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Authors

Genta, Pedro R
Owens, Robert L
Edwards, Bradley A
et al.

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

Pedro R Genta[a], **Robert L. Owens**[a], **Bradley A. Edwards**[a], **Scott A. Sands**[a], **Danny J. Eckert**[b], **James P. Butler**[a], **Stephen H Loring**[c], **Atul Malhotra**[d], **Andrew C. Jackson**[e], **David P. White**[a], and **Andrew Wellman**[a]

[a] Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, 02115, Boston, MA, USA

[b]Neuroscience Research Australia (NeuRA) and the School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia

[c]Department of Anesthesia, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, 02215, Boston, MA, USA

[d]Pulmonary and Critical Care Medicine, University of California San Diego, 9300 Campus Point Drive, La Jolla, CA, 92037, USA

[e]Department of Engineering, Boston University, 44 Cummington Mall, 02215 Boston, MA, USA

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±6kg/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.

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Corresponding author: Pedro R. Genta, MD 221 Longwood Avenue, BL038A, Boston, MA, 02115, USA Phone: +1(617)732-6541 Fax: +1(617)732-7337 prgenta@gmail.com.

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Disclosures

AW is a paid consultant for Philips Respironics and Galleon. AW's interests were reviewed and are managed by the Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict of interest policies. DPW is Chief Scientific Officer for Apnicure and a consultant for Philips Respironics. DPW's interests were reviewed and are managed by the Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict of interest policies. RLO is a paid consultant for Philips Respironics. AM has relinquished all outside personal income since May 2012.

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Pharyngeal anesthesia led to a 33% reduction in EMG_{GG} activity ($p<0.001$), but NED worsened only by 3.6±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.

Keywords

obstructive sleep apnea; Starling resistor; flow limitation; negative effort dependence; genioglossus; eletromyography

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 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.

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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 hours 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 1000Hz. The electrodes consisted of two stainless steel Teflon-coated 30-gauge 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 30Hz and 1kHz), rectified, and electronically integrated over a 100ms 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%.

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

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decrease in epiglottic pressure. Once in stable NREM sleep without flow limitation, CPAP was reduced to suboptimum levels for 2-3 minute 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 minutes after the end of anesthesia induction, as previous studies have shown that the duration of action for lidocaine under these conditions is approximately 30 minutes.(Fogel, et al., 2000) Furthermore, we tested the gag reflex of two volunteers at 5 minute intervals after anesthetizing the pharynx. We also found that the gag reflex started to return after approximately 30 minutes.

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 -8cmH_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 (Figure 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 after pharyngeal anesthesia, we measured EMG_{GG} activity during spontaneous swallows before and after pharyngeal anesthesia.

2.4. Statistical analysis

Continuous variables are reported as the mean ± SD or the median [interquartile range] as appropriate. Normal distribution was tested using the Shapiro-Wilk test. Pre and post-anesthesia data were compared using a paired Student's t-test or Wilcoxon signed-rank test. A p-value less than 0.05 was considered significant. The association between the percent changes in NED and EMG_{GG} before and after pharyngeal anesthesia was tested using Pearson correlation coefficient.

3. Results

Twenty-four subjects were enrolled in the study. Twelve subjects were excluded because they could either not fall asleep within 30 minutes after pharyngeal anesthesia

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administration (n=9), or because the EMG signal quality was poor (n=3). The characteristics of the 12 patients included in the analysis are presented in Table 1.

The average amount of lidocaine used was 3.5±1.0 ml. The median number of breaths analyzed from each patient was 15.5 [13.3-25.8] and 14.0 [8.5 17.5] before and after anesthesia, respectively. Overall, despite a 33% reduction in phasic EMG_{GG} activity (from 2.7 [1.2–29.4] to 1.8 [0.5–12.6]% max, p<0.001), pharyngeal anesthesia led to a near-significant reduction of NED (compare 31±17 to 35±19%, p=0.056, Table 2, Figures 2 and 3). There was a trend for the percent change in EMG_{GG} to be correlated with the percent change in NED before and after anesthesia (r= -0.503, P=0.100). Since there was some variability in the responses (see Figure 3), we analyzed the 6 subjects with the highest EMG_{GG} activity at baseline. In this subgroup, EMG_{GG} reduced from 27[16-37] to 12[4-21]% max (p=0.031). Nevertheless, in these individuals NED remained unchanged (from 24±12 to 25±14%, p=0.661) after pharyngeal anesthesia. We also assessed the change in NED among the 6 subjects with the largest decrease in EMG_{GG} (71% change, from 1.7[0.8-22.8] to 0.5[0.2-6.5]% max; p=0.031) and found that NED worsened by 7±6% after anesthesia (from 33±18 to 40±20, p=0.029). During baseline conditions, 66.7% of the breaths analyzed were taken from NREM Stage 2 and 33.3% were from Stage 3. During the anesthesia period, 89% of breaths analyzed were from Stage 2 and 11% from Stage 3 (P<0.001 for the comparison of sleep stage proportions between baseline and anesthesia periods). We compared EMG_{GG} activity during spontaneous swallows before and after lidocaine application in order to confirm that EMG_{GG} electrodes did not move, EMG_{GG} activity during spontaneous swallows before (64.2%) and after pharyngeal anesthesia (55.5%) was similar (P=0.36).

4. Discussion

The main finding of the present study was that upper airway anesthesia had little effect on the magnitude of NED observed. Our findings therefore suggest that the variability in NED found between OSA patients is not likely due to individual differences in inspiratory phasic pharyngeal muscle activation in response to negative luminal pressure.

Similar to previous studies, we were able to successfully attenuate inspiratory phasic EMG_{GG} response to negative luminal pressure using pharyngeal anesthesia. Horner et al. showed that pharyngeal anesthesia using a combination of benzocaine and lidocaine in 6 patients was able to reduce phasic EMG_{GG} activity response to negative pressure stimuli by 21% during wakefulness.(Horner, et al., 1991) Fogel et al studied 13 OSA patients during wakefulness before and after pharyngeal anesthesia with lidocaine and also showed a significant (33%) reduction in EMG_{GG} activity in response to negative pressure stimuli. Berry et al studied 6 OSA patients during sleep before and after pharyngeal anesthesia with topical lidocaine and showed a 68% decrease in phasic EMG_{GG}, as well as a significantly reduced slope of EMG_{GG} versus peak negative esophageal pressure.(Berry, et al., 1997) Therefore, our findings on the attenuation of phasic EMG_{GG} activity by 33% with pharyngeal anesthesia during sleep are consistent with previous reports (Berry, et al., 1997, Fogel, et al., 2000, Horner, et al., 1991).

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While the current study did not find a significant effect of pharyngeal anesthesia on NED per se, previous studies have shown that pharyngeal anesthesia worsens airway obstruction in general.(Berry, et al., 1995, Cala, et al., 1996, Chadwick, et al., 1991, Fogel, et al., 2000) Furthermore, pharyngeal anesthesia has been reported to increase apnea duration.(Berry, et al., 1995) Another report showed an increase in the number of obstructive events but not in event duration.(Chadwick, et al., 1991) This finding suggests that pharyngeal anesthesia increases pharyngeal collapsibility. However, a worsening of pharyngeal collapsibility with topical anesthesia is not a universal observation.(Fogel, et al., 2000)

The significance of our findings are that they could lead to the development of more accurate models of pharyngeal collapse. The conventional model is a Starling resistor, which is characterized by a collapsible segment (pharynx) within a box (upper airway soft tissue and bony structures) interposed by rigid extremities (nose and trachea).(Gold and Schwartz, 1996) Flow limitation will develop when intraluminal pressure equals the pressure inside the box. Importantly, reductions in downstream pressure below the box pressure will not affect the upstream segment and thus flow will remain constant.(Gold and Schwartz, 1996)

The Starling resistor model is an attractive model when flow truly flattens or plateaus. (Figure 4-A) However, in many patients we do not see such flattening, but rather NED is observed (Figure 4-B and C).(Owens, et al., 2012, Owens, et al., 2014a, Owens, et al., 2014b) An alternative model of collapse is what we refer to as a piston-type model (Figure 5).(Butler, et al., 2013) This model has a sizable portion of the airway wall connected to a spring (which models tissue compliance) and a force generator which models muscle activity (see F_m in Figure 5). The spring alone (without F_m) would produce severe NED with full collapse at mid to late inspiration. However, phasic bursts of F_m, we hypothesized, could prevent the airway from collapsing during mid/late inspiration, thereby increasing mid inspiratory flow, e.g. from B to C or C to A in Figure 4. Contrary to our original hypothesis, however, we found that phasic bursts of F_m do not appreciably increase mid-inspiratory flow. Therefore, the flattening of inspiratory flow may be an intrinsic property of the tissue, i.e., a true Starling resistor, rather than a piston model with strong muscle activation.

Our study has several limitations that require consideration. First, this was a technically challenging study as patients were required to fall asleep after the application of anesthesia, and that we only had a small window of opportunity to assess the negative pressure reflex post anesthesia. Thus, many subjects were excluded, leaving a limited number of subjects with complete data sets. However, since the observed increase in NED before and after anesthesia was only 4%, we feel that increasing the sample size would be unlikely to change the interpretation of the results, i.e., the attenuation of phasic muscle activation has only a small effect on NED. Second, we were not able to completely abolish phasic EMG_{GG} activity with pharyngeal anesthesia. Nevertheless, while the magnitude of the reduction in EMG_{GG} activity we obtained during pharyngeal anesthesia was similar to previous reports, (Fogel, et al., 2000, Horner, et al., 1991) a larger reduction in phasic muscle activation could possibly produce a greater worsening of NED. However, even among subjects with the greatest reduction in EMG_{GG} after anesthesia (71% reduction in EMG_{GG}), there was only a 7% increase in NED. Third, our group of patients had a relatively high AHI, raising concerns that EMG_{GG} activation could be impaired at baseline. Nevertheless, subjects

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showed a wide range of phasic activity at baseline (0.6-43.8%max). Fourth, a larger proportion of the analyzed breaths were taken from NREM Stage 3 at baseline than during anesthesia. Both increased (Basner, et al., 1991) and unaltered (Jordan, et al., 2009) phasic EMG_{GG} activity during Stage 3 as compared to Stage 2 have been reported. However, a potential mechanism that could lead to an increased phasic EMG_{GG} activity during Stage 3 would be by an increased tolerance to negative pharyngeal pressure (higher arousal threshold) and, consequently, larger reflex muscle activation. (Ratnavadivel, et al., 2010). By matching analyzed breaths for CPAP level and epiglottic pressure, we believe that sleep stage differences in EMG_{GG} were minimized. Fifth, we cannot rule out the possibility that lidocaine reduced pharyngeal mucosa surface tension. However, previous studies reported an increase in the frequency of obstructive events (Chadwick, et al., 1991) and apnea duration (Berry, et al., 1995) after topical lidocaine administration. These observations suggest that a possible reduction in surface tension induced by lidocaine is probably small. Finally, the effect of pharyngeal anesthesia on NED could be limited if the magnitude of NED at baseline was already high. However, when we analyzed the effect of pharyngeal anesthesia among those with high (>25% NED (n=7)) and low (<25% NED (n=5)) at baseline, no significant worsening of NED was present (p=0.055 and 0.551, high and low NED, respectively).

In conclusion, we have shown that phasic EMG_{GG} activation had little effect on NED. This finding suggests that phasic EMG_{GG} activation does not likely explain the variability of NED among OSA patients. Further investigation on the mechanisms of NED and alternative models for pharyngeal narrowing that incorporate driving pressure are needed.

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Highlights

- The shape of inspiratory flow limitation in obstructive sleep apnea varies
- Some exhibit little, others demonstrate considerable negative effort dependence (NED)
- We assessed NED before and after pharyngeal topical anesthesia with lidocaine
- The effect of pharyngeal anesthesia on NED was small
- This suggests a limited role of airway muscle activation in NED

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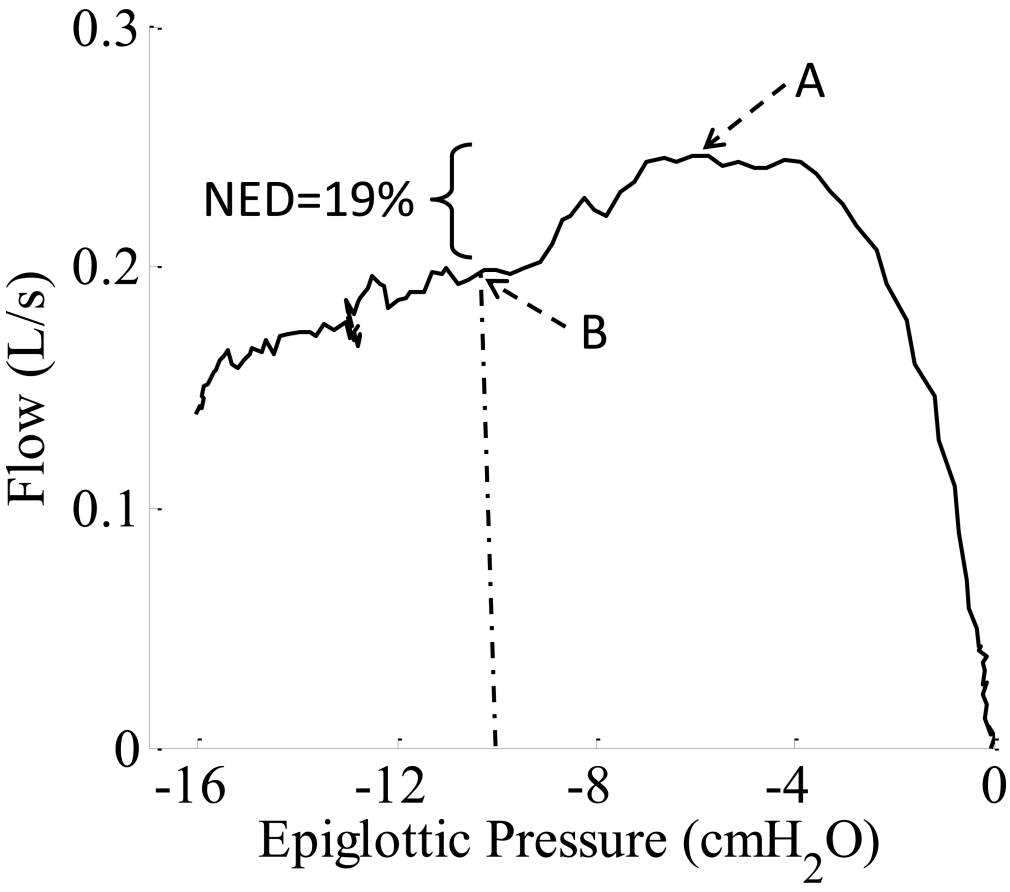

Figure 1.

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).

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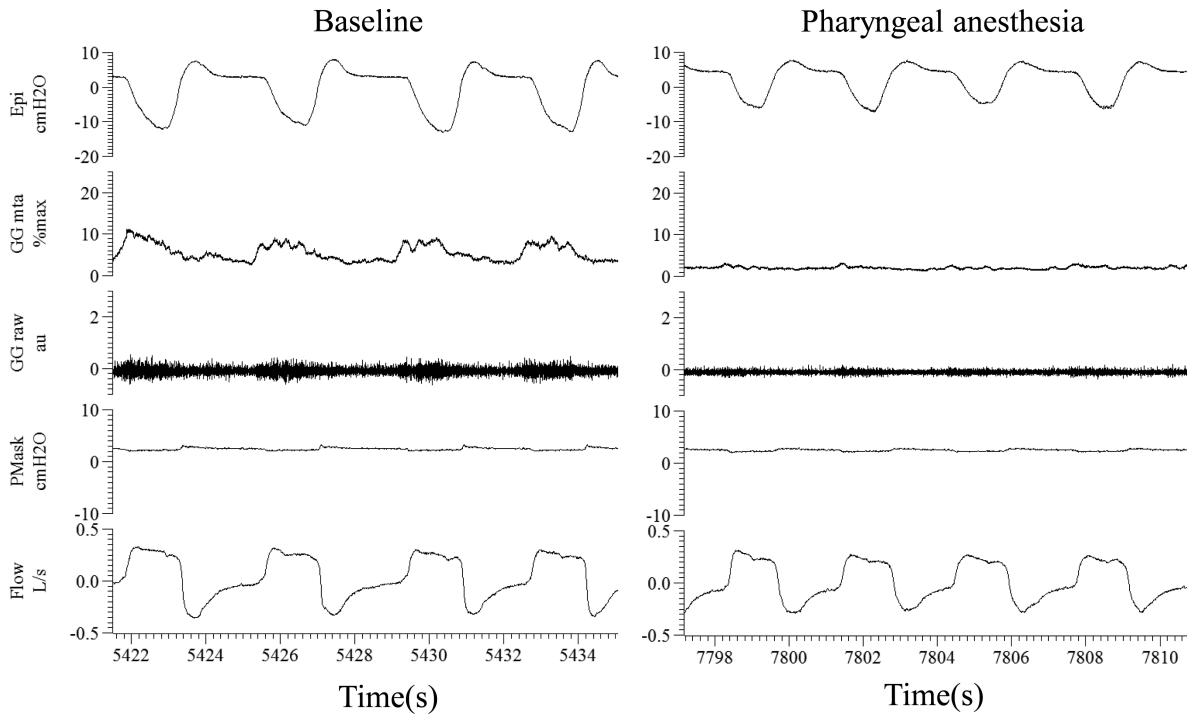

Figure 2.
Raw tracing of a subject.

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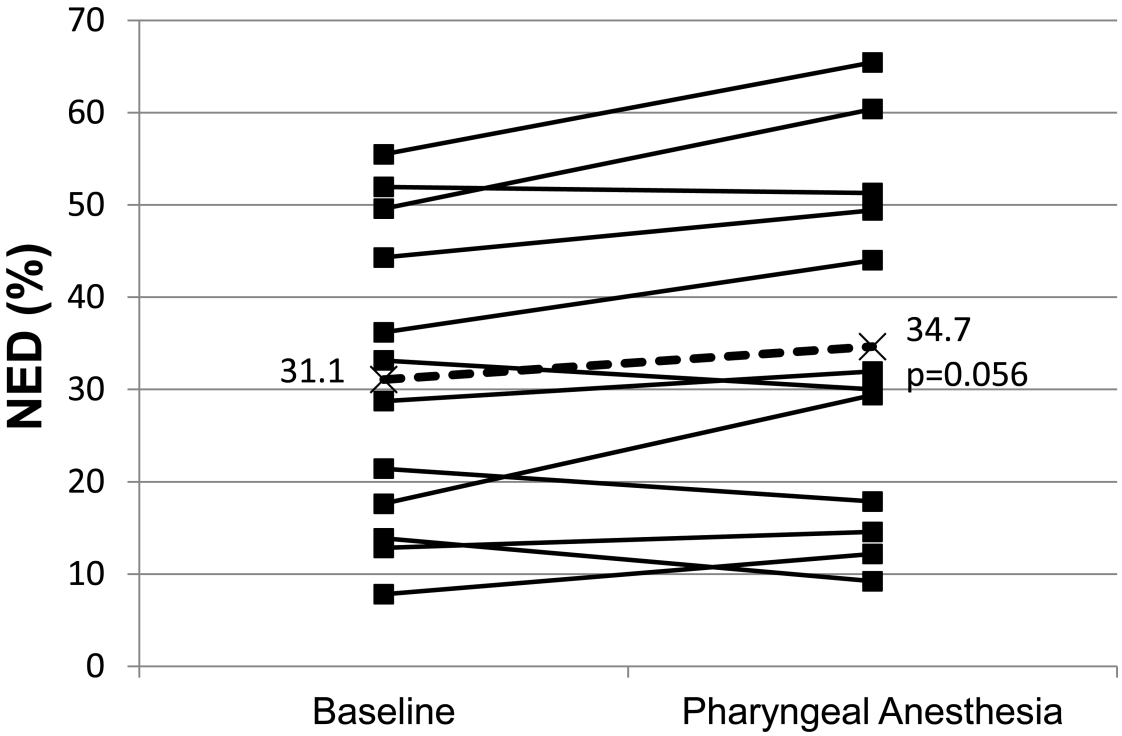

Figure 3.
Individual data showing the change in NED due to pharyngeal anesthesia. The dashed line represents the mean change in NED for the group.

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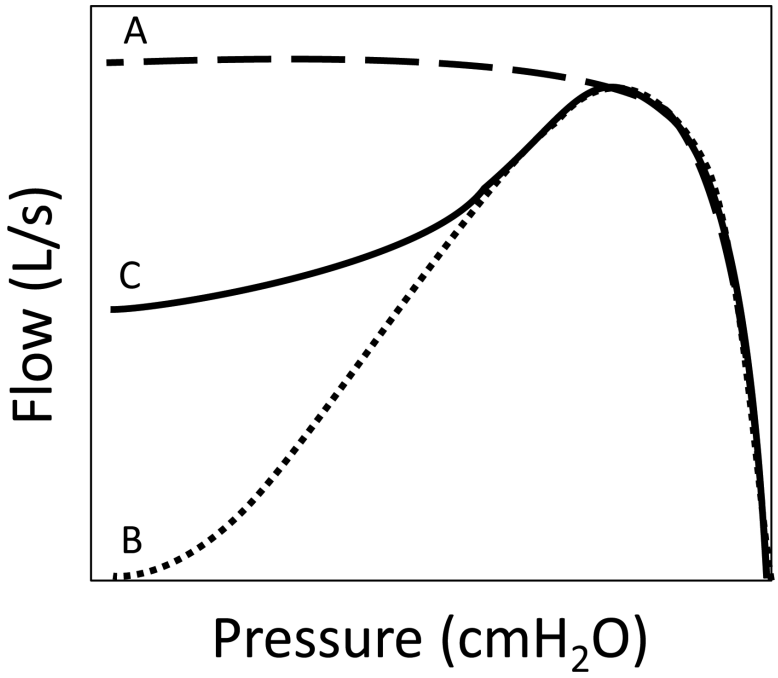

Figure 4.
Flow vs. downstream pressure relationship as predicted by the Starling resistor model (A), according to the proposed piston-type model (B), and the effect of added muscle activity (C).

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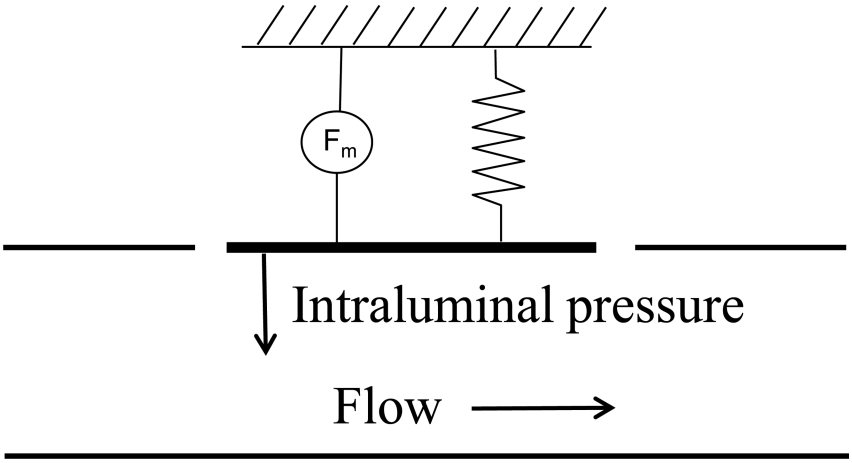

Figure 5.
Piston-type model, where the spring reproduces tissue compliance, Fm (force generator) models muscle activation, and the moving plate is the pharyngeal wall.

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Table 1

Patient characteristics

Parameter	Values
Age (years)	50 ± 10
Gender (% Males)	58
BMI (Kg/m2)	35±6
AHI (events/h)	51.5 ± 27.7

Data are presented as mean +/− SD.

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Table 2

Negative effort dependence, inspiratory flow, epiglottic presssure swings and maximum genioglossus EMG activity before and after anesthesia

	Baseline	Pharyngeal Anesthesia	Difference	p
NED (%)	31.1 ± 16.6	34.7 ± 19.3	3.6 ± 5.8	0.056
EMG_{GG} (%max)	2.7 [1.2 – 29.4]	1.8 [0.5 – 12.6]	−1.7 [−0.5 - -13.8]	**<0.001**
Delta Epi	−10.5 ± 2.9	−10.5±2.8	−0.01	0.642
Peak flow	0.349 ± 0.070	0.333 ± 0.087	−0.016 ± 0.076	0.471
Plateau flow	0.236 ± 0.052	0.216 ±0.082	−0.020	0.219

Data are presented as mean +/− SD or median [interquartile range].