglottis. The subjects breathed via a nasal mask attached to a modified CPAP device (Philips Respironics, Murrysville, PA) capable of delivering both positive and negative pressures. Airflow was measured with a pneumotachometer (Hans-Rudolph, Kansas City, MO) and a pressure transducer (Validyne, Northridge, CA) attached to the mask. Mask pressure was monitored with a differential pressure transducer (Validyne, Northridge, CA) referenced to atmosphere.

The activity of the genioglossus muscle (EMG_{GG}) was obtained from intramuscular electrodes at a sampling frequency of 1000 Hz. The electrodes consisted of two stainless steel Teflon-coated 30-Ga wires that were inserted per orally approximately 15 mm into the body of the genioglossus muscle just lateral to the frenulum. Each electrode was referenced to a common ground (placed on the forehead) to yield a bipolar recording. The raw EMG_{GG} was amplified, band-pass filtered (between 30 Hz and 1 kHz), rectified, and electronically integrated over a 100 ms window. The EMG_{GG} was quantified as a percentage of the maximum, which was established during maximal tongue protrusion against the incisors. The highest single value was considered 100% and electrical zero was defined as 0%.

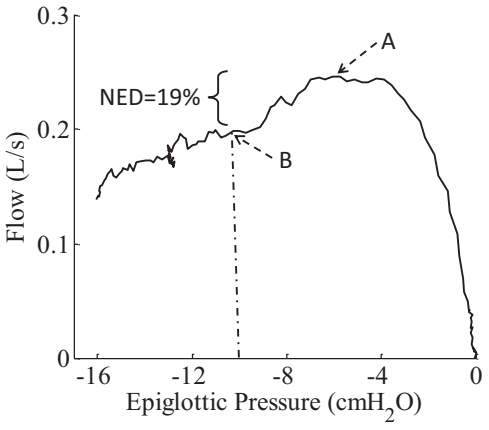

Fig. 1. Example of a flow versus epiglottic pressure plot from a representative subject. NED was defined as the percent change in flow from peak flow (A) to the flow at the epiglottic pressure cut-off (B, dashed line) selected for the group of breaths being compared ((A − B)/A × 100).

2.2. Protocol

After instrumentation, the subjects laid in the supine position and the nasal mask was connected to the CPAP device. After sleep onset, CPAP was titrated upwards to overcome flow limitation, defined as the failure of inspiratory flow to increase concomitantly with the decrease in epiglottic pressure. Once in stable NREM sleep without flow limitation, CPAP was reduced to suboptimum levels for 2–3 min intervals in order to induce flow-limitation. After several series of flow limited breaths were obtained at different CPAP levels, the subject was awakened and the head of the bed was raised. Topical pharyngeal anesthesia was induced using 3 to 5 ml of 4% lidocaine sprayed through the nostrils and mouth until the gag reflex was abolished. The gag reflex was tested by pushing a tongue blade against the posterior pharynx. The bed was then lowered back to the horizontal position and the subject was allowed to fall asleep again on optimum CPAP. After stable NREM sleep was reestablished, flow limitation was again induced as described above using the same CPAP levels that were previously used pre-anesthesia. The study was stopped 30 min after the end of anesthesia induction, as previous studies have shown that the duration of action for lidocaine under these conditions is approximately 30 min (Fogel et al., 2000). Furthermore, we tested the gag reflex of two volunteers at 5 min intervals after anesthetizing the pharynx. We also found that the gag reflex started to return after approximately 30 min.

2.3. Data analysis

Flow-limited breaths at the same CPAP levels pre and post anesthesia were initially selected. All breaths at the same CPAP level that reached an epiglottic pressure of $-8\ cm{\cdot}H_2O$ or lower (to ensure that a significant swing in epiglottic pressure was present) post anesthesia were matched by at least the same number of breaths during baseline. Flow vs. pressure graphs were plotted for all matched breaths. An epiglottic pressure cut-off was defined by the lowest epiglottic pressure common to both pre and post anesthesia breaths previously selected. Peak inspiratory flow and flow at the pressure cut-off were then obtained for each of the matched breaths. The magnitude of NED for each breath was then calculated as ((peak inspiratory flow − flow at pressure cut-off)/peak inspiratory flow) × 100 (Fig. 1). An average NED value for each condition was calculated by averaging the individual breath NED data. Sleep was staged according to the latest AASM criteria (Berry et al., 2012). In order to confirm that EMG_{GG} electrodes did not move