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Authors

Sunwoo, Bernie Y

Malhotra, Atul

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Mechanical Interactions Between the Upper Airway and the Lungs that Affect the Propensity to Obstructive Sleep Apnea in Health and Chronic Lung Disease

Bernie Y. Sunwoo, MBBS[*], **Atul Malhotra, MD**[1]

Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego, San Diego, CA, USA

Keywords

Obstructive sleep apnea; Chronic lung disease; Overlap syndrome; Pharyngeal critical closing pressure; End-expiratory lung volume

INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive narrowing and collapse of the upper airways during sleep. The precise pathophysiological mechanisms leading to the airway obstruction remain unknown but are likely multifactorial due to anatomic and nonanatomic factors, including ineffective upper airway dilator muscles, low arousal threshold, and an overly sensitive ventilatory control system (also referred to as high loop gain).[1] End-expiratory lung volume (EELV) is also an important factor as increased EELV can stabilize the upper airway via caudal traction forces. That is, mechanical interactions between the upper airways and the lungs can affect the propensity for OSA, both in health and chronic lung disease. This article reviews these mechanical interactions, understanding there is little research specific to this topic.

Pharyngeal Critical Closing Pressure and Upper Airway Collapsibility

The upper airway can be viewed as a tube with a collapsible segment. By applying the principles of the Starling resistor, pressure-flow relationships of the pharyngeal airways and the factors contributing to airflow obstruction can be better understood (Fig. 1).[2,3] The collapsible segment sits within a sealed box flanked by relatively rigid segments, the upstream nasal and the downstream tracheal airways, and patency depends on transmural pressure (pressure inside minus pressure outside the pharyngeal airway). The pharyngeal critical closing pressure (P_{CRIT}) is a measure of upper airway collapsibility.[4] It is measured while participants are on continuous positive airway pressure (CPAP) to minimize pharyngeal dilator muscle activity, and is the estimated nasal pressure at which the ‘passive’ upper airway collapses and airflow ceases. Using the described model, it can be thought of as the surrounding pressure that equals the pressure within the collapsible

[*]Corresponding author. 4520 Executive Drive, Suite P2, San Diego, CA 92121. besunwoo@health.ucsd.edu.
[1]Present address: 9500 Gilman Drive, La Jolla, CA 92093.</address>

segment at the moment of collapse. Flow cannot occur until the pressure upstream of the collapsible segment exceeds Pcrit. When upstream pressure (P_{US}) is lower than P_{CRIT}, complete occlusion of the tube occurs. When downstream pressure (P_{DS}) is decreased below P_{CRIT}, inspiratory flow limitation occurs. Under these circumstances, the level of maximal inspiratory airflow (Vimax) is determined by upstream and critical closing pressures and the upstream nasal resistance (Rus), that is, Vimax 5 (P_{US}-P_{CRIT})/R_{US}. Pressures downstream from P_{CRIT} do not influence flow as long as P_{DS} is less than P_{CRIT}.

P_{CRIT} or pharyngeal collapsibility has been studied during sleep in normal subjects, snorers, and patients with OSA, and there is a continuum of P_{CRIT} associated with increasing levels of sleep-related airflow obstruction.[2,4–7] When P_{CRIT} is positive relative to atmospheric nasal pressure, the airway occludes and airflow becomes zero. Conversely, the more negative P_{CRIT} becomes, the lower the tendency toward pharyngeal collapse. In normal subjects, P_{CRIT} is negative and the upper airway is patent. Schwartz and colleagues[7] showed a P_{CRIT} of −13.3 ± 3.2 cm H_2O and a normal inspiratory airflow during sleep in healthy individuals with a P_{CRIT} of below −8 cm H_2O. As P_{CRIT} increased above −8 cm H_2O, airway pressures fell below P_{CRIT} during inspiration leading to pharyngeal collapse and flow limitation. Conversely, in patients with OSA, P_{CRIT} has been shown to be positive, inducing collapse and occlusion of the upper airways during sleep. Studies looking at the effects of sleep stage on P_{CRIT} have been mixed, likely in part due to challenges in accurate P_{CRIT} measurements, but a larger study by Carberry and colleagues[8] showed P_{CRIT} to be higher (more collapsible) during rapid eye movement (REM) sleep versus slow-wave and N2 sleep.[8–10] This study also showed a reduction in genioglossus activity from wakefulness off CPAP to on CPAP and from slow-wave sleep to N2 to REM sleep.

Relationship Between Critical Closing Pressure and End-Expiratory Lung Volume

The etiology for the increased P_{CRIT} seen in OSA is again likely due to structural factors but P_{CRIT} is affected by lung volumes, thereby potentially pre-disposing or protecting patients with chronic lung disease from OSA. EELVs have been shown to affect P_{CRIT} independently, both in healthy individuals and in OSA.[11–16] Squier and colleagues[15] studied the relationship between changes in absolute EELV and pharyngeal collapsibility using P_{CRIT} in 18 healthy subjects. P_{CRIT} varied inversely with absolute EELV. Similarly, Stanchina and colleagues[14] sought to investigate systematically the isolated effects of lung volume changes on pharyngeal collapsibility in 19 healthy adults. Using a rigid head-out shell, adapted with a vacuum/blower allowing manipulations of extrathoracic pressure and thus lung volumes, they also demonstrated increased pharyngeal collapsibility with reduced lung volumes during non-REM sleep. Studies have also shown lung volumes influence P_{CRIT} measurements in OSA. Owens and colleagues[13] looked at EELV in 15 OSA patients and 7 controls and found passive P_{CRIT} decreased substantially with increased lung volumes, although by a similar amount in OSA and control subjects, concluding a role for lung volumes in the pathogenesis of OSA and consideration of lung volumes during the assessment of pharyngeal mechanics. Others have demonstrated greater reductions in EELV in patients with moderate OSA than those without OSA. Stadler and colleagues[17] measured expiratory diaphragmatic activity (eEMGdia) and EELV in 8 obese men with OSA and 8 healthy-weight men without OSA in the supine position using intraesophageal catheters and

magnetometer coils. OSA patients experienced a greater fall in eEMGdia and EELV (61 mL in OSA vs 34 mL in controls) following sleep onset with greater falls at transitions accompanied by respiratory events, again suggesting a role for decreasing lung volumes to increased propensity for upper airway collapse in OSA. Tagaito and colleagues[16] examined the static mechanical properties of the passive pharynx before and during lung inflation by applying negative extrathoracic pressure in 8 anesthetized and paralyzed patients with OSA. Application of −50 cm H_2O negative extrathoracic pressure produced an increase in lung volume of approximately 0.72 L, and resulted in a significant reduction of velopharyngeal closing pressure.

Studies on CPAP further support the role of lung volumes in OSA. CPAP acts as a pneumatic splint to increase upper airway transmural pressure but is also known to increase EELV to counteract airway collapse. The apnea-hypopnea index (AHI) was shown to decrease from 62.3 ± 10.2 events/hr off CPAP to 37.2 + 5.0 events/hr on CPAP and 31.2 + 6.7 events/hr on 500 mL above the treating CPAP volume in 12 subjects with OSA where lung volumes were increased using the rigid head-out shell described earlier.[12] The same group sought to determine the influence of lung volumes on the level of CPAP required to prevent flow limitation in 17 adults with OSA during non-REM selep.[11] When lung volumes were increased by 1035 ± 22 mL, the CPAP level could be decreased from 11.9 ± 0.7 to 4.8 ± 0.7 cm H_2O without flow limitation, while when lung volumes were reduced by 732 ± 74 mL, the CPAP level had to be increased from 11.9 ± 0.7 to 17.1 ± 1.0 cm H_2O to prevent flow limitation, suggesting even small changes in lung volumes have an important effect on upper airway patency in OSA.

End-Expiratory Lung Volume, Tracheal Traction, and Upper Airway Collapse

Animal and human models suggest the mechanisms by which lung volumes influence airway size and collapsibility are through caudal traction forces whereby the pharyngeal airway is stiffened with increasing lung volume. Various animal models have explored the effects of tracheal traction on upper airway patency.[18–21] The effects of airway elongation and dilation was explored in a feline model by displacing the trachea caudally and the tongue anteriorly, respectively, under complete neuromuscular blockade.[19] With caudal-tracheal displacement, P_{CRIT} fell progressively, while anterior-tongue displacement decreased P_{CRIT} when the trachea had been caudally displaced but not with the trachea in the neutral position, suggesting longitudinal tension within the airway mucosa modulates both P_{CRIT} and the response in P_{CRIT} to dilating forces. In another animal study using anesthetized, tracheostomized dogs, both mediastinal traction and the force generated by changes in intrathoracic pressure were shown to explain thoracic traction on the trachea.[21] Consequently lung volumes again play a central role. Hillman and colleagues[22] used phrenic nerve–stimulated diaphragmatic contraction to evaluate the effects of selective diaphragm contraction on upper airway collapsibility and the extent with which any of the observed change was attributable to lung volume-related changes in pressure gradients or to diaphragm descent–related mediastinal traction in 9 anesthetized healthy subjects. Peak inspiratory flow only increased when diaphragmatic contraction was associated with an increase in lung volumes suggesting lung volume–induced changes in transthoracic pressure gradients and not mediastinal caudal traction was the primary mediator of upper

airway stabilization. Kairaitis and colleagues[18] hypothesized a threshold lung volume for optimal mechanical effects on upper airflow dynamics using and anesthetized rabbit model. Lung volume change, airflow, pharyngeal pressure, upper airway extraluminal tissue pressures laterally and anteriorly, tracheal displacement, and sternohyoid muscle activity were measured with extrathoracic pressure changes. Increasing lung volume displaced the trachea caudally, reduced extraluminal tissue pressures, and abolished flow limitation but had little effect on resistance or conductance.

EELV falls at sleep onset increasing susceptibility to upper airway collapse.[23] EELV are further decreased during REM sleep, when there is reduced tone of upper airway and chest wall and neck muscles.[24,25] Additionally, obesity and body position influence functional residual capacity (FRC) and lung volumes. The relationship between obesity, body position, and lung volumes is complex. Central obesity increases transdiaphragmatic pressure, reducing lung volumes and subsequently causing caudal tracheal traction to increase upper airway collapsibility.[26] However, body position and assuming the recumbent position are also associated with cephalad displacement of the diaphragm and decreases in lung volumes. Even in normal individuals with normal body mass index (BMI), FRC falls moving from the lateral to supine position. Teasing out the differential effects of sleep, obesity, and body position on lung volumes is challenging and weight may mediate positional changes, possibly by increased tonic diaphragm muscle activity.[17] Obese individuals have been shown to have smaller decreases in FRC and EELV going from the seated to supine position compared to nonobese individuals.[27–30]

Positional effects in OSA have been clearly shown and can be used to improve OSA. Neill and colleagues[31] measured upper airway closing pressure and upper airway opening pressure in 8 patients with OSA in the supine, 30° elevation, and lateral positions using a specially adapted nasal CPAP mask. The elevated posture resulted in a less collapsible airway compared with both the supine and lateral positions. In contrast, studies exploring pharyngeal cross-sectional size have not consistently shown significant changes between the lateral and supine position in OSA, although studied when awake.[32–34] Joosten and colleagues[34] studied airway cross-sectional area and shape using 4-dimensional computed tomography (CT) scanning of the upper airways and FRC, in the seated, supine, and lateral decubitus positions, in patients with supine OSA (more than twice the number of respiratory events in supine when compared with non-supine position), patients with REM-predominant OSA and patients without OSA, matched for age, gender, and BMI. Patients with supine OSA demonstrated a significant decrease in FRC of 340 mL when moving from the lateral to supine position compared to controls with no OSA and REM-predominant OSA. There was no significant difference in upper airway size and shape, but all groups showed a significant change in airway shape with the velopharyngeal airway adopting a more elliptical shape (long axis laterally orientated) with reduced anteroposterior diameter in the supine airway, which may be of relevance in patients with airways disease as discussed in the following sections.

Chronic Lung Disease

These normal mechanical interactions between the upper airway and the lungs can further impact the propensity for OSA in patients with chronic lung disease, but few studies have explored mechanisms causing upper airway collapse in the various chronic lung diseases.

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction. Expiratory flow limitation results in gas trapping or hyperinflation, reduces dynamic pulmonary compliance, and imposes increased load on respiratory muscles. Based on BOLD (Burden of Obstructive Lung Disease) and other large scale epidemiologic studies, it is estimated that the global prevalence of COPD is 10.3%.[35,36] Given the high prevalence of both OSA and COPD, the 2 diseases can coexist. The coexistence of OSA and COPD was coined by David Flenley in 1985 as the overlap syndrome and is associated with worse outcomes including mortality than either condition alone.[37]

Despite the potential mechanical risk factors for OSA in COPD, epidemiologic studies have not consistently supported that having 1 disorder increases risk for the other.[38] Studies, however, are largely restricted to cohorts with mild COPD, and studies including more severe COPD suggest a possible increased risk of OSA.[39] In a study of adult males with more moderate to severe COPD (forced expiratory volume in the first second [FEV_1] mean[standard deviation] of 42.8[19.8]%, FEV_1/FVC 42.3[13.1]), 52% had OSA as defined by an AHI greater than 5 events/hr.[40] Differences in prevalence may also be explained by heterogeneity of COPD clinical phenotypes that vary in pre-disposition to upper airway obstruction. Studies have suggested a protective mechanism for OSA with the ‘pink puffer’ phenotype versus the ‘blue bloater’ phenotype of COPD, due to the described effects of lung volumes on upper airways.

Expiratory flow limitation and increases in lung volumes seen in COPD can affect upper airway patency and compensatory responses to inspiratory flow limitation during sleep. Biselli and colleagues[41] completed sleep studies and quantified P_{CRIT} and respiratory timing responses to experimentally induced inspiratory flow limitation in 18 patients with COPD and 18 controls matched by age, BMI, sex, and OSA severity. COPD patients had lower passive P_{CRIT} (less collapsible airway) than their matched controls and a greater compensatory timing response during airway obstruction. Krachman and colleagues[42] investigated lung inflation using spirometry and volumetric chest CT in 51 smokers in the COPDGene project with emphysema and FEV_1 58 ± 14% predicted who underwent polysomnography for suspected OSA. 57% had OSA and there was an inverse correlation between the AHI and CT-derived measures of emphysema and air trapping, both for the entire study group and when just those patients with OSA were evaluated ($r = -0.43$ [$P = .04$] and $r = -0.49$ [p+.03], respectively). Multiple linear regression revealed that, in addition to CT-derived percent emphysema and CT-derived percent gas trapping, sex and BMI were important in determining the AHI in these patients. The Sleep Heart Health Study cohort also suggested a possible protective mechanism of hyperinflation in OSA.[43] For every 200 mL decrease in FEV_1, all-cause mortality increased by 11.0% in those without OSA (hazard

ratio [HR] 1.11; 95% confidence interval, 1.08–1.13) but by only 6.0% in participants with OSA (HR 1.06; 95% confidence interval, 1.04–1.09), and the incremental influence of lung function on all-cause mortality was less with increasing severity of OSA.

Dynamic hyperinflation in COPD may reduce upper airway collapsibility due to tracheal traction, but airflow obstruction is also associated with significant changes in tracheal morphology that may further modify risk of upper airways collapse. In COPD, the tracheal index, the ratio between coronal and sagittal diameter of the trachea at the same level, is significantly reduced and shown to correlate with severity of emphysema.[44,45] At its more extreme, the saber-sheath trachea, which consists of marked coronal narrowing associated with sagittal widening, is a specific radiographic parameter for COPD linked to the functional severity of airway obstruction.[46] The propensity to airway collapse is related to airway size and shape. According to Laplace's law, a more rounded airway is inherently more stable than an elliptically shaped one as the transmural pressure gradient required to collapse the airway varies inversely with the radius of curvature. It is possible that in obstructive lung disease the reduced tracheal index offers some protection against the normal reductions in anteroposterior diameter that occur with supine positioning described earlier.

In contrast to the pink puffers, 'blue bloaters' may be at increased risk for upper airways obstruction due to rostral fluid shifts when supine. Changes in leg fluid volume and neck circumference were measured in 23 non-obese healthy men referred for sleep studies for suspected OSA, from the beginning to the end of the night and the time spent sitting during the previous day.[47] Overnight changes in leg fluid volume and neck circumference correlated strongly with the AHI, together explaining 68% of the variability in AHI. In blue bloaters with cor pulmonale, rostral shift of peripheral edema when supine could in theory lead to fluid accumulation in the neck, contributing to pharyngeal narrowing and increased risk of OSA.

There are even fewer studies studying OSA in fibrotic lung disease. The relationship between interstitial lung disease (ILD) and OSA remains unclear, but a possible association has been suggested.[48–50] Cross-sectional analyses of 1690 adults in the Multi-Ethnic Study of Atherosclerosis cohort who underwent both chest CT and polysomnography found an association between moderate to severe OSA and subclinical ILD.[48] An obstructive AHI ≥ 15 events/hr was associated with a 35% increased odds (95% CI 13%–61%, P=.001) of interstitial lung abnormalities on CT, although the association varied by BMI with the strongest association seen among normal-weight individuals. Theoretically, in contrast to obstructive lung diseases, small lung volumes in ILD can reduce caudal traction in the upper airways, increasing the collapsibility and risk of OSA. However, Pereira and colleagues[51] determined potential predictive factors of OSA in 49 patients with fibrotic lung disease and BMI less than 30 kg/m^2. AHI showed a statistically significant correlation with age, BMI, duration of immunosuppressant treatment, and FEV_1 but only BMI remained an independent predictor of OSA in a multivariate correlation model adjusted for the other statistically meaningful variables, and additional studies are needed investigating the relationship between ILDs and OSA.

SUMMARY

Of note, there is generally a lack of rigorous research regarding upper airway mechanics in the context of chronic lung disease. A number of possible links exist (Table 1). First, as stated, caudal traction forces may affect upper airway patency in patients with lung disease.[11,12,20,21,52,53] Hyperinflation in emphysema may thus have a protective effective on the upper airway. However, an argument could be made that loss of elastic recoil in emphysema could reduce caudal traction and thus may not have the same mechanical benefit as compared to increased EELV in patients with normal lung parenchyma. Similarly, increased lung elastic recoil in pulmonary fibrosis may, in theory, have benefits despite low EELVs due to increased caudal traction forces. Second, the role of airway inflammation has been debated in the pathogenesis of OSA. In theory, inflamed airways may attenuate upper airway protective reflexes contributing to OSA risk.[54–56] Third, changes in body weight are common in chronic lung disease. Cachexia is seen in late COPD which in theory could be protective of OSA risk.[57] In contrast, glucocorticoid therapy can increase body fat and risk for OSA.[58,59] Fourth, as stated, rostral fluid shifts have been hypothesized to contribute to pharyngeal collapsibility.[60] The importance of this mechanism in chronic lung disease is unclear, but, given recent observations in asthma, may be a topic for future investigation.[61] Fifth, a sedentary lifestyle is common in patients with chronic lung disease who are limited by dyspnea. Exercise can clearly be helpful in reducing obesity, but exercise per se has also been associated with reduced OSA risk, independent of body weight.[62] Increased motor output to the diaphragm during exercise is also associated with increased output to the upper airway dilator muscles which may be helpful in mitigating OSA risk. Sixth, hypoxemia is common in chronic lung disease which has complex effects on control of breathing. Hypoxia can increase respiratory drive which may be destabilizing as seen in periodic breathing at high altitude.[63–65] On the other hand, chronic lung disease may reduce the efficiency of carbon dioxide excretion (so called plant gain) which may actually stabilize breathing.[66] In aggregate, the impact of COPD on overall ventilatory control instability is variable and thus its impact on OSA risk is unclear. In summary, the relationships between chronic lung diseases and OSA pathogenesis are complex and likely extend beyond direct mechanical and/or neuromuscular effects. Only by further rigorous research studies in this area are new therapeutic targets likely to emerge.

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KEY POINTS

- Obstructive sleep apnea (OSA) is caused by multiple anatomic and nonanatomic factors, but end-expiratory lung volume (EELV) is an important contributor. Increased EELV can stabilize the upper airway via caudal traction forces, and as such, mechanical interactions between the lungs and upper airway can impact the propensity to OSA.
- The pharyngeal critical closing pressure (PCRIT) is a measure of upper airway collapsibility and there is a continuum of PCRIT associated with increasing levels of sleep-related airflow obstruction. P_{CRIT} is normally negative but in patients with OSA, PCRIT is positive inducing collapse and occlusion of the upper airways during sleep. PCRIT is affected by lung volumes.
- There is a complex relationship between sleep stages, weight, and body position on EELV and consequently OSA risk.
- In obstructive lung diseases, like chronic obstructive pulmonary disease, air trapping and hyperinflation can reduce upper airway collapsibility due to tracheal traction, and be potentially protective against OSA. There are even less data on the mechanical interactions between the upper airways and restrictive lung diseases, highlighting the need for research in this area.

CLINICS CARE POINTS

- Animal and human models suggest lung volumes influence airway size and collapsibility through caudal traction forces whereby the pharyngeal airway is stiffened with increasing lung volume.
- Expiratory flow limitation and dynamic hyperinflation in COPD may reduce upper airway collapsibility due to tracheal traction, but airflow obstruction is also associated with significant changes in tracheal morphology that may further modify risk of upper airways collapse.
- CPAP acts as a pneumatic splint to increase upper airway transmural pressure but is also known to increase EELV to counteract airway collapse.

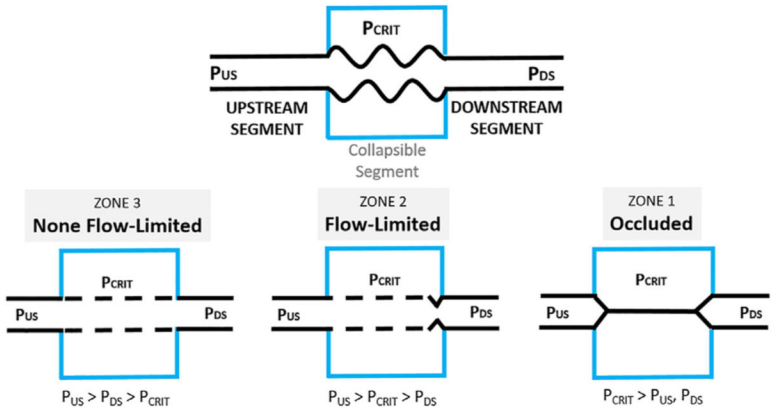

Fig. 1.

Using the Starling resistor model, a collapsible segment is interposed within a sealed box, bound by a rigid upstream and downstream segment with corresponding upstream and downstream pressures (P_{US} and P_{DS}) and resistances. When there is no flow limitation (open airway), the critical opening pressure is the most negative with $P_{US} > P_{DS} > P_{CRIT}$, as in zone 3 of the Starling resistor model. When flow is present but slowed, as inan obstructive hypopnea, the downstream pressure is less than P_{CRIT} because of partial closure of the airway, and $P_{US} > P_{CRIT} > P_{DS}$ as seen in zone 2. When flow is completely occluded, as in an obstructive apnea, $P_{CRIT} > P_{US} > P_{DS}$ as seen in zone 1. (Susheel P. Patil et al., Adult Obstructive Sleep Apnea: Pathophysiology and Diagnosis, Chest, 132 (1), 2007, 325–337, https://doi.org/10.1378/chest.07–0040.)

Table 1

Potential factors influencing upper airway collapsibility in chronic lung disease[67]

Promotion of airway collapse	Promotion of airway patency
• Negative pressure on inspiration	• Pharyngeal dilator muscle contraction (genioglossus)
• Extraluminal positive pressure Fat deposition Small mandible Rostral fluid shifts	• End-expiratory lung volume through caudal traction forces

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