Research suggests that identifying the OSA phenotype (i.e., the root cause of upper airway collapse) is essential to select an effective therapy for each patient.[4,5]

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# Phenotypes of Velopharyngeal Tube Law in Obstructive Sleep Apnea


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## Abstract

**Introduction:** Different modes of upper airway (UA) collapse are routinely observed in patients with obstructive sleep apnea (OSA) during drug induced sedated endoscopy (DISE). These different modes of collapse may reflect differences in UA biomechanical properties with potential implications for therapy selection.

**Methods:** The area-pressure relationship (tube law) of the velopharynx was quantified during DISE in 13 OSA patients via step reductions in nasal mask pressure. The minimal area of the velopharyngeal airspace was estimated from video endoscopy, while the intraluminal pressure was recorded with a catheter. The tube law was quantified for nasal mask pressures from 0 to 16 cmH2O at mid-inspiration (tube law A) and mid-expiration (tube law B) in all patients. The tube law was also quantified during multiple points of the breathing cycle at a constant nasal mask pressure of 0 or 4 cmH2O (tube law C) in three patients representing different phenotypes.

**Results:** Tube laws A and B revealed three phenotypes, namely collapse during inspiration (phenotype 1, 1 patient), collapse during expiration (phenotype 2, 3 patients), and collapse during both inspiration and expiration (phenotype 3, 9 patients). Tube law C revealed that phenotype 3 displays a nearly constant airway size (i.e., low pharyngeal compliance) during the breathing cycle, while phenotypes 1 and 2 display sizeable changes in airway size (i.e., high pharyngeal compliance) during the breathing cycle.

**Conclusion:** Three phenotypes of velopharyngeal collapse were observed, namely collapse driven by a negative intraluminal pressure with high intra-breath pharyngeal compliance (phenotype 1) or low intra-breath pharyngeal compliance (phenotype 3), or expiratory collapse (phenotype 2). Future studies should investigate how these phenotypes of UA collapse affect therapeutic outcomes.


## Introduction

### Background

- Airway collapse is described by the tube lab with the exponential shape implying that airway compliance increases as intraluminal pressure approaches the closing pressure (Figure 1A), meanwhile the linear tube law implying that airway compliance remains (Figure 1B).
- Airway compliance varies in the respiratory cycle due to changes in pressure, muscle tone, and lung volume
- Understanding airway compliance is critical to phenotype the upper airway to develop methods to better direct proper treatment

### Aim of Study

- The goal of this study is to evaluate compliance at different phases of the respiratory cycle compare the velopharyngeal tube law at peak inspiration versus peak expiration

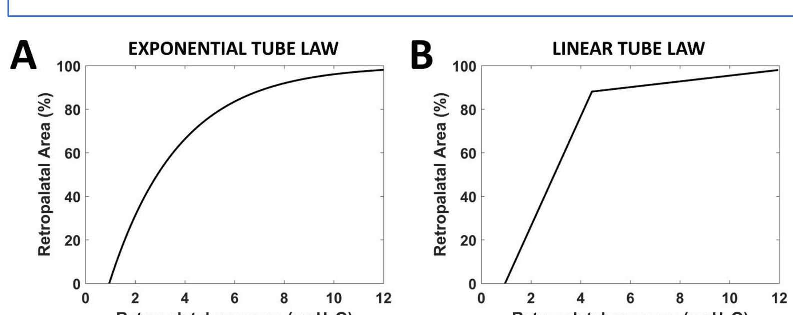



**Figure 1.** (A) Exponential tube law of the velopharynx based on Isono et al. (1993).[7] (B) Linear tube law of the velopharynx based on Oliven et al. (2010).[8]

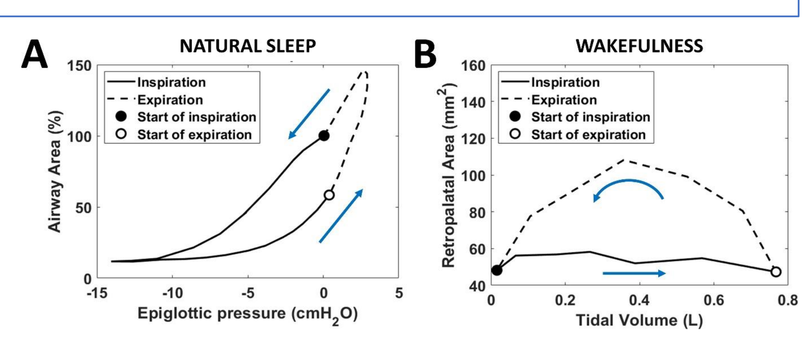



**Figure 2.** Dynamic changes in pharyngeal airspace cross-sectional area in a single breath during (A) natural sleep based on Genta et al. (2016)[9] and (B) wakefulness based on Schwab et al. (1993).[10]

## Methods and Materials

- 13 OSA patients during drug-induced sedated endoscopy (DISE)
- Millar Mikro-Cath pressure catheter (0.77 mm) was positioned in the velopharynx to measure intraluminal pressure.
- CPAP varied from 14 $cmH_2O$ to 0 $cmH_2O$, in steps of 2 $cmH_2O$ (Figure 3)
- The minimal airspace cross-sectional area was estimated by the endoscopy video and was manually outlined in GIMP software.
- The velopharyngeal closing pressure ($P_{CLOSE}$) is the local intraluminal pressure at which the area is zero (i.e., $P_{VP} = P_{CLOSE}$ when $A = 0$; see **Figure**). Substituting $A = 0$ in equation (1), we have $P_{CLOSE} = -\frac{A_{P0}}{C}$
- The tube law was quantified by measuring $A$ and $P_{VP}$ at peak inspiration and peak expiration at multiple CPAP pressures.
- The two-sided Wilcoxon signed rank test at the level p < 0.05..

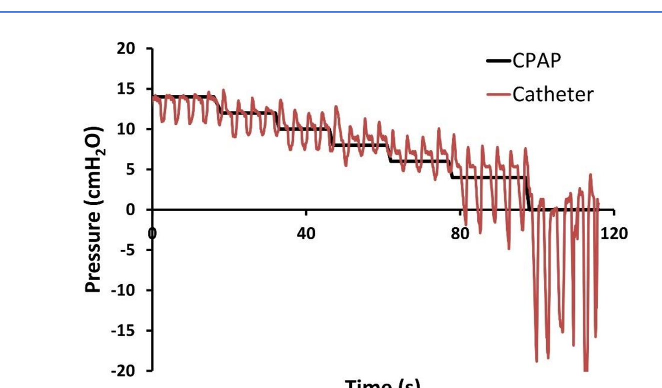



**Figure 3.** Protocol to measure the velopharyngeal closing pressure. The CPAP pressure) was reduced in steps of 2 $cmH_2O$ starting from a holding pressure of 14 cmH2O until CPAP was turned off. Air pressure at the velopharynx was recorded with a pressure catheter.

**Figure 4.** The airway perimeter was outlined by hand (dashed line) and the number of pixels inside the perimeter was computed. Conversion from number of pixels to CSA in mm2 was based on the known diameter of the pressure catheter, which was also measured on the image (circle and plus sign).

Patients with

- Primary inspiratory collapse classified as Phenotype 1
- Primary expiratory collapse as Phenotype 2
- Equal collapse during inspiration and expiration as Phenotype 3.

## Results

| | $P_{CLOSE}$ (cm$H_2$O) | | | $A_{P0}$ (mm²) | | | $C$ (cm$H_2$O/mm²) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Insp. | Exp. | p | Insp. | Exp. | p | Insp. | Exp. | p |
| Phenotype 1 | -3.5 ± 0 | -2.9 ± 0 | - | 103 | 83 | - | 30 | 29 | - |
| Phenotype 2 | -1.0 ± 0.8 | 5.0 ± 1.0 | - | 31 ± 11 | -226 ± 43 | - | 41 ± 19 | 47 ± 18 | - |
| Phenotype 3 | 0.4 ± 3.1 | 0.5 ± 2.8 | 0.91 | -24±62 | -22 ± 54 | 0.82 | 20 ±16 | 17 ± 14 | 0.03 |
| All subjects | -0.2 ± 2.8 | 1.3 ± 3.3 | 0.13 | -2 ± 64 | -61 ± 109 | 0.22 | 26 ± 18 | 25 ± 19 | 0.27 |

**Table 1.** Velopharyngeal closing pressure ($P_{CLOSE}$) (mean ± standard deviation), intercept ($A_{P0}$), and velopharyngeal compliance ($C$) for the tube law quantified at peak inspiration or peak expiration in patients with phenotype 1, phenotype 2, and phenotype 3, and the entire cohort of OSA patients.

**Figure 5.** Phenotype 1

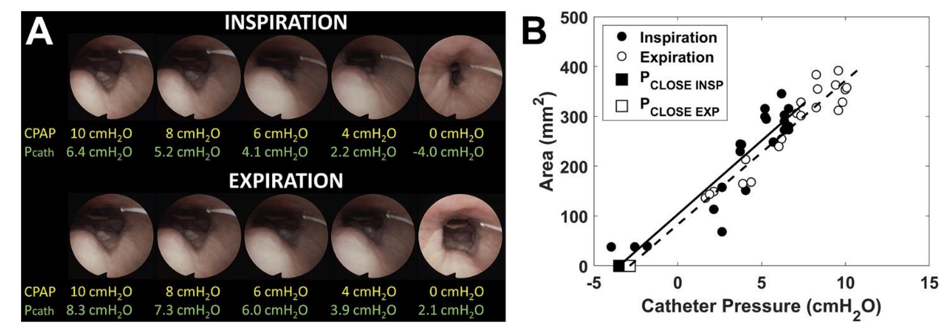



**Figure 6.** Phenotype 2

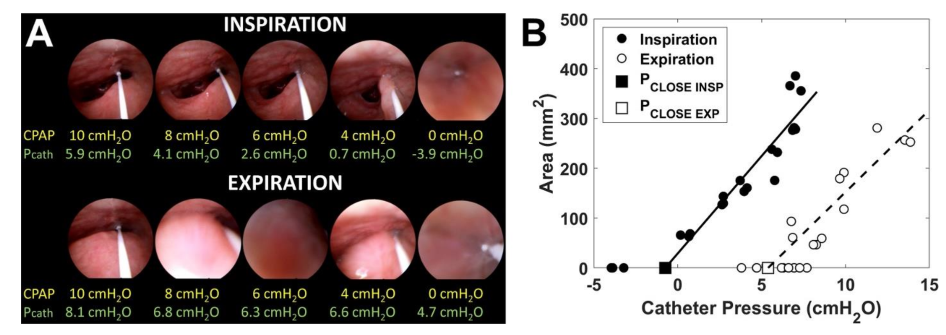
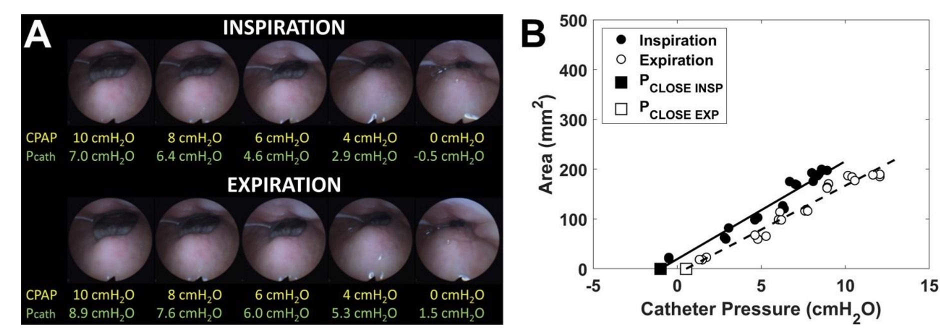



**Figure 7.** Phenotype 3




**(A)** Endoscopic view of the velopharynx during peak inspiration and expiration at various CPAP pressures in an OSA patient with similar collapse during inspiration and expiration. The nasal mask pressure (CPAP) and catheter pressure ($P_{cath}$) corresponding to each image are shown in yellow and green, respectively.

**(B)** Velopharyngeal tube law at peak inspiration and expiration. The pharyngeal closing pressure ($P_{CLOSE}$) was estimated using a linear fit to estimate the $P_{cath}$ at which the velopharynx closes.

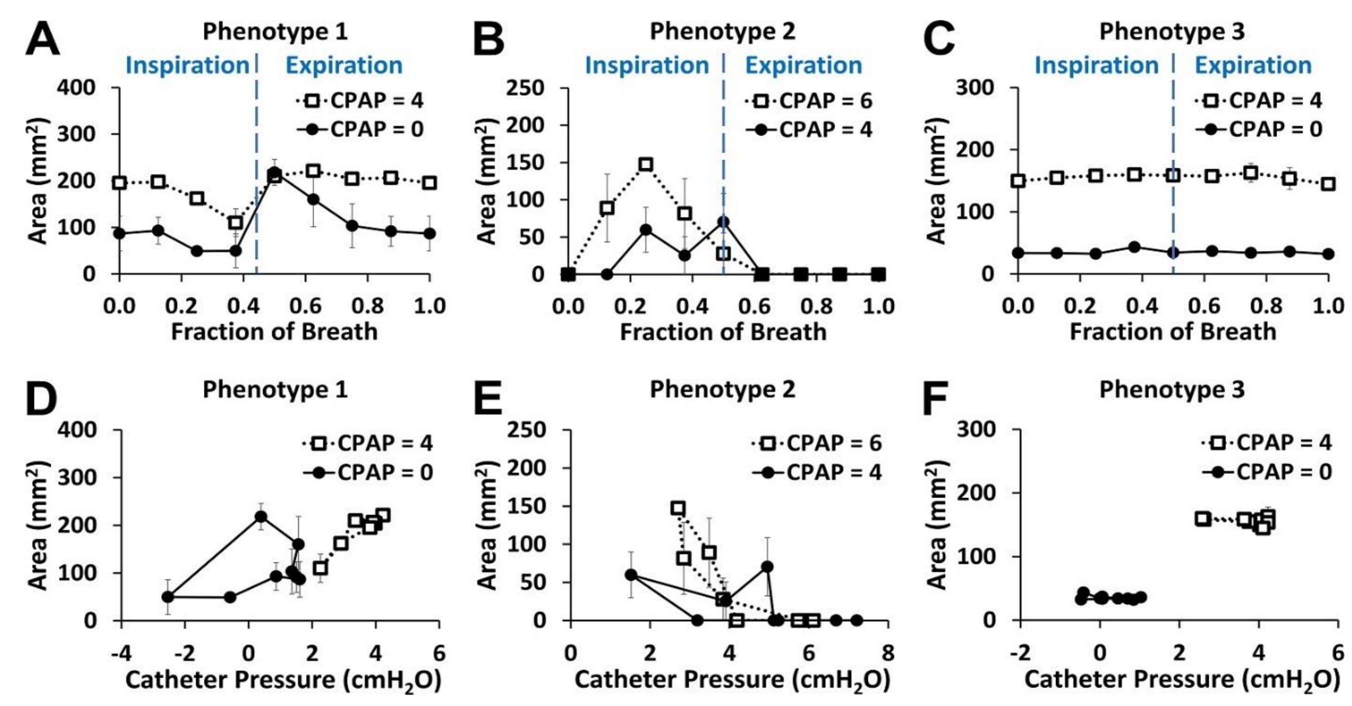



**Figure 8** – (A-C) Changes in airway area and (D-F) tube law during a single breath at low CPAP pressures in patients' representative of phenotype 1 (inspiratory collapse), phenotype 2 (expiratory collapse), and phenotype 3 (similar collapse during inspiration and expiration).

## Discussion

- **First study** to compare the tube law measured at peak inspiration versus peak expiration
- Three phenotypes of upper airway collapse were identified.
- In **phenotype 3 (most common)**, the velopharynx size remained stable during the breathing cycle despite the intraluminal pressure oscillations
  - The velopharyngeal size responded to changes in CPAP pressure (**Figure 7**), but the intra-breath tube law was flat (**Figure 8F**).
  - Velopharyngeal compliance was lower in this group compared to other phenotypes (**Table 1**)
- Expiratory flow limitation due to palatal prolapse was first described in OSA patients by Azarbarzin et al. (2018).[14]
  - Although Azarbarzin didn't report the tube law associated with palatal prolapse, our study showed that palatal prolapse is associated with a paradoxical tube law where larger areas are associated with lower intraluminal pressures, contradicting the paradigm that upper airway collapse in OSA pts is driven by negative intraluminal pressures like a Starling resistor.
- **Speculation:** palatal prolapse occurs when the soft palate is not mechanically linked to the tongue by surface tension forces which allows the soft palate to move freely and move toward the posterior wall when the pressure gradient due to the Bernoulli effect (i.e., higher pressure in the concave side where there is no airflow and lower pressure in the convex side where there is airflow) is sufficient to prolapse the palate.
- **Limitations**
  - Other phenotypes (i.e., other modes of airway collapse) may exist but were not observed in this study due to the small sample size.
  - Small sample size did not allow a statistical analysis to quantify the significance of the observed differences in the tube law metrics among the different phenotypes.
  - The accuracy of estimating velopharyngeal cross-sectional areas by outlining the airway perimeter in endoscopic video frames is limited by the difficulty of outlining the cross-section of a 3-dimensional object on a 2-dimensional image
  - We estimated the tube law based on relatively few data points due to the labor-intensive nature of manually outlining the airway perimeter to estimate the airway size and the fact that the lowest pressure generated by our CPAP device was 4 $cmH_2O$.
- Future studies may provide a higher resolution of the tube law, particularly near the closing pressure.

## Conclusions

- Three phenotypes of velopharyngeal tube law were observed and are likely associated with interindividual differences in velopharyngeal compliance and the physiological mechanisms that regulate velopharyngeal compliance.
- Additional studies are needed to investigate how these phenotypes may affect therapeutic outcomes.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