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## The compensatory responses to upper airway obstruction in normal subjects under propofol anesthesia\*

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### Abstract

Upper airway obstruction during sleep can trigger compensatory neuromuscular responses and/or prolong inspiration in order to maintain adequate minute ventilation. The aim of this study was to investigate the strength of these compensatory responses during upper airway obstruction during propofol anesthesia. We assessed respiratory timing and upper airway responses to decreases in nasal pressure in nine propofol anesthetized normal subjects under condition of decreased (passive) and increased (active) neuromuscular activity. Critical closing pressure ( $P_{\text{CRIT}}$ ) and upstream resistance ( $R_{\text{US}}$ ) were derived from pressure-flow relationships generated from each condition. The inspiratory duty cycle (IDC), maximum inspiratory flow ( $\dot{V}_I \text{ max}$ ) and respiratory rate ( $f$ ) were determined at two levels of mean inspiratory airflow ( $\bar{V}_I$ ; mild airflow limitation with  $\bar{V}_I \geq 150 \text{ ml s}^{-1}$ ; severe airflow limitation with  $\bar{V}_I < 150 \text{ ml s}^{-1}$ ). Compared to the passive condition,  $P_{\text{CRIT}}$  decreased significantly ( $5.3 \pm 3.8 \text{ cm H}_2\text{O}$ ,  $p < 0.05$ ) and  $R_{\text{US}}$  increased ( $7.4 \text{ cm H}_2\text{O ml}^{-1} \text{ s}$ ,  $p < 0.05$ ) in the active condition. The IDC increased progressively and comparably as  $\bar{V}_I$  decreased in both the passive and active conditions ( $p < 0.05$ ). These findings imply that distinct compensatory mechanisms govern the modulation of respiratory pattern and pharyngeal patency during periods of airway obstruction under propofol anesthesia.

### Keywords

Propofol anesthesia; Critical closing pressure; Inspiratory duty cycle; Upper airway; Obstructive sleep apnea

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## 1. Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive obstruction of the upper airway that results in recurrent hypoxemia and arousal from sleep and increases in cardiovascular morbidity and mortality (Remmers et al., 1978; Malhotra and White, 2002). Upper airway obstruction during sleep can result from alterations in either the passive structural pharyngeal properties or from disturbances in neuromuscular control. Methods for quantifying the contribution of anatomic alterations have been established in both sleeping and anesthetized subjects (Isono et al., 1997; Eastwood et al., 2002a; Patil et al., 2007), while those for assessing active neuromuscular responses to upper airway obstruction have been limited to sleeping subjects (Schwartz et al., 1988; Smith et al., 1988; Patil et al., 2007).

When the upper airway first obstructs, the upper airway musculature remains in a relatively hypotonic or *passive state* (Schwartz et al., 1998; Patil et al., 2004, 2007). Initially, mechanoreceptor activity in airway pressure receptors and pulmonary stretch receptors can produce immediate alterations in respiratory timing in experimental animals and sleeping humans. Recent evidence suggests that a prolongation of the inspiratory duty cycle can help stabilize ventilation during periods of upper airway obstruction (Tagaito et al., 2002; Schneider et al., in press). Thereafter, upper airway obstruction can elicit compensatory neural responses that can mitigate the obstruction during spontaneous breathing in sleeping and anesthetized subjects. As upper airway obstruction persists, disturbances in gas exchange ensue, leading to increases in upper airway neuromuscular activity, improvements in airway patency and greater ventilatory stability (*active state*) (Schwartz et al., 1993; Seelagy et al., 1994; Rowley et al., 1997; Patil et al., 2007; McGinley et al., 2008). When compensatory mechanisms are inadequate to stabilize ventilation, upper airway obstruction often terminates in an arousal from sleep and the prompt restoration of upper airway patency (Younes, 2004). Arousals can therefore interfere with the assessment of compensatory upper airway and respiratory timing responses.

We have previously reported that passive measurements of upper airway collapsibility in sedated subjects were similar to non-REM sleep (Ayuse et al., 2004; Inazawa et al., 2005; Ikeda et al., 2006). Active compensatory neuromuscular responses, however, have not been characterized in anesthetized subjects. We hypothesized that compensatory neuromuscular responses can be readily characterized under anesthesia and that these responses increase progressively with the severity and duration of upper airway obstruction. To address this hypothesis, we examined passive and active upper airway properties and timing responses to acute and sustained periods airflow obstruction under propofol anesthesia, respectively.

## 2. Methods

### 2.1. Subjects

Upper airway pressure-flow relationships were assessed under propofol anesthesia in nine subjects (male 4, female 5), who were of  $22.2 \pm 3.0$  years of age and had a mean body weight of  $56.0 \pm 9.6$  kg, height of  $1.60 \pm 0.1$  m and body mass index (BMI) of  $20.9 \pm 2.6$  kg/m<sup>2</sup>. Subjects who reported a history of snoring or anatomical deformation in upper airway (e.g., deviated septum, retrognathia) were excluded from this study. The protocol was approved by the Human Investigation Committee of the Nagasaki University School of Dentistry and written informed consent was obtained from all subjects.

### 2.2. Experimental procedures and monitoring

**2.2.1. Polysomnographic and anesthetic monitoring**—All subjects underwent routine hemodynamic monitoring (systolic and diastolic blood pressure as well as pulse rate) and

electrocardiogram (ECG), polysomnographic monitoring of sleep, with bilateral electro-oculograms (EOG; left and right), electroencephalograms (EEG; C3-A2 and O2-A1) and submental electromyogram (EMG) to confirm anesthetic level. EEG signals were processed by the BIS monitor (Aspect Medical Systems, Inc., Natick, MA) in order to determine the depth of anesthesia. Oxygen saturation was measured by pulse oximetry ( $SpO_2$ ) and transcutaneous  $P_{CO_2}$  ( $TcCO_2$ ) was measured by transcutaneous  $CO_2$  analyser (Tina, TCM4, Radiometer, Tokyo, Japan).

**2.2.2. Respiratory measurements**—Thoracic and abdominal movements were also measured using inductance plethysmography. Esophageal pressure ( $P_{ESO}$ ) was determined from a Hyatt-type esophageal balloon (Ackrad laboratories, Cranford, NJ, USA) where the tip of catheter was positioned ~45–50 cm from nares. Airflow ( $\dot{V}$ ) was measured using a pneumotachometer (model 3830, Hans Rudolph, Inc., Kansas City, MO, USA) and nasal pressure ( $P_N$ ) measured using a differential pressure transducer (model 1100, Hans Rudolph, Inc., Kansas City, MO, USA). The outflow from this valve was then connected in series to the pneumotachometer and nasal mask (Fig. 1). Air leaks from the mouth were prevented by applying surgical tape across the lips. The changes in  $P_N$  were able to be made utilizing a pressure generator (MAP/ResMed, Martinsreid, Germany) operating over a –15 to +15 cm  $H_2O$  range connected to the nasal mask. All the measurements were displayed and recorded simultaneously on a computer using data acquisition device (either Embla S7000 or A-10, Medcare, NY, USA).

**2.2.3. Genioglossus EMG ( $EMG_{GG}$ ) measurements**—Genioglossus EMG activity was recorded and analyzed utilizing previously described methods (Mezzanotte et al., 1992). Briefly,  $EMG_{GG}$  was measured by using a pair of unipolar percutaneous intramuscular electrodes referenced to a single ground, thus producing a bipolar recording. Tonic  $EMG_{GG}$  (lowest integrated genioglossus EMG activity value during expiration) was defined as the difference between electrical zero and minimum level near end-expiration. Phasic  $EMG_{GG}$  was defined as the difference between the end-expiratory value and peak-inspiratory  $EMG_{GG}$  (at  $\dot{V}_I$  max). The  $EMG_{GG}$  measurements made for the “activation phase” were made at the  $P_N$  where sustained flow limitation was induced for 2 min. Measurements were expressed as a percent change from the maximal value obtained during voluntary tongue protrusion and swallows prior to anesthesia.

### 2.3. Experimental protocols

**2.3.1. Propofol anesthesia**—No premedication was given. Propofol anesthesia was induced with intravenous propofol (Dipriva; Astra Zeneca, Alderley Park, Cheshire, United Kingdom), administered via a Diprifusor (Astra Zeneca) target-controlled infusion system (Terumo TCI pump TE371, Tokyo, Japan), which calculated effect site concentration on the basis of a three-compartment pharmacokinetic algorithm (Marsh et al., 1991; Coetzee et al., 1995; Eastwood et al., 2005). The propofol target blood concentration was increased and kept constant between 1.5 and 2.0  $\mu\text{g/ml}$  to obtain adequate level of anesthesia. We required the subject's BIS value be between 40 and 60 in order to obtain an adequate level of anesthesia. At the conclusion of the measurements, all the subjects were kept in the supine position until they showed a spontaneous emergence from anesthesia.

**2.3.2. Assessing passive and active upper airway and timing responses**—Specific experimental paradigms for manipulating the  $P_N$  were used to assess passive and active upper airway and timing characteristics during anesthesia (Patil et al., 2007; McGinley et al., 2008). During these protocols, the subject's head was positioned in the Frankfurt plane and the mandible in the occluded neutral position. At least two series of passive and active  $P_{CRIT}$  measurements were conducted in random order over an approximately 10min interval.

**2.3.2.1. Passive  $P_{\text{CRIT}}$ :** Following the establishment of an adequate level of stable anesthesia, the subjects were initially allowed to breathe under atmospheric pressure.  $P_{\text{N}}$  was then gradually increased to a holding pressure where inspiratory airflow limitation was abolished (“*passive state*”), as previously described (Schwartz et al., 1998; Boudewyns et al., 2000). To establish the passive  $P_{\text{CRIT}}$ ,  $P_{\text{N}}$  was rapidly lowered from the holding pressure to specific levels for five successive breaths before returning to the holding pressure (Fig. 2). Nasal pressure levels traversed a range of pressures encompassing zero flow (airway occlusion). Passive pressure-flow relationships were generated from at least two series of pressure ‘drops’ over this range.

**2.3.2.2. Active  $P_{\text{CRIT}}$ :** Nasal pressure was lowered step-wise to load the ventilatory control system, utilizing a modification of a previously described protocol (Patil et al., 2007; McGinley et al., 2008). In brief, a stable unobstructed breathing pattern was initially maintained at a positive holding pressure. Thereafter,  $P_{\text{N}}$  was lowered by 2 cm H<sub>2</sub>O steps until a quasi-steady state flow limited breathing pattern was achieved in association with a 40–50% reductions in  $\dot{V}_{\text{I max}}$  (“activation phase”). This level of airflow obstruction was maintained for 2 min during which genioglossal EMG activity rose, the  $\text{SpO}_2$  fell by 3–5% and the  $\text{TcCO}_2$  increased by 5–10 mmHg above baseline (accounting for a 5–10 s delay in  $\text{TcCO}_2$ ). Subsequently,  $P_{\text{N}}$  was lowered in a stepwise fashion by 2 cm H<sub>2</sub>O every 5 breaths until zero flow was obtained or  $\text{SpO}_2$  reached a lower limit of 88–90% (Fig. 2).

**2.3.3. Severity of upper airway obstruction—**All of the respiratory parameters were obtained from non-flow limited breaths at baseline and two levels of  $\dot{V}_{\text{I}}$  obtained from breaths during the passive and active conditions. The severity of upper airway obstruction was established based on the specific ranges of  $\dot{V}_{\text{I}}$  above and below a clinically and physiologically relevant cut-off of 150 ml s<sup>-1</sup>. When  $\dot{V}_{\text{I}}$  is below this cut-off, upper airway obstruction is known to lead to periodic obstructive hypopneas, whereas breathing patterns stabilize when  $\dot{V}_{\text{I}}$  exceeds this cut-off (Gleahill et al., 1991). Mild flow limitation was therefore defined by a  $\dot{V}_{\text{I max}}$  of greater than 150 ml s<sup>-1</sup> and severe flow limitation was defined as a  $\dot{V}_{\text{I max}}$  between 25 and 150 ml s<sup>-1</sup>.

## 2.4. Data analysis

**2.4.1. Upper airway pressure-flow relationship—**At each level of  $P_{\text{N}}$ , breaths were evaluated for the presence of inspiratory airflow limitation, as previously described (Schwartz et al., 1988, 1989; Boudewyns et al., 2000; Ayuse et al., 2004). Inspiratory flow limitation was defined as the presence of a plateau in inspiratory airflow in association with a continued fall in esophageal pressure by at least 1 cm H<sub>2</sub>O beyond the onset of the plateau. Breathes that were associated with arousal were excluded from analysis. Non-flow limited breaths from the baseline condition at holding pressure were analyzed to determine the peak inspiratory airflow ( $\dot{V}_{\text{I peak}}$ ) at baseline. Maximal inspiratory flow ( $\dot{V}_{\text{I max}}$ ) and the corresponding  $P_{\text{N}}$  were obtained for each flow limited breath in the obstructed conditions. Least-squares linear regression was used to generate the pressure-flow relationship (Gold and Schwartz, 1996), and fit by the following equation:

$$\dot{V}_{\text{I max}} = \frac{P_{\text{N}} - P_{\text{CRIT}}}{R_{\text{US}}} \quad (1)$$

where  $P_{\text{CRIT}}$  is the critical closing pressure ( $P_{\text{N}}$  at zero flow) and  $R_{\text{US}}$  is the resistance of the portion of the tube upstream to the site of collapse. The difference between the active  $P_{\text{CRIT}}$  and passive  $P_{\text{CRIT}}$  ( $\Delta P_{\text{CRIT A-P}}$ ) was considered a measure of the strength of dynamic neuromuscular responses to upper airway obstruction.

**2.4.2. Respiratory parameters ( $f$ ,  $\bar{V}_E$ , IDC,  $\bar{V}_{Ipeak}$ ,  $\dot{V}_I \max$ ,  $\bar{V}_I, V_T$ ,  $\bar{V}_{ALV}$ )**—The respiratory parameters were obtained in baseline and two different level of flow limitation. The respiratory parameters evaluated were as follows: respiratory rate ( $f$ ), minute ventilation ( $\bar{V}_E$ ), inspiratory duty cycle (IDC;  $IDC = T_I/T_{TOT}$ ) where  $T_I$  is the duration of inspiration and  $T_{TOTAL}$  is the duration of the inspiration and expiration; peak inspiratory airflow ( $\bar{V}_{Ipeak}$ ) during non-flow limited breathing; maximum inspiratory airflow ( $\dot{V}_I \max$ ) during airflow limited breathing; mean inspiratory airflow ( $\bar{V}_I = V_T/T_I$ ) where  $V_T$  is the tidal volume.

Dead space volume ( $V_{DS}$ ) was calculated with the formula,  $24 \times \text{height}^2$  (in.)/703 ml. Alveolar ventilation ( $\bar{V}_{ALV}$ ) was calculated by subtracting dead space ventilation, which is the product of dead space volume ( $V_{DS}$ ) and respiratory frequency ( $f$ ), from minute ventilation, as shown in the following equation:

$$\bar{V}_{ALV} = \bar{V}_E - (V_{DS} \times f). \quad (2)$$

## 2.5. Statistical analysis

All statistical analyses were performed using SPSS version 16.0 (SPSS, Inc., USA). The differences between the active and passive  $P_{CRIT}$  ( $\Delta P_{CRIT A-P}$ ), the passive  $P_{CRIT}$ , the active  $P_{CRIT}$ ,  $R_{US}$ , and tonic and peak phasic  $EMG_{GG}$  were statistically analyzed. The effects of the time course of the responses in IDC,  $\dot{V}_I \max$ ,  $\bar{V}_I, \bar{V}_E, f, V_T, \bar{V}_{ALV}$  were analyzed using General Linear Model for repeated measures with a post hoc protected Bonferroni adjustment test. Differences between the passive and active  $R_{US}$ , tonic and peak phasic  $EMG_{GG}$  were assessed with by Mann–Whitney  $U$ - and paired  $T$ -tests. Statistical significance was assumed for  $p < 0.05$ . Results are presented as mean  $\pm$  standard deviation (SD) unless otherwise noted.

## 3. Results

### 3.1. Effect of propofol anesthesia on consciousness and breathing parameters

During stable awake conditions before administration of propofol,  $f$  was  $17.2 \pm 1.0$  breaths  $\text{min}^{-1}$ ,  $V_T$  was  $310.6 \pm 73.5$  ml,  $\bar{V}_E$  was  $5503 \pm 1141$  ml  $\text{min}^{-1}$ , and IDC was  $0.39 \pm 0.05$ . The mean target blood concentration of propofol was  $1.54 \pm 0.23$   $\mu\text{g/ml}$ , which produced adequate anesthesia, and a BIS score  $52.5 \pm 4.5$ . For both the passive and active states, there was no significant difference in BIS score ( $51.4 \pm 6.5$  and  $53.7 \pm 5.3$ , respectively;  $p = 0.33$ ). The EEG power spectrum was predominantly comprised of frequencies between 0.5 and 4 Hz, similar to that of natural non-REM sleep stages 3–4. The average holding pressure required to abolish flow limitation in all subjects was  $3.4 \pm 2.6$  cm  $\text{H}_2\text{O}$ . During stable anesthesia at the baseline holding pressure, the  $f$  increased slightly to  $19.1 \pm 2.1$  breaths  $\text{min}^{-1}$  ( $p < 0.05$ ),  $V_T$  decreased to  $281.6 \pm 61.1$  ml ( $p < 0.05$ ) and  $\bar{V}_E$  decreased to  $5362 \pm 1071$  ml  $\text{min}^{-1}$  ( $p < 0.05$ ), whereas the IDC remained constant ( $0.40 \pm 0.04$ ;  $p = 0.17$ ) compared to quiet wakefulness.

### 3.2. The effect of passive and active condition

**3.2.1. Passive and active  $EMG_{GG}$  responses**— $Tc_{CO_2}$  did not differ significantly between the baseline and passive state ( $39.7 \pm 3.7$  and  $41.7 \pm 4.2$  mmHg, respectively). In contrast,  $Tc_{CO_2}$  increased from baseline ( $39.8 \pm 3.6$  mmHg) to the active condition ( $44.7 \pm 4.8$  mmHg;  $p < 0.05$ ). Similarly, there was no change in  $Sp_{O_2}$  for the passive state, whereas the lowest value of  $Sp_{O_2}$  fell from a baseline of  $97.2 \pm 0.9\%$  to  $91.3 \pm 1.5\%$  in the active condition ( $p < 0.05$ ). Tonic  $EMG_{GG}$  activity did not differ between the baseline and the passive state ( $5.7 \pm 4.2\%$ ), but increased in the active state ( $12.5 \pm 11.3\%$ ;  $p < 0.05$ ). Similarly, peak phasic  $EMG_{GG}$  activity increased in the active state, relative to both the baseline and passive state (baseline,  $4.9 \pm 3.5\%$ ; passive state,  $4.9 \pm 3.5\%$ ; active state,  $9.5 \pm 8.4\%$ ;  $p < 0.05$ ).

**3.2.2. Passive and active upper airway responses**—Passive  $P_{\text{CRIT}}$  and active  $P_{\text{CRIT}}$  values are shown up in Table 2 and Fig. 3. The mean passive  $P_{\text{CRIT}}$  of  $-4.4 \pm 1.7$  cm H<sub>2</sub>O was significantly higher than the mean active  $P_{\text{CRIT}}$  of  $-9.7 \pm 3.5$  cm H<sub>2</sub>O ( $p < 0.05$ ). There was a significant difference between the passive  $R_{\text{US}}$   $14.2 \pm 3.6$  cm H<sub>2</sub>O ml<sup>-1</sup> s and active  $R_{\text{US}}$   $21.6 \pm 8.1$  cm H<sub>2</sub>O ml<sup>-1</sup> s ( $p = 0.02$ ).  $\Delta P_{\text{CRIT A-P}}$  was  $5.3 \pm 3.8$  cm H<sub>2</sub>O ( $p = 0.003$ ), suggesting a substantial neuromuscular responses to upper airway obstruction (Patil et al., 2007).

**3.2.3. Comparison of respiratory patterns between passive and active conditions**— $\dot{V}_{\text{I max, f}}$ ,  $V_{\text{T}}$ ,  $\bar{V}_{\text{E}}$ , and  $\bar{V}_{\text{ALV}}$  are represented for each level of airflow obstruction ( $\bar{V}_{\text{I}}$ , baseline non-flow limited, mild obstruction and severe obstruction) in both passive and active conditions in Table 1. We observed that  $\dot{V}_{\text{I max}}$  decreased significantly in severe obstruction compared to  $\dot{V}_{\text{I peak}}$  in the baseline condition ( $p < 0.05$ ), and compared flow-limited breaths during mild obstruction ( $p < 0.05$ ) in both the passive and active conditions.  $V_{\text{T}}$  and  $\bar{V}_{\text{E}}$  also decreased significantly ( $p < 0.05$ ) in severe obstruction compared to in baseline condition in both passive and active conditions ( $p < 0.05$ ).  $f$  did not change at different levels of airflow obstruction in the passive and active conditions. Alveolar ventilation  $\bar{V}_{\text{ALV}}$  significantly increased in mild obstruction in the passive and active compared to the baseline condition. Fig. 4 shows the change in IDC in different levels of  $\bar{V}_{\text{I}}$  in both the passive and active conditions. The IDC increased significantly as  $\bar{V}_{\text{I}}$  decreased in passive and active conditions, but did not differ significantly between passive and active conditions.

## 4. Discussion

There were two major findings in our study. First, upper airway obstruction induced immediate progressive increases in the inspiratory duty cycle as the severity of airflow obstruction ( $\bar{V}_{\text{I}}$ ) increased in the passive condition, an effect that persisted in the active condition. Second, upper airway obstruction induced significant increases in  $\dot{V}_{\text{I max}}$  in the active state compared to passive state. These increases in  $\dot{V}_{\text{I max}}$  were related to significant decreases in  $P_{\text{CRIT}}$  from the passive to active condition, reflecting decreasing upper airway collapsibility over time. These decreases in  $P_{\text{CRIT}}$  were also associated with significant increases in EMG<sub>GG</sub> activity, suggesting that neuromuscular activation mediated improvements in airway patency. As in our previous study in non-REM sleep (Patil et al., 2007), our findings suggest that compensatory responses in upper airway and timing parameters are well preserved under propofol anesthesia. They also suggest that immediate responses in the inspiratory duty cycle and time-dependent responses in  $\bar{V}_{\text{I}}$  determine the degree of ventilatory compensation to upper airway obstruction when arousal is suppressed pharmacologically.

### 4.1. Mechanical and neuromuscular control of upper airway patency

Our study was based on prior work demonstrating substantial increases in pharyngeal collapsibility (Patil et al., 2007) in spontaneously breathing patients during sedation and anesthesia (Drummond, 1996; Oshima et al., 1999). Although anesthesia and/or neuromuscular blockade can produce elevations in upper airway collapsibility (Isono et al., 1997; Eastwood et al., 2002a, 2005), we found that the passive  $P_{\text{CRIT}}$  ( $-4.4$  cm H<sub>2</sub>O) under propofol anesthesia was comparable to that found during natural non-REM stage 2 sleep (passive  $P_{\text{CRIT}} = -4.5$  cm H<sub>2</sub>O) in normal subjects (Patil et al., 2007; Kirkness et al., 2008). In contrast, our passive critical pressures were much more negative than that reported under isoflurane anesthesia ( $P_{\text{CRIT}} = 1.2$  cm H<sub>2</sub>O) (Eastwood et al., 2002b), which produced marked decreases in pharyngeal neuromuscular tone and patency. Therefore, it is likely that the collapsibility of the hypotonic pharynx is similar during propofol anesthesia to that observed during natural non-REM sleep.

As previously demonstrated in normal sleeping subjects, we also found a significant reduction in the active compared to passive  $P_{\text{CRIT}}$  ( $-4.4 \pm 1.7$  cm H<sub>2</sub>O vs.  $-9.7 \pm 3.5$  cm H<sub>2</sub>O) under propofol anesthesia. The active  $P_{\text{CRIT}}$  fell by  $5.3 \pm 3.8$  cm H<sub>2</sub>O in the present study ( $\Delta P_{\text{CRIT}_{\text{A-P}}}$ ) and was marginally less than that observed in non-REM sleep in normal individuals ( $\Delta P_{\text{CRIT}_{\text{A-P}}}$ ,  $6.9 \pm 5.7$  cm H<sub>2</sub>O) (Patil et al., 2007), indicating that dynamic neuromuscular responses during propofol anesthesia remain largely intact in normal anesthetized subjects as compared to natural non-REM sleep. Activation of upper airway dilator muscles (e.g., genioglossus) can mitigate the obstruction (Mezzanotte et al., 1992; Malhotra et al., 2000; Fogel et al., 2001). Despite depression of dilator activity under propofol anesthesia, dilator responses to sustained periods of upper airway obstruction were evident, and can account for increases in upper airway patency (increased in  $\dot{V}_I \text{ max}$ ) and for decreases in  $P_{\text{CRIT}}$ . These responses could have also helped to maintain  $\dot{V}_I \text{ max}$  in the mildly flow-limited active condition at levels that were comparable to  $\dot{V}_I \text{ peak}$  levels observed at baseline (non-flow limited). Despite comparable levels of airflow, airflow became limited during sustained reductions in nasal pressure because negative tracheal pressure swings increased as ventilatory drive increased.  $R_{\text{US}}$  also increased in the active compared to passive condition, reflecting progressive decreases in intraluminal pressures (Schwartz et al., 1993; Rowley et al., 1997) and/or decreases in  $P_{\text{CRIT}}$  caused by reductions in the level of nasal pressure (Schwartz et al., 1988; Smith et al., 1988). These findings imply that neuromuscular responses served to stabilize upper airway patency during sustained periods of airflow obstruction. The time course of these active responses is most consistent with chemo- rather than mechanoreceptor stimulation, which results from prolonged periods of upper airway obstruction and hypoventilation (Schwartz et al., 1993; Seelagy et al., 1994).

#### 4.2. Inspiratory duty cycle responses to airflow limitation

During periods of inspiratory airflow limitation, inspiratory duty cycle (IDC) increased immediately and progressively as the severity of airflow obstruction increased. This prolongation of duty cycle occurred instantaneously, consistent with the time course to mechano- rather than chemo-reflex responses (Chow et al., 1994; Iber et al., 1995; Kimoff et al., 2001; Leervers et al., 1993; Dejours, 1962; Manchanda et al., 1996). This increase in inspiratory duty cycle ( $T_I/T_{\text{TOT}}$ ) will act to restore ventilation at any given level of upper airway obstruction, as described by the relationship:  $\dot{V}_E = V_T/T_I \times T_I/T_{\text{TOT}}$ , where  $V_T/T_I$  represents the mean inspiratory flow rate, which was varied experimentally with the severity of upper airway obstruction. In fact, IDC increased initially with the development of upper airway obstruction and decreased over time as obstruction abated ( $\dot{V}_I \text{ max}$  rose) with the activation of pharyngeal neuromuscular responses (Tagaito et al., 2002; Schneider et al., 2003). Moreover, the IDC responses were superimposable in both passive and active conditions, suggesting that these responses are chiefly determined by the severity of upper airway obstruction ( $\dot{V}$ ), and independent of concomitant alterations in gas exchange over time (Tagaito et al., 2002; Schneider et al., 2003). These findings suggest that distinct physiologic mechanisms govern inspiratory duty cycle and upper airway responses to airway obstruction. The IDC response offers immediate relief from nocturnal hypoventilation during periods of upper airway obstruction during sleep (Schneider et al., 2003), and is well preserved during propofol anesthesia.

#### 4.3. Methodological critique: study limitations

There were several limitations to consider in evaluating compensatory timing and pharyngeal responses to upper airway obstruction during propofol anesthesia. First, we could not produce maximum activation of dilator muscles including genioglossus muscle, because subjects' exposure to hypoxemia was limited on ethical grounds. In OSA patients and anesthetized patients, obstruction may cause severe hypoxia and/or hypercapnia which were avoided by imposing a lower limit on the  $\text{SpO}_2$  at 90% for reasons of safety. This limitation may have

attenuated the degree of activation during step-wise decreases in nasal pressure, leading to an underestimation of the full strength of the active response. Second, although propofol presumably exerted a direct suppressant effect on EMG<sub>GG</sub> activity, some degree of activation was undoubtedly present in the passive condition compared to that produced by neuromuscular blockade (Isono et al., 1997). Nevertheless, the main purpose for utilizing propofol anesthesia was to suppress arousal responses to upper airway obstruction in order to examine compensatory responses to acute and sustained upper airway obstruction. Thus, propofol anesthesia induced some degree of neuromuscular suppression in the passive state while enhancing our ability to examine dynamic upper airway and timing responses to obstruction.

#### 4.4. Clinical implications

Our findings have two major clinical implications. First, they serve to characterize distinct upper airway and timing responses to airway obstruction that can stabilize ventilation during sleep. The preservation of compensatory neuromuscular responses in respiratory control (i.e., IDC to sustained upper airway obstruction during propofol anesthesia) suggests that upper airway patency can be restored during sleep even if arousal is pharmacologically suppressed (Younes, 2004; Jordan et al., 2007). In fact, Younes (2004) has suggested that if arousal can be prevented with sedative agents, these compensatory mechanisms should help to stabilize the breathing patterns during sleep in sleep apnea subjects. Our study further suggests that immediate responses in IDC can prevent a precipitous fall in ventilation during obstructive hypopneas (but not apneas), whereas more sustained periods of upper airway obstruction in the absence of arousal are required for the restoration of upper airway patency. Although the threshold to arousal responses and EMG<sub>GG</sub> activation is significantly depressed during propofol anesthesia, compensatory mechanisms may be still function to varying degrees. Our study implies that OSA can be mitigated by immediate timing responses and/or delayed upper airway responses, if they can restore ventilation prior to arousal or oxyhemoglobin desaturation.

Second, our findings establish that methods for assessing upper airway collapsibility during propofol anesthesia are comparable to those during non-REM sleep. In this study, our results demonstrate that the mechanical upper airway properties (passive  $P_{\text{CRIT}}$ ) and the strength of the compensatory neuromuscular responses (active  $P_{\text{CRIT}}$ ) to upper airway obstruction is similar to natural non-REM sleep and upper airway neuromuscular reflexes remain intact during propofol anesthesia. In addition, the use of propofol anesthesia holds the advantage of a short half-life and accurate control depths of anesthesia based on a target-controlled infusion system, which calculates effect site concentrations on the basis of a three-compartment pharmacokinetic algorithm (Marsh et al., 1991; Coetzee et al., 1995). Recently, Eastwood et al. (2005) reported that increasing depths of propofol anesthesia are associated with increases in upper airway collapsibility. These investigators suggested that suppression of neuromuscular drive by propofol anesthesia would facilitate studies examining the influence of mechanical factors on human upper airway collapsibility. Our findings also provide new evidence that patients can be evaluated during propofol anesthesia to model the effects of both mechanical factors and neuromuscular activity on upper airway function during sleep. Observed increases in inspiratory airflow with neuromuscular activation suggest that compensatory responses can maintain airway patency, independent of central arousal mechanisms. Pharmacologic suppression of these arousal responses can also help to standardize the assessment of passive and active upper airway properties.

In conclusion, our findings demonstrate that compensatory neuromuscular responses to upper airway obstruction remain intact during propofol anesthesia. They also imply that distinct mechanisms serve to maintain ventilation in the face of upper airway obstruction with specific latencies to responses in inspiratory duty cycle (immediate) and inspiratory airflow (delayed).



Partitioning the upper airway properties between its structural and neuromuscular components could also serve to established physiologic phenotypes that aid in uncovering specific genetic susceptibilities to obstructive sleep apnea and to perioperative respiratory complications of anesthesia.

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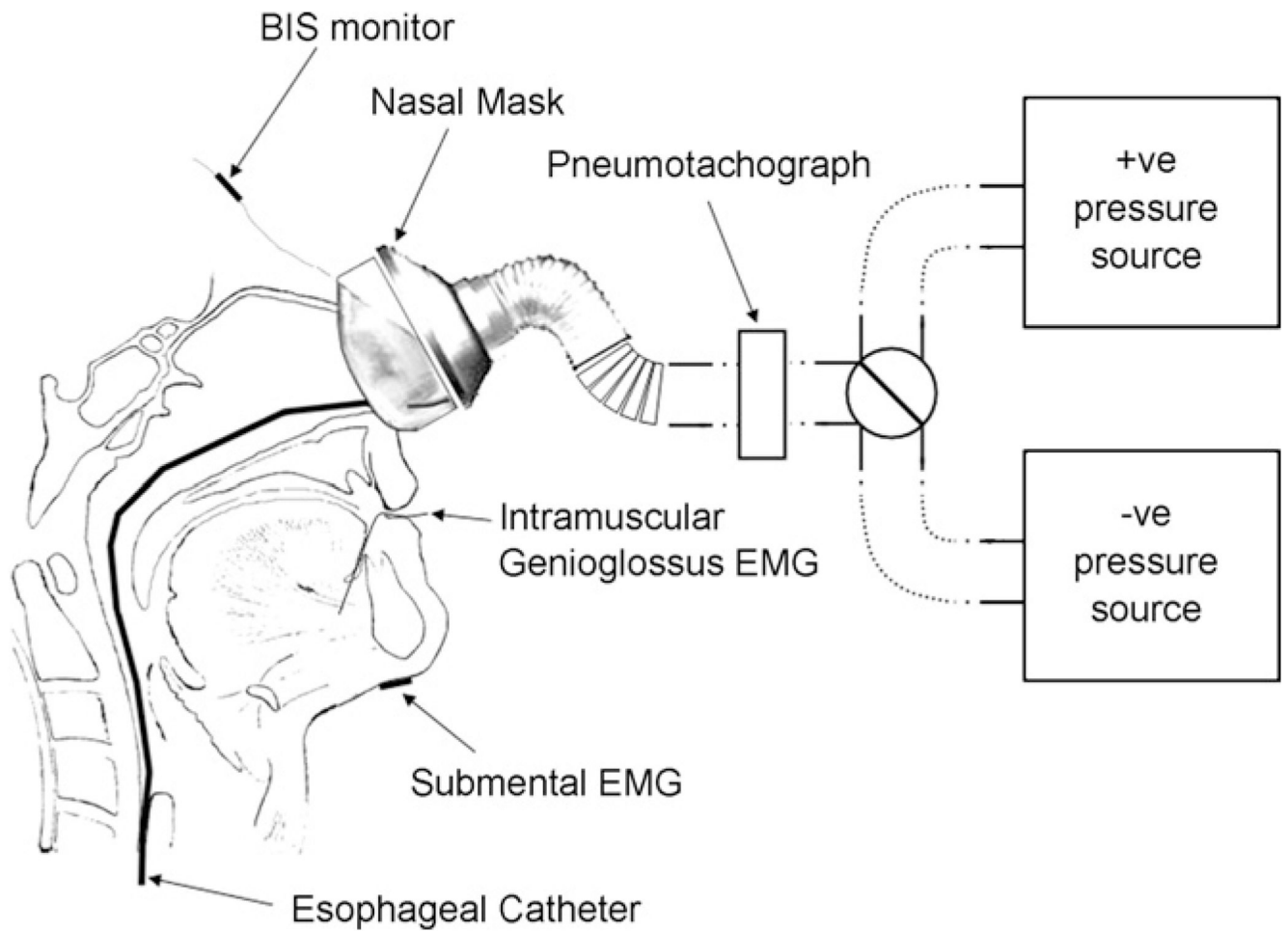
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**Fig. 1.**

Diagram of the experimental setup. A nasal mask attached to a pneumotachograph is connected via tubing to either a positive (+ve) or negative (-ve) pressure source. Genioglossus electromyography ( $EMG_{GG}$ ) was recorded from fine wire intramuscular electrodes positioned percutaneously. Respiratory effort was determined by an esophageal pressure transducer tipped catheter was inserted via the nares. Bispectral Index (BIS) monitor, electroencephalographic leads and submental surface EMG were recorded to monitor state of sedation.

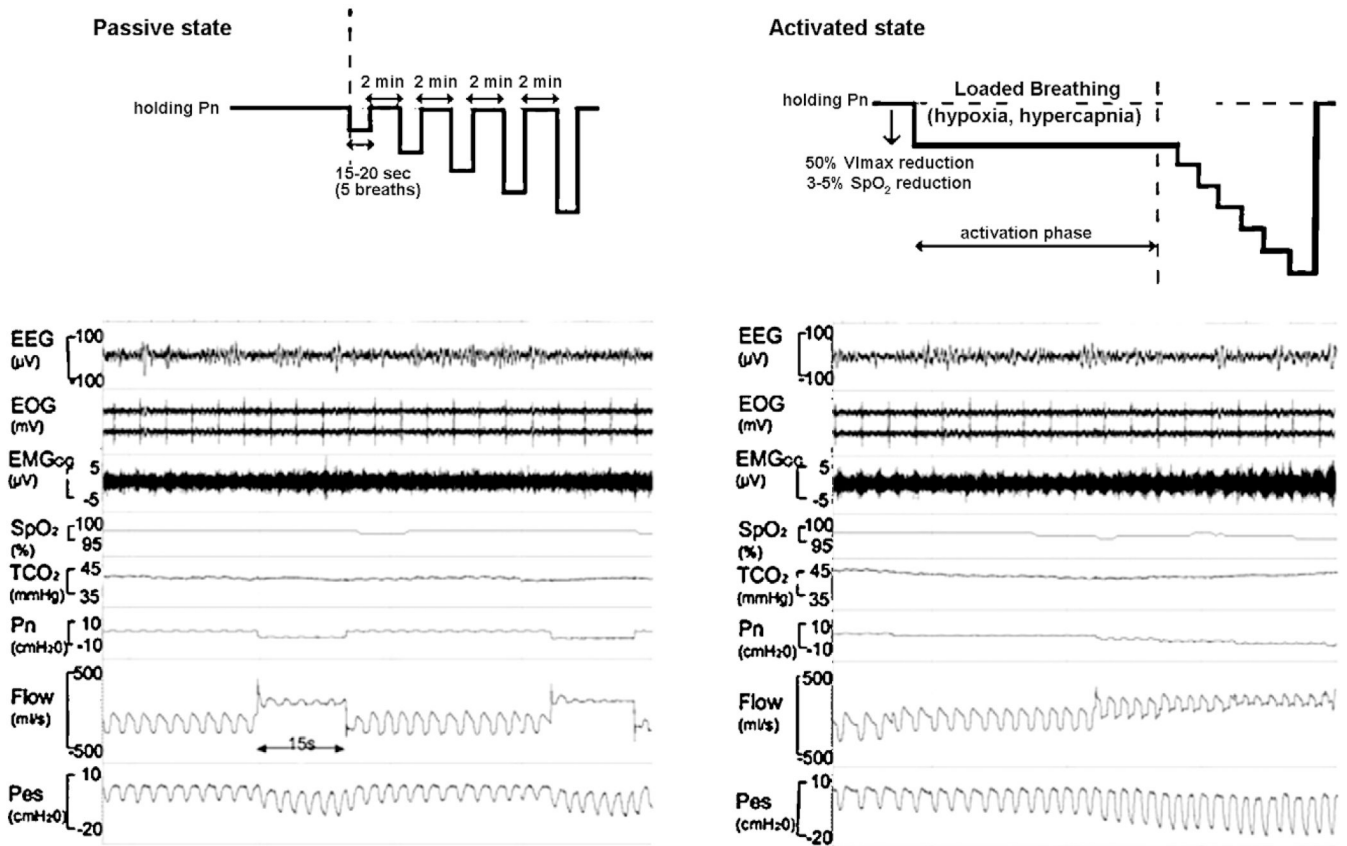
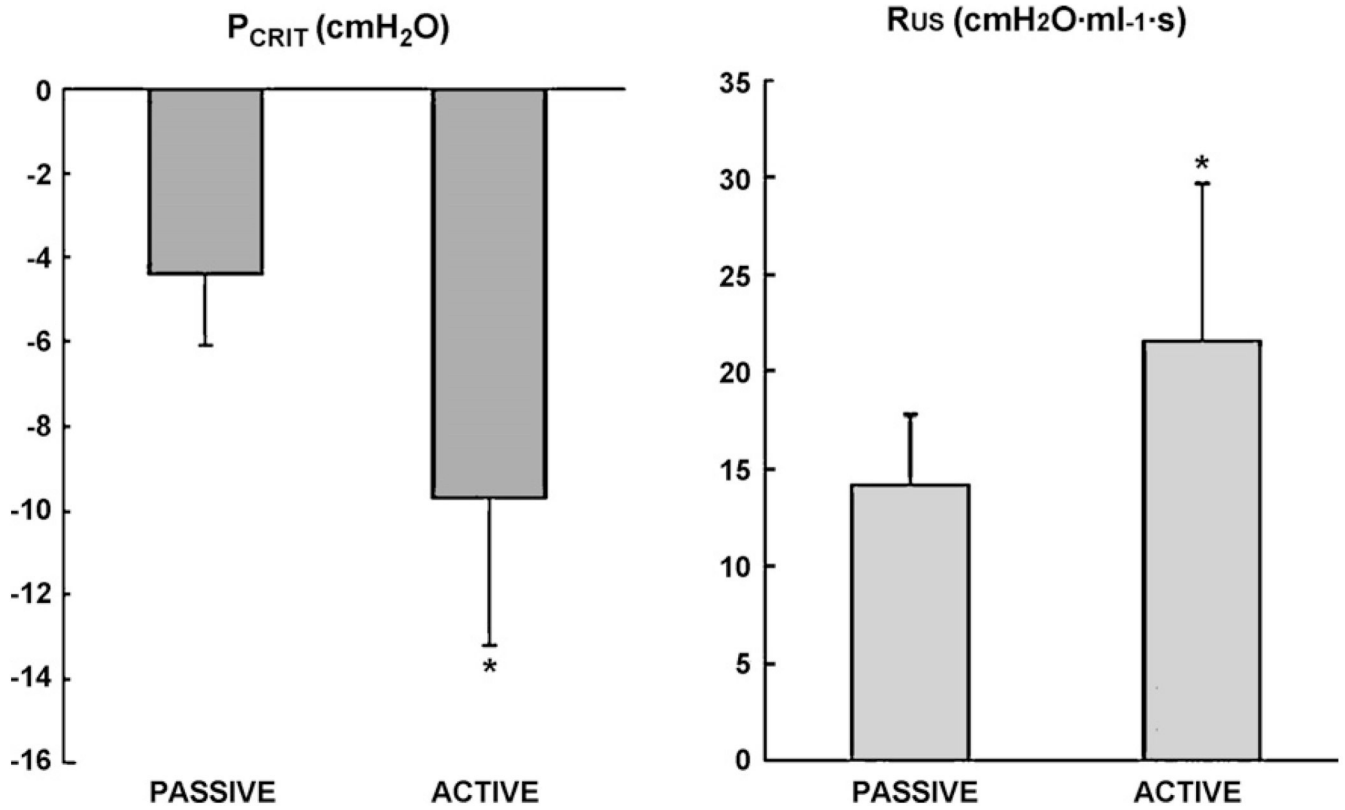


Fig. 2.

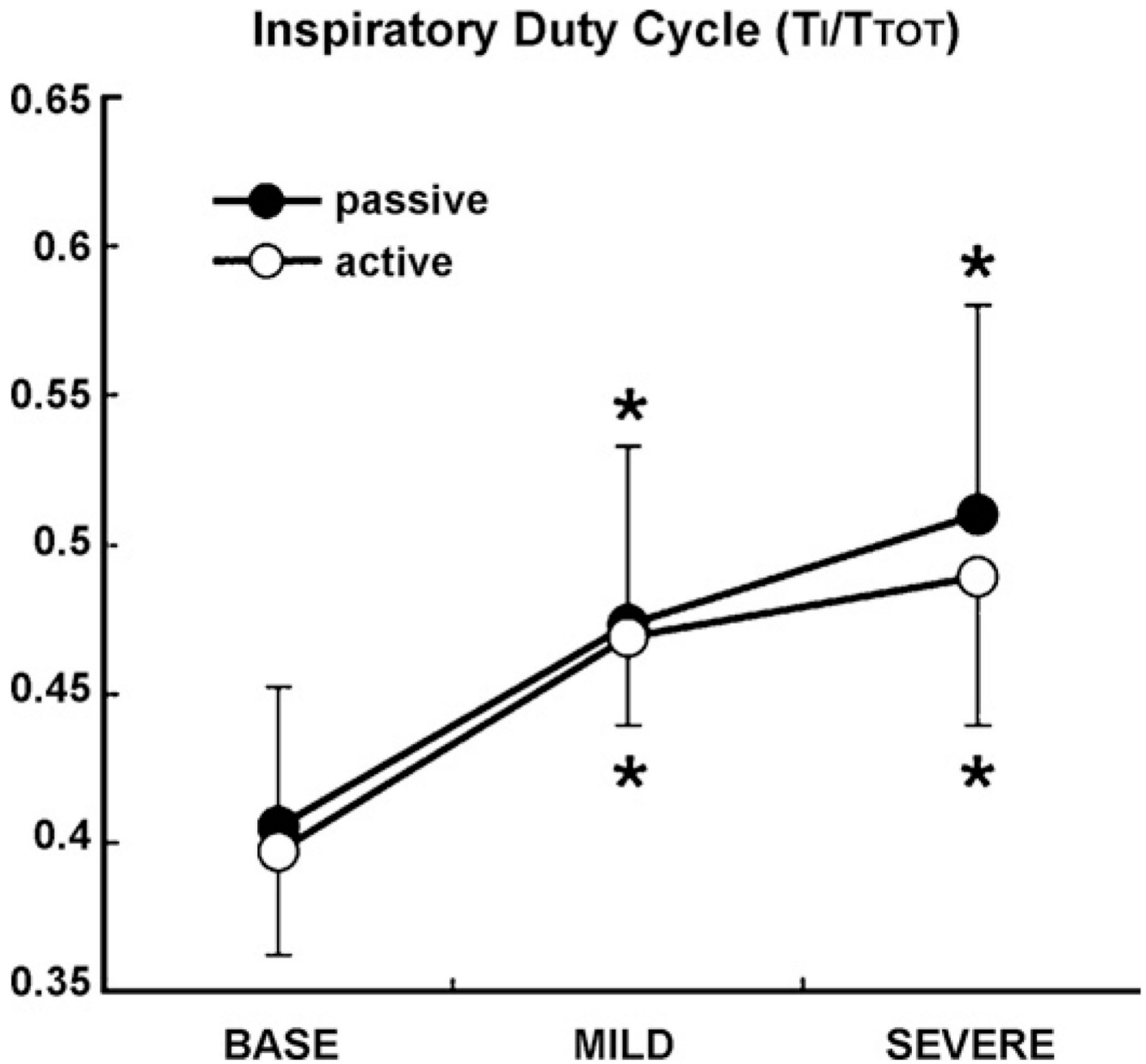
A schematic of the experimental protocol for producing upper airflow obstruction in the passive state (shown at the left) and in the active state (shown at the right). The polysomnographic recording in a one subject in passive and active condition is shown electroencephalogram (EEG), electrooculograms (EOG), intramuscular genioglossus electromyogram (EMG<sub>GG</sub>), oxyhaemoglobin saturation (SpO<sub>2</sub>), transcutaneous carbon dioxide (TcCO<sub>2</sub>), nasal mask pressure (P<sub>N</sub>), pneumotach airflow (Flow), and esophageal pressure (P<sub>ES</sub>).

In the passive condition, P<sub>N</sub> is abruptly reduced from an elevated holding pressure to a level that induced airflow limitation (plateau in airflow with increasing esophageal pressure). Note that the drop in P<sub>N</sub> from holding pressure to lower pressure levels decreases the flow.

In the active condition, a stable unobstructed breathing pattern was initially maintained at a positive holding pressure. Thereafter, P<sub>N</sub> was lowered by 2 cm H<sub>2</sub>O steps until a quasi-steady state flow limited breathing pattern associated with a 40–50% reductions in  $\dot{V}_I$  max (“activation phase”) was achieved. This level of airflow obstruction was maintained for 2 min during which genioglossal EMG activity rose, and SpO<sub>2</sub> fell by 3–5% and TcCO<sub>2</sub> increased by 5–10 mmHg above baseline (accounting for a 5–10s delay in TcCO<sub>2</sub>). Subsequently, P<sub>N</sub> was lowered in a stepwise fashion by 2 cm H<sub>2</sub>O every 5 breaths until zero flow was obtained or SpO<sub>2</sub> reached a lower limit of 88–90%.



**Fig. 3.**  $P_{CRIT}$  and  $R_{UA}$  for passive and active states.  $P_{CRIT}$  decreased ( $*p < 0.05$ ) whereas  $R_{US}$  increased ( $*p < 0.05$ ) in the active state compared to passive state. These changes reflect an improvement in upper airway patency (see Section 4 for details).



**Fig. 4.** IDC at three different level of airflow obstruction (baseline, mild and severe obstruction) in passive and active states. IDC significantly increased progressively in mild and severe obstruction compared to baseline ( $*p < 0.05$  vs. baseline) in both passive and active conditions. There was no significant difference between passive and active condition.

Table 1

Respiratory pattern in different level of obstruction.

	Baseline	Passive		Active	
		Mild	Severe	Mild	Severe
$P_N$ (cm H <sub>2</sub> O)	3.4 (2.6)	-1.4 (2.2)*	-3.7 (1.3)*#	-4.3 (2.0)*	-8.2 (2.0)*#
Upper airway					
$V_I$ max (ml s <sup>-1</sup> ), $V_I$ peak (ml s <sup>-1</sup> )	276.8 (50.7) <sup>a</sup>	229.8 (13.5)	87.1 (25.5)*#	304.9 (63.5)	91.0 (34.2)*#
$\bar{V}_I$ (ml s <sup>-1</sup> )	222.6 (26.5)	185.5 (12.7)	60.1 (12.7)*#	247 (51)	65.6 (28.8)*#
Respiratory pattern					
$f$ (breaths min <sup>-1</sup> )	19 (2)	20 (3)	20 (3)	19 (2)	19 (3)
$V_T$ (ml)	281.6 (61.1)	265.8 (20.8)	94.1 (34.7)*	378 (77.9)*	103.5 (47.7)*
Ventilation					
$\bar{V}_E$ (ml min <sup>-1</sup> )	4989 (1070)	5076 (344)	2206 (576)*#	7000 (2696)	1901 (883)*#
$\bar{V}_{ALV}$ (ml min <sup>-1</sup> )	2204 (997)	1813 (513)	0	3920 (1424)*	0

Maximum inspiratory flow ( $\dot{V}_I$  max).<sup>a</sup> Peak inspiratory airflow ( $\dot{V}_I$  peak) refers to baseline non-flow limited condition only, mean inspiratory air flow ( $\bar{V}_I$ ), respiratory rate ( $f$ ), tidal volume ( $V_T$ ), minutes ventilation ( $\bar{V}_E$ ), estimate of alveolar ventilation ( $\bar{V}_{ALV}$ ).\*  $p < 0.05$  mild and severe vs. baseline.#  $p < 0.05$  severe vs. mild.



**Table 2**

Individual upper airway characteristics of participants during propofol anesthesia.

Passive		Dynamic responses	Active	
$P_{\text{CRIT}}$ (cm H <sub>2</sub> O)	$R_{\text{US}}$ (cm H <sub>2</sub> O ml <sup>-1</sup> s)	$\Delta P_{\text{CRIT}_{\text{A-P}}}$ (cm H <sub>2</sub> O)	$P_{\text{CRIT}}$ (cm H <sub>2</sub> O)	$R_{\text{US}}$ (cm H <sub>2</sub> O ml <sup>-1</sup> s)
-1.1	22.0	9.3	-10.3	18.0
-5.0	17.2	10.8	-15.7	41.4
-4.7	15.1	8.0	-12.7	24.3
-3.6	11.9	0.6	-4.2	20.6
-4.9	12.6	4.1	-9.0	11.8
-7.5	15.0	1.6	-9.0	19.2
-5.5	11.3	1.1	-6.6	18.7
-3.4	12.5	4.0	-7.5	20.2
-4.3	10.4	8.1	-12.4	20.0
-4.4 (1.7)	14.2 (3.6)	5.3 (3.8)	-9.7 (3.5)*	21.6 (8.1)*

Individual data for all subjects is presented in the table. Abbreviations for columns are as follows: critical closing pressure ( $P_{\text{CRIT}}$ ), upstream resistance ( $R_{\text{US}}$ ), differences between passive and active  $P_{\text{CRIT}}$  ( $\Delta P_{\text{CRIT}_{\text{A-P}}}$ ).

\*  $p < 0.05$  active vs. passive.