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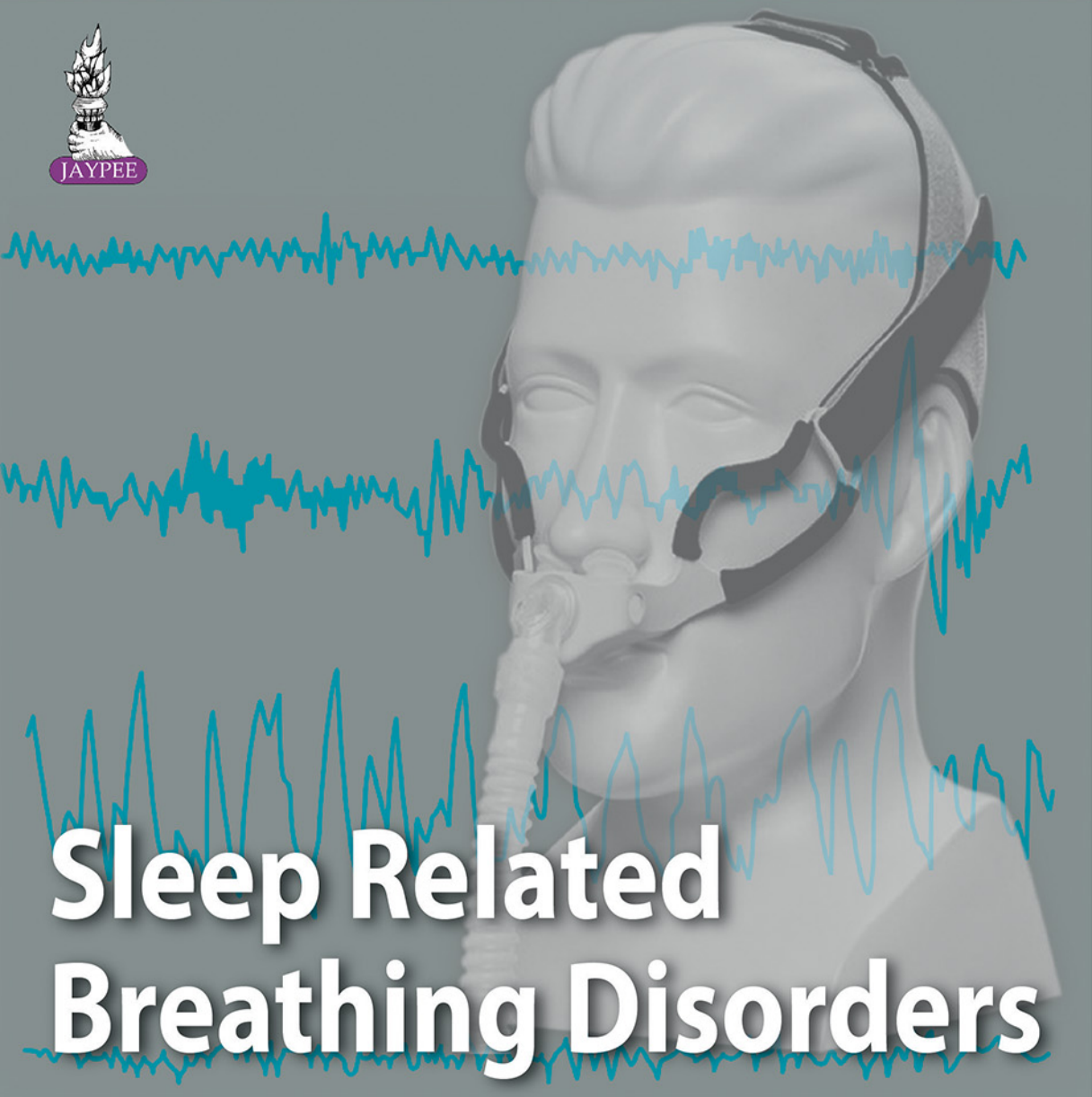

Sleep Related Breathing Disorders

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Contents

Contributors *ix*
Preface *xiii*
Acknowledgements *xv, xvii*

CHAPTER 1 Normal Human Sleep 1
Vikram Sarbhai, Naveen P Shah, Poulomi Chatterjee

CHAPTER 2 Anatomy and Physiology of Obstructive Sleep Apnea Airways 10
Ashwini Malhotra, Vivek Nangia

CHAPTER 3 Clinical Approach to Patient with Sleep Related Breathing Disorders 22
Manoj K Goel

CHAPTER 4 Diagnostic Approach to Sleep Disordered Breathing 30
Nagarajan Ramakrishnan, Anup Bansal

CHAPTER 5 Snoring and Upper Airways Resistance Syndrome 39
Raja Dhar, Debdeep Sen

CHAPTER 6 Obstructive Sleep Apnea 46
Vivek Nangia, Shivani Swami

CHAPTER 7 Central Sleep Apnea 56
Manas K Sen

CHAPTER 8 Obesity Hypoventilation Syndrome and Complex Sleep Apnea 67
Vivek Nangia, Shivani Swami

CHAPTER 9 Cardiac Effects of Sleep Related Breathing Disorders 79
Manish Bansal, Kapil D Mohindra

CHAPTER 10 Systemic Effects of Sleep Related Breathing Disorders: Noncardiac 98
Gopi C Khilnani, Neetu Jain

CHAPTER 11 Positive Airway Pressure Treatment in Obstructive Sleep Apnea 116
Vijay K Chennamchetty, Maramreddy Aparna, Praveen SV

CHAPTER 12 Pharmacotherapy 130
Shivani Swami, Vivek Nangia

CHAPTER 13 Surgical Management of Obstructive Sleep Apnea 140
Rajeev Kumar, Alok Thakar

CHAPTER 14 Dental Sleep Medicine: An Overview 151
Anmol S Kalha, Jayan Balakrishnan

CHAPTER 15 Obstructive Sleep Apnea in Children 169
Praveen Khilnani, Neha Sood

CHAPTER 16 Perioperative Management of Sleep Related Breathing Disorders 182
Roop Kaw, Vivek Nangia

Index *191*

CHAPTER 2

Anatomy and Physiology of Obstructive Sleep Apnea Airways

Ashwini Malhotra, Vivek Nangia

JAYPEE BROTHERS

INTRODUCTION

The airways form the connection between the outside world and the terminal respiratory units. They are of central importance to our understanding of lung function in health and disease (Figure 1). Intrapulmonary airways are divided into three major groups: bronchi, membranous bronchioles, and respiratory bronchioles/gas exchange ducts.

Bronchi, by definition, have cartilage in their wall. Respiratory bronchioles serve a dual function as airways and as part of the alveolar volume (gas exchange). The membranous bronchioles (non-cartilaginous airways of approximately 1 mm diameter or less), although exceedingly numerous, are short in length. They consist of about five branching generations and end at the terminal bronchioles. In contrast to the bronchi, the membranous bronchioles are tightly embedded in the connective tissue framework of the lung and, therefore, enlarge passively as lung volume increases

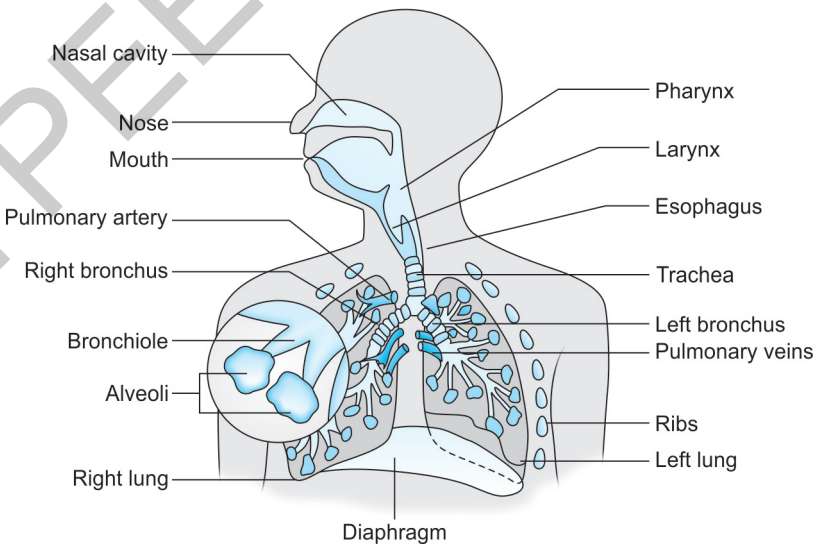

Figure 1: Respiratory system.

Most airway resistance resides in the upper airways and bronchi. Normally, the large airways maintain partial constriction due to bronchomotor tone. Minimal airway diameter in the human lung, about 0.5 mm, is reached at the level of the terminal bronchioles; succeeding generations of exchange ducts (respiratory bronchioles and alveolar ducts) are of constant diameter.

ANATOMY OF UPPER AIRWAY OBSTRUCTION

Obstructive sleep apnea (OSA) is known to be associated with alterations in upper airway anatomy. With a change in state comes a change in upper airway collapsibility.

Patency of pharyngeal airway is maintained by opposing forces: the activity of upper airway muscles, which dilates and stiffens the airways and negative intraluminal pressure, which tends to collapse them. This balance can be disturbed by abnormalities involving neural control and/or upper airway anatomy. Patients with OSA have been shown to have a narrowed, more collapsible pharyngeal airway. Sleep related decrease in upper airway dilating muscle activity can lead to greater negative intraluminal pharyngeal pressure, which leads in turn to further narrowing and complete closure of the airway.

Possible Sites of Upper Airway Obstruction

- Nose
  - Blocked nose due to choanal atresia/foreign body/polyps/allergy
- Oropharynx
  - Adenoidal hypertrophy, micrognathia, craniofacial abnormalities, large tongue
- Supraglottis
  - Epiglottitis: *H. influenzae* type B
- Larynx
  - Laryngomalacia due to obstruction, laryngeal papillomata
- Subglottis
  - Laryngotracheobronchitis (Croup).

The upper airway is a common passage for digestive, respiratory, and phonatory systems. Traditionally, it is divided to three sections: (1) the nasopharynx; (2) oropharynx; and (3) hypopharynx (Figure 2).

Nasopharynx

Nasopharynx extends from the posterior margin of the nasal turbinates; it lies above the soft palate and continues inferiorly with the oropharynx. Adenoids occupy the posterior wall, which when inflamed can partially obstruct the upper airway.

Soft palate is nearly a vertical flap which extends from the posterior edge of hard palate and terminates in the uvula. All the muscles of the soft palate are innervated by the pharyngeal branch of vagus nerve except the tensor veli palatini, which is innervated by the medial pterygoid nerve. A posterior elevation of the soft palate toward the posterior pharyngeal wall can cause enlargement of the oral cavity during swallowing and produce narrowing of the nasopharynx. Adenotonsillar disease can lead to sleep-disordered breathing. Polysomnography

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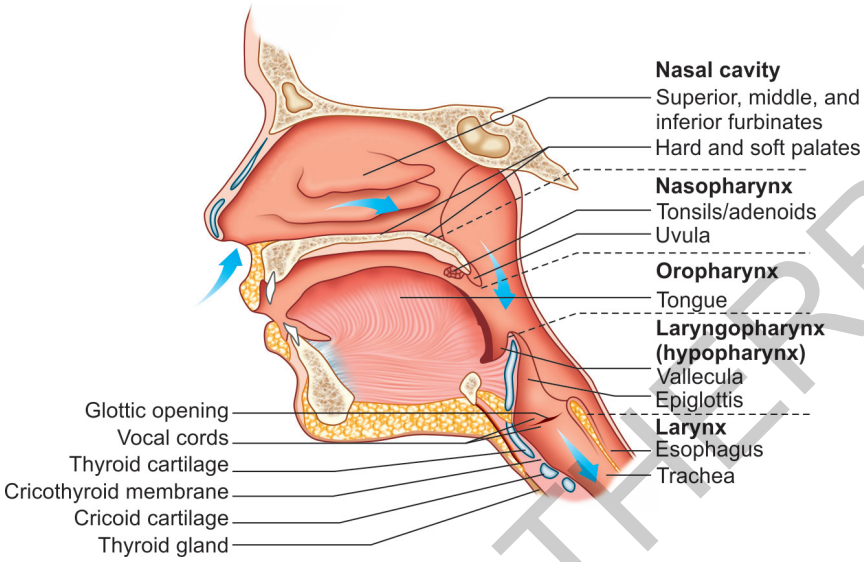

Figure 2: Nasal cavity.

in children with allergic rhinitis and adenoidal hypertrophy found that 2/3rd of such have mild apnea during sleep.[1] Amongst children, tonsillectomy and/or adenoidectomy is the first therapeutic modality to be considered for the treatment of OSA.[2]

Natural breathing in humans is through nose, particularly during sleep, when the daily oral fraction of breathing, estimated at 7%, drops to 4% during sleep.[3] Nasal and oral resistances are equal during wakefulness, but nasal resistance is lower than the oral at night[4] but increases in the supine position.[5]

Connection between the nose and breathing in sleep was first mentioned by Hippocrates[6] when he described a role of nasal polyps in restless sleep. Nasal obstruction can occur secondary to deviated nasal septum, chronic rhinosinusitis, and nasal polyps. Nasal congestion has been associated with a threefold increase in the incidence of snoring and daytime sleepiness.[7] Few earlier studies have indicated that acute nasal obstruction could increase apnea-hypopnea index, prolong rapid eye movement (REM) latency, and increase non-REM sleep.[8] However, nasal obstruction alone is not thought to cause any moderate or severe OSA.[6,9]

Oropharynx

The roof of the oral cavity is formed by *hard and soft palate* (Figure 3) and the lingual mucosa covers the floor. Buccal mucosa and anterior pillars of palatine tonsils covers the lateral part of the oral cavity, which define the junction with oropharynx. The oropharynx extends from the soft palate to the epiglottis (Figure 4). The anterior part of oropharynx is formed by the posterior part of the tongue and the soft palate, whereas the posterior part is formed by the pharyngeal constrictor muscles. The lateral pharyngeal walls are formed by the pharyngeal constrictors, muscles of the extrinsic muscles of the soft palate, and the larynx.

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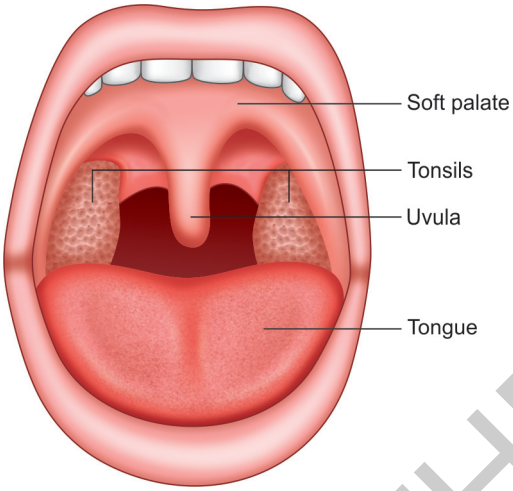

Figure 3: Tonsils.

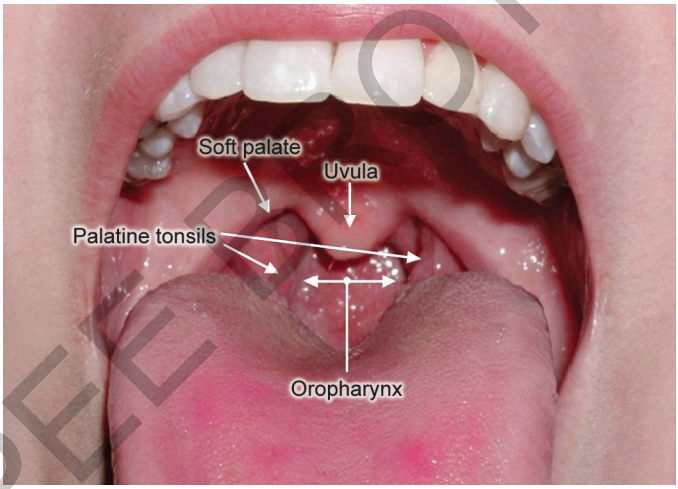

Figure 4: Oropharynx.

Other structures that contribute to upper airway lume, located in the retropalatal area, are the palatine tonsils and parapharyngeal fat pads.

The *tongue* occupies the major part of the oral cavity and has both extrinsic and intrinsic muscle groups. The four extrinsic tongue muscles are (1) genioglossus; (2) hyoglossus; (3) palatoglossus; and (4) styloglossus. The genioglossus is the largest and most-studied pharyngeal dilator muscle. All of these muscles are innervated by the hypoglossal nerve except the palatoglossus, which is innervated by the vagus nerve. The intrinsic muscles of the tongue (superior and inferior longitudinal, transverse, and vertical muscles) are confined to the tongue. The anterior two-thirds of the tongue is innervated by the facial nerve, whereas the posterior one-third is innervated by cranial nerve IX. The size of the tongue is an important risk factor for OSA.[10]

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An increase in the size of type II muscle fibers is seen in OSA compared with normal subjects, which could represent a response to vibratory strain or perhaps neuronal activity.[11,12] The hypoglossal nerve is a critical component in the motor control of upper airway dilatation. The muscle fibers in the posterior part of the tongue are fatigue-resistant, thereby sustaining the forward tongue position and preventing its collapse into the retroglossal area. Using this mechanism, the therapeutic effect of proximal hypoglossal nerve stimulation can be used to treat OSA.[13]

It was found that there is a smaller minimum airway area in patients with OSA in the retropalatal region, and particularly in the lateral dimension, compared with individuals with normal breathing.[14] Independent risk factors of OSA are the volume of the tongue and lateral walls.[15]

Most common site of airway collapse in patients with OSA is oropharynx,[16] which is more likely to occur during REM sleep.[17] The role of parapharyngeal fat in the predisposition to OSA has been studied using magnetic resonance imaging (MRI).

Those patients with retropalatal airway closure had a more parapharyngeal and soft palate fat, whereas patients with retroglossal airway closure had more of the tongue and parapharyngeal fat pad.[18]

Hypopharynx

Hypopharynx is the caudal portion of upper airways, which extends from the superior border of the epiglottis to the inferior border of the cricoid cartilage.

Obstruction at the level of the hypopharynxis is less common than at the oropharynx. The structures in the hypopharynx, such as the lingual tonsils, can have a potential role in OSA.[19] In children with tonsillar hypertrophy, tonsillectomy is an effective treatment for snoring and OSA.[20]

Epiglottic prolapse (Figure 5) during inspiration has been described as a cause of OSA, with a partial laser epiglottidectomy reported as a cure.[21,22]

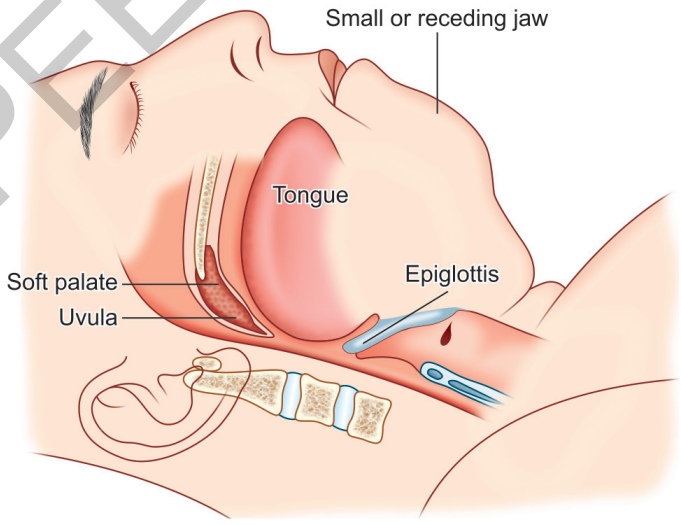

Figure 5: Epiglottic prolapse.

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PHYSIOLOGY

The goals of respiration are to provide oxygen to the tissues and to remove carbon dioxide. To achieve these goals, respiration can be divided into four major functions: (1) pulmonary ventilation, which means the inflow and outflow of air between the atmosphere and the lung alveoli; (2) diffusion of oxygen and carbon dioxide between the alveoli and the blood; (3) transport of oxygen and carbon dioxide in the blood and body fluids to and from the body's tissue cells; and (4) regulation of ventilation and other facets of respiration.

The lungs can be expanded and contracted in two ways: (1) by downward and upward movement of the diaphragm to lengthen or shorten the chest cavity and (2) by elevation and depression of the ribs to increase and decrease the anteroposterior diameter of the chest cavity.

The lung is an elastic structure that collapses like a balloon and expels all its air through the trachea whenever there is no force to keep it inflated. Also, there are no attachments between the lung and the walls of the chest cage, except where it is suspended at its hilum from the mediastinum. Instead, the lung "floats" in the thoracic cavity, surrounded by a thin layer of pleural fluid that lubricates movement of the lungs within the cavity.

PATHOPHYSIOLOGY

Obstructive sleep apnea is characterized by recurrent collapse of the pharyngeal airway during sleep, resulting in substantially reduced (hypopnea) or complete cessation (apnea) of airflow despite ongoing breathing efforts. These disruptions to breathing lead to intermittent blood gas disturbances (hypercapnia and hypoxemia) and surges of sympathetic activation. Loud snoring is a typical feature of OSA and in most cases the culmination of a respiratory event is associated with a brief awakening from sleep (arousal). These events result in a cyclical breathing pattern and fragmented sleep as the patient oscillates between wakefulness and sleep. In severe cases, respiratory events can occur more than 100 times per hour and typically each event lasts 20–40 seconds.

The multifactorial pathophysiology of OSA comes with individual variability. The complex interaction among pharyngeal dilator tone, arousal threshold, respiratory control instability, and changes in lung volume during sleep plays an important role in OSA.

Collapsibility of Upper Airways

Although the ability of the upper airway to change shape and momentarily close is essential for speech and swallowing during wakefulness, this feature also provides the opportunity for collapse at inopportune times such as during sleep.

From a purely anatomic perspective, a narrow upper airway is generally more prone to collapse than a larger one.

Due to changes in transmural pressure, the vulnerable airway which is from the hard palate to the larynx, can collapse while sleeping.

Apneic airway has thicker lateral pharyngeal walls with an anteroposterior elliptical configuration, in contrast to the horizontal configuration of normal airways. This fact of thickened airways is more important than the enlargement of parapharyngeal fat pads for causing airway narrowing in apneic patients.[14]

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The minimal airway area is also smaller in apneic patients, contributing to the airway collapse. Threshold pressure required to maintain patency of the upper airways is called pharyngeal critical closing pressure (Pcrit). Pcrit has been shown to correlate with OSA severity.[23]

Pharyngeal airway is a collapsible tube surrounded by tissue within a bony box.[24] The luminal size is determined by the properties of the tube and the transmural pressure. Increase in the pressure outside the tube will promote luminal narrowing.

Pharyngeal closing pressure increases as the tissue pressure increases, which can happen in following conditions—a high-arched palate, midface hypoplasia, reduction in size of the bony box from micrognathia or from soft tissue crowding caused by macroglossia, adenotonsillar hypertrophy, and central adiposity.[25] Obesity acts synergistically with narrowing of the bony box. The receded mandibles in apneic patients contribute to increased tissue pressure[26] and, consequently, pharyngeal collapse. Conversely, weight loss has been shown to reduce Pcrit[27] and the resolution of sleep disordered breathing depends on the degree of Pcrit reduction. Similarly, a stepwise advancement of the mandible in apneic patients leads to dose dependent reductions in Pcrit.[28]

Effects of Lung Volumes

The interaction between pharyngeal patency and lung volume is believed to be an important contributor to OSA pathogenesis.

Caudal traction and elongation of the airway reduces Pcrit through stiffening the airway and mitigating the surrounding tissue pressures.[29,30]

Lung volumes are reduced in supine position in apneic patients, which decreases caudal traction on the airway. By increasing end-expiratory lung volume using continuous positive airway pressure (CPAP) apnea severity is reduced and sleep architecture is improved.[31] While sleeping in the semi-recumbent position also reduces apnea severity.[32]

Upper Airway Dilator Muscle Activity and Reflex Responsiveness

Pharyngeal dilator muscle activity is offset by collapsing forces related to tissue pressure and intraluminal negative pressure. Genioglossus, the largest and most extensively studied upper airway dilator muscle in humans, has higher activity in patients with OSA compared with control subjects.[33] During wakefulness, upper airway dilator tone is high, and this maintains an open airway. With sleep onset, a decrease in the tone of the genioglossus muscle occurs. Airway instability occurs in apneic patients who rely on heightened genioglossus tone to support the airway.[34] The degree to which this occurs also depends on the sleep stage. Heightened genioglossus tone is present in slow wave sleep, which might be protective against OSA.[35] During REM sleep, a reduction in tonic genioglossus activity occurs, which potentiates further apneas.[36] Genioglossus and tensor palatine tone increases with local reflexes generated by negative pharyngeal pressure during sleep, especially in the supine position.[37,38] Genioglossus activity increases during inspiration but decreases during expiration.[33] The genioglossus has both excitatory and inhibitory responses to airway collapse, but the response is variable.[39]

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AROUSAL RESPONSE IN OBSTRUCTIVE SLEEP APNEA

Arousal from sleep at the cessation of a hypopnea or an apnea has long been believed to be an important protective mechanism for airway re-opening. Most apneic episodes are followed by arousals, which are thought to be mediated via negative intrathoracic pressure generation.[40] With the accumulation of stimuli, such as chemical drive and negative intrapharyngeal pressures, apnea termination can occur without arousals.[41-43] OSA impairs the arousal threshold, and therefore apneic patients need greater inspiratory efforts to trigger an arousal.[44]

Heightened arousal threshold in apneic patients is reduced with the treatment using CPAP.[45] Slow-wave sleep may stabilize the breathing in apneic patients via the arousal threshold. Ratnavadivel and colleagues[46] showed that the arousal threshold is further increased in slow-wave sleep compared with N2 sleep, but they did not find evidence supporting increased ventilatory drive or increased upper airway responses during slow-wave sleep compared with N2 sleep.

Ventilatory Control Stability and Pharyngeal Neuropathy

Typical feature of OSA is the cyclical breathing pattern that develops whereby the patient oscillates between obstructive breathing events (sleep) and arousal (wakefulness).

Ventilatory control stability contributes to OSA pathogenesis but is incompletely understood.[22] Loop gain is the feedback loop that controls the respiratory response to airway collapsibility and arousal, and which refers to the magnitude of the response relative to the intensity of the input.[47] Elevated loop gain is found in apneic patients, particularly those with severe OSA,[48,49] which leads to excessive increase of ventilatory response to apneas and arousal, leading to disproportionately lowered carbon dioxide (CO_2).

In a recent study, Yuan and colleagues[50] found that obese adolescents with OSA had a higher CO_2 sensitivity during wakefulness compared with the lean control group. In few studies, the ventilatory response during wakefulness in OSA has been inconsistent.[51] Importantly, the sensitivity decreased during sleep in the apneic adolescents. This blunting would lead to prolonged obstructive events. However, the magnitude of the ventilatory response to spontaneous arousal may promote driving the CO_2 below the apneic threshold, leading to further sleep-disordered breathing.[50] In a study by Edwards and colleagues,[52] acetazolamide reduced the ventilator response to spontaneous arousal in patients with OSA treated with CPAP, and improved this ventilatory instability.

Pharyngeal neuropathy is well described in OSA patients.[53-55] Two-point discrimination and vibratory tests are used to show the selective impairment of the ability to detect mechanical stimuli in the upper airway of patients with OSA and snorers.[53] Air pressure pulses during endoscopy is used to show the abnormal laryngeal sensation in patients with OSA.[54] Inflammation and denervation affect the oral mucosa and upper airway muscles in patients with OSA.[55] Whether it is the vibratory strain[56] or intermittent hypoxia[57] that plays a major role in promoting the pharyngeal neuropathy is still not clear. A recent study found neurogenic changes in the genioglossus[58] using measurements of motor unit potentials.

Saboisky and colleagues[58] reported evidence of collateral sprouting and re-innervation in the genioglossus, which correlated with lowest oxygen

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desaturation in patients with OSA. How this neuropathy affects upper airway function during sleep remains to be determined.

Increased fat deposits in the soft tissue surrounding the upper airway is found in obese patients, including in the soft palate.[59,60] Obesity is a major risk factor in OSA. Finding of a small increase in upper airway soft tissue volume in apneic patients compared with normal controls was confirmed in Japanese patients.[61]

Furthermore, a small decrease of 17 cm^3 in upper airway volume from overall weight loss (average of 7.8 kg) led to a 31% decrease in the AHI.[62] A reduction in functional residual capacity (FRC) is seen in obese individuals[63] and decreased upper airway patency from low FRC is an additional mechanism contributing to OSA in obese patients.[64] Consequently, weight loss and improvement in FRC would augment upper airway patency.

CONCLUSION

Understanding of the pathogenesis of OSA is evolving. Airway obstruction can occur at several sites in the upper airway, with the oropharynx being the most common. The hypoglossal nerve is a key player in upper airway dilator function. Retrognathia, adenotonsillar hypertrophy, enlarged tongue, lateral pharyngeal wall thickening, and parapharyngeal fat pads are important anatomic risk factors. The arousal response is heightened in apneic patients. Elevated loop gain leads to an overshoot of ventilator response in OSA, contributing to ventilator instability. The role of pharyngeal neuropathy in the pathophysiology of OSA is being investigated.

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