

Online supplement for:

Mechanisms Used To Restore Ventilation After Partial Upper Airway Collapse During Sleep In Humans.

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METHODS

Subjects:

11 patients with at least moderately severe obstructive sleep apnea (Apnea Hypopnea Index >20 events/hr) and 19 healthy non-snorers were studied. The sample size was based on the prior report of the magnitude of increase in genioglossus muscle activity with resistive loading [1] and the desired minimum detectable difference of 25% increase in genioglossus activity between patients with OSA and controls. This calculation determined that 10 subjects would be required in each group to achieve significance at the 5% level with 80% power. We recognised that some subjects would not sleep well in the laboratory and thus we recruited additional subjects. All non-snorers and 6 subjects with OSA were not taking any medications. Approximately equal numbers of men and women were studied (16 men, 14 women). Women who were pre-menopausal (3 patients with OSA and 7 non-snorers) were studied in the follicular menstrual phase (4-11 days after the onset of menses). The remaining 5 subjects with OSA were taking oral hypoglycemic agents (2 subjects), cholesterol lowering medications (3 subjects) or allergy medications (3 subjects). Patients with OSA reported nightly use of CPAP for more than 3 months prior to the study. However, CPAP usage was not objectively measured.

Procedures:

Subjects lay supine wearing a nasal mask (Gel Mask, Respironics, Murrysville, PA) with pneumotachograph (model 3700A, Hans Rudolf Inc, Kansas City, MO) and differential pressure transducer (Validyne Corp., Northridge, CA) for measurement of inspired flow and calculation of breath timing and ventilation (\dot{V}_I). The pneumotachograph was connected to a leak valve and a modified CPAP device that could deliver either CPAP or CNAP. The expirate was continuously sampled from one nostril to determine the end-tidal partial pressure of CO₂ (PETCO₂, Capnograph monitor, BCI, Waukesha, WI) and mask pressure (P_{MASK}) was continuously monitored (Validyne Corp., Northridge, CA). Epiglottic pressure (P_{EPI}) was measured with a pressure tipped catheter (model MCP-500, Millar, Houston, TX) advanced through a nostril to 1 cm below the tongue base under direct visualisation through the mouth after both nostrils were decongested (0.05% oxymetazoline HCl) and the nostril through which the catheter passed anaesthetised (4% lidocaine HCl). Breath by breath measures of epiglottic

pressure were corrected for changes in CPAP/CNAP from atmospheric pressure by subtracting the CPAP/CNAP value.

The genioglossal electromyogram (EMG_{GG}) was recorded in the standard manner [2] with 2 intramuscular wire electrodes inserted 3-4 mm on either side of the frenulum to a depth of ~15mm after surface anesthesia (4% lidocaine hydrochloride). Both the raw and rectified/moving time averaged EMG were recorded. The peak value during inspiration (Peak) and minimum value during expiration (Tonic) of the averaged signal were quantified. The genioglossus muscle activity was expressed as the percent of maximal activity which was determined by having the subject perform three of each of the following maneuvers: swallows, deep breaths and maximal tongue protrusions against the top teeth. Care was taken to ensure all subjects gave maximal efforts during the tongue protrusions by verbal encouragement.

Data Analysis:

We recognised that the magnitude of airway collapse/ventilatory impairment for a given CPAP drop may differ between patients and non-snorers and thus the equivalent CPAP drops may cause a different “stimulus” in each group. We therefore plotted the mask pressure (P_{MASK}) versus peak inspiratory flow (PIF) for the 3rd to 5th breaths after each pressure drop where flow limitation occurred as is typically done for determination of the pharyngeal critical closing pressure (P_{CRIT}). The slope of this relationship (l/s drop in flow per cmH_2O reduction in P_{MASK}) was then compared between subject groups with Student’s t-tests. The PIF- P_{MASK} relationship was also extrapolated to zero flow for standard P_{CRIT} measurement [3, 4].

Pressure drops were only analysed if no leak was present (leaks were detected by a positive baseline shift in the airflow signal during CPAP or negative baseline shift during CNAP) and if flow limitation developed during the pressure drop. In addition, if a cortical arousal occurred during the first 3 breaths of the pressure drop this was considered to be related to the change in pressure itself, not the airflow limitation induced by the change in CPAP and thus these trials were excluded.

For the primary analysis, ventilatory recovery was assumed to have occurred if the subject remained asleep for the full 5 minutes, or if P_{EPI} and $PETCO_2$ were both stable ($<2\text{cmH}_2\text{O}$ drop in P_{EPI} , $<2\text{mmHg}$ rise in $PETCO_2$) for 30s prior to a cortical arousal (spontaneous arousals). Younes [5] recently reported that arousals from sleep are sometimes preceded by a sudden increase in airflow. Whether this occurs because of sudden airway opening inducing arousal, or whether it reflects the delay of the rising CO_2 reaching medullary chemoreceptors and stimulating arousal is unknown. However, if the former possibility is correct, then recovery of ventilation may have occurred and these trials should be considered to have adequate restoration of ventilation. We therefore conducted a secondary analysis where pressure drops in which airflow increased more than 20% immediately prior to cortical arousal were also considered to have adequate recovery of ventilation.

The baseline conditions were measured as the average of the 60s period immediately preceding each pressure drop.

RESULTS

Online Figure 1: Examples of pressure drops from 1 non-snoring subject with ventilatory Recovery (A) and No Recovery (B). Flow, epiglottic pressure (P_{EPI}), mask pressure (P_{MASK}), raw (volts) and rectified (% Max) genioglossus muscle activity (EMG_{GG}) and electroencephalogram (EEG) before and during pressure drops are shown. An expanded portion of the EEG is included to indicate the absence (A) and presence (B) of cortical arousal during the sudden increase in flow. In figure B, the arousal is assumed to be related to airway collapse because P_{EPI} falls more than $2\text{ cmH}_2\text{O}$ in the 30s prior to arousal.

Online Figure 2: Inspiratory (T_I) and expiratory (T_E) times for 60s prior to the reduction of CPAP (Baseline) and on the first 3 and last 3 breaths of reduced CPAP in 10 patients with OSA and 15 non-snoring subjects. The last 3 breaths are the average of the last 3 breaths prior to arousal or at the end of reduced CPAP if no arousal occurred. Means \pm SEM are presented, * $p<0.05$ compared to baseline for both groups.

DISCUSSION

Comparison to a prior study in healthy subjects.

A prior report in 5 healthy males in whom continuous negative airway pressure was applied during sleep [6] reported that inspiratory time and genioglossus EMG increased across 20 breaths at -7.5 cmH₂O, but tidal volume and minute ventilation as measured by RespiTrace, did not increase until arousal from sleep occurred. There are numerous differences between these studies which may explain the disparate results. Firstly, non-snorers were placed on CPAP prior to the pressure drop in the current study, as opposed to breathing at atmospheric pressure in the prior study. By not using CPAP, the subjects in the prior study may have already activated some compensatory mechanisms prior to CNAP and thus further activation of these mechanisms may have been less effective. It is also likely that the subjects had lower lung volumes in the prior study and lung volume has been shown to influence upper airway collapsibility [7-9]. Second, the pressure was held at the lower level for longer in the current study (5 minutes as opposed to 20 breaths) thus providing a longer interval for an increase in ventilation. Finally, the mean pressure level was only -0.11 cmH₂O in the non-snorers in the current study (optimal CPAP = $+5.7$ cmH₂O with an average reduction of 5.8 cmH₂O) which is less negative than in the prior study.

Limitations

Arousals from sleep were scored according to the ASDA criteria (>3 seconds of increased EEG activity) [10] and it is therefore possible that we missed some subtle “sub-cortical” or “autonomic” arousals from sleep. Heart rate, a potential measure of autonomic arousal, is difficult to interpret with increasing CO₂ and large negative intrathoracic pressures. However, we defined an autonomic arousal as >4 beat per minute increase in heart rate followed by >3 beat per minute decrease in heart rate [11, 12] and found that only 6% of pressure drops without cortical arousals had such events and in all cases ventilatory recovery had already occurred.

The healthy non-snorers were often placed on CNAP during CPAP drops whereas patients with OSA were always still on positive pressure. Negative pressure may stimulate negative pressure receptors, but may also cause greater reductions in lung volume than occurred in OSA patients. However, the OSA patients were more obese and were potentially already at lower lung volumes

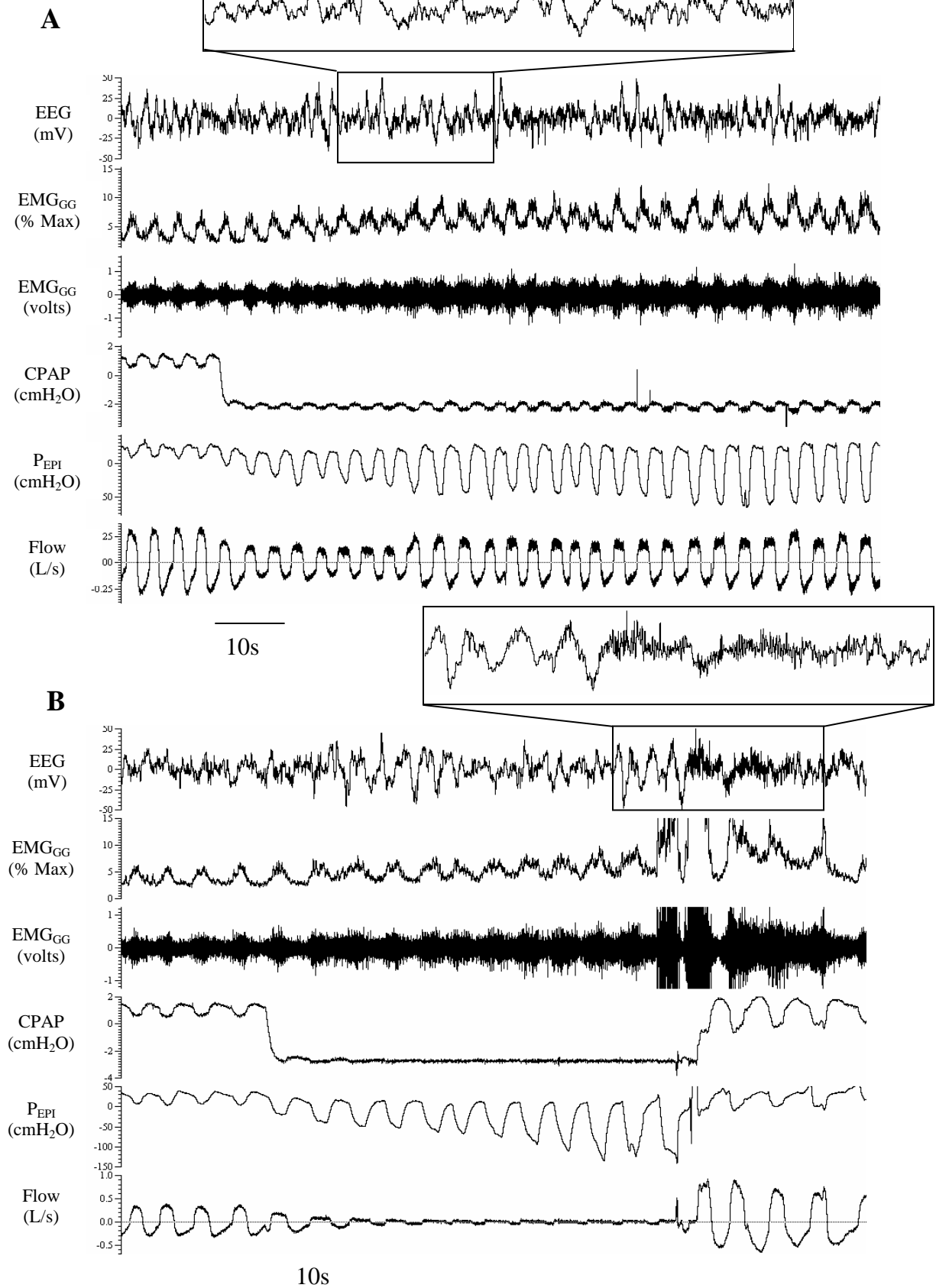
than the non-snorers (although the effect of obesity may have been somewhat counteracted by the higher CPAP levels). Thus without documentation of lung volume changes during pressure drops it is difficult to predict whether lung volume changes would be similar between groups or not.

The initial changes in duty cycle and breathing frequency observed in the current study were a result of the reduction in expiratory time, which remained reduced for the duration of reduced CPAP. This finding may simply be a result of the sudden reduction in expiratory pressure, because similar reductions in T_E are not reported with the application of inspiratory resistive loads [13]. Thus such a reduction in T_E and immediate increase in T_I/T_{TOT} may not occur during naturally occurring airway collapse during sleep. In contrast, however, the more delayed increase in duty cycle is a result of increased inspiratory time which is also seen with load application [13] and CNAP [6] and likely occurs during naturally occurring upper airway obstruction during sleep.

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Online Figure 1



Online Figure 2

