Obstructive apnea (OSA) is the prototype of all disorders characterized by sleep-disordered breathing (SDB). The prevalence of OSA with daytime impairment, that is, OSA syndrome (OSAS), has been estimated to be 4–5% among adults; minimally symptomatic or asymptomatic OSA is estimated to occur in 24% of the population1,2. In India, the prevalence of SDB has been found to be 4.6% among adults and 4.8% among school-going children3,4. Also, SDB was estimated to afflict 10.3% of the elderly population and 9.5% of pregnant subjects in studies conducted by the author5,6.

The sine qua non of OSA is a repetitive partial or complete closure of the upper airway during sleep. The anatomical characteristic of the pharynx has been conventionally considered to be the primary determinant of the occurrence of OSA. However several other mechanisms contribute to a varying extent to the pathogenetic traits of this disease. The upper airway
occupies a position of seminal importance in the pathogenesis of OSAS. The lateral wall of pharynx, soft palate, uvula, tongue volume, and facial skeletal characteristics such as maxilla, mandible, and dental arch occlusion are the major determinants of the disorder. Various methodologies have been used to assess upper airway structure and function, which include anterior rhinoscopy, nasopharyngoscopy, cephalometry, computed tomography, acoustic reflection, and optical coherence tomography.

**Pathogenesis**

**Anatomical factors**

The upper airway in humans is designed to undertake multiple functions of speech, breathing, as well as swallowing. It essentially comprises the conduit from nose to supraglottic larynx, along with its bony framework namely maxilla, mandible, hyoid, palatine bones, base of skull (basiocciput), and cervical vertebrae. The anatomical and physiological attributes of this segment are, therefore, appropriately well suited for its functions. The portion of the upper airway between the choana and the glottis, that is the pharyngeal tube, is devoid of any bony or cartilaginous support and hence is vulnerable to collapse. The patency of the fibromuscular conduit is determined by the transmural pressure across the pharyngeal lumen and follows the principles of tube law. It is this part of the upper airway that assumes a major role in OSA. The anatomic obstruction can be seen at various levels. Primary oropharyngeal obstruction may be due to a low palatal arch with a long low-hanging soft palate, large tongue, patulous posterior pillar mucosa, large tonsil, and redundant mucosal folds of lateral and posterior pharyngeal wall. Hypopharyngeal obstruction can result from a large base of tongue, hypertrophic lingual tonsil, or a floppy epiglottis. Primary skeletal changes such as micrognathia, maxillary hypoplasia, a decrease in the size of nasal capsule, choanal atresia, or stenosis or a decrease in pharyngeal circumference, and distorted pharyngeal orientation caused by abnormal angulation of the cranial base can also contribute to the occurrence of OSA.

**Impact of gender and age on anatomical and pathophysiological aspects of OSA**

OSA is more common in men and its prevalence increases with aging. This is despite the fact that the male pharynx is wider. The prevalence of OSA increases with age, so does the closing pressure of the pharynx. This is presumably due to an increased collapsibility of the aging pharynx.

**Other dynamic changes in pathogenesis of OSA**

Several other factors have been observed to impact the pathogenesis of OSA. Leg edema due to non-cardiopulmonary cause has been shown to be associated with a smaller upper airway cross-sectional area. Gastroesophageal reflux worsens OSA, perhaps by increasing arousals, causing bronchoconstriction, and lowering lung volumes, all of which may decrease upper airway stability or produce tissue damage and edema.

**Role of the nose**

Several pathophysiological mechanisms have been suggested to explain a contributory role of the nose in the multilevel anatomic obstruction in the causation of SDB. The Starling resistor model (upstream obstruction generating a suction force downstream), nasal obstruction promoting an unstable oral breathing, decreased nasal airflow resulting in decreased activation of nasal ventilatory reflex, and a reduction in nitric oxide have all been implicated as pathogenetic processes.

**Fat deposition within the pharynx**

Deposition of fat within the maxillomandibular enclosure increases and thus encourages pharyngeal narrowing. Tongue volume and lateral pharyngeal volume are independent risk factors for OSA. The fat content in the posterior region of the tongue is higher than in its other regions. Tongue volume is not always greater in patients with OSA, and it does not reduce after weight reduction. Also, intermittent hypoxia due to upper airway obstruction in sleep often results in a transition from endurance type IIa muscle fibers to fatigable type IIb muscle fibers in genioglossus and geniohyoid muscles. This is often reversible with continuous positive airway pressure (CPAP) therapy. However, the anatomical balance of the upper airway (i.e., ratio of relative soft tissue volume to maxillomandibular dimensions) is a better indicator of the occurrence of OSA. The volume of excess soft tissue associated with the development of OSA differs between races and in those with craniofacial abnormalities. Even a small reduction in upper airway fat volume (17 cm³) that may be brought about by weight reduction has been shown to be associated with significant...
The excessive deposition of fat in the maxillomandibular bony enclosure may often lead to a caudal displacement of soft tissue through the submandibular space. This may partly mitigate the impact of $P_{\text{intra}}$ on airway patency and is detected in patients with OSA as an increased neck circumference, reduced crico-mental space, a “double chin,” and a greater distance between the mandibular and the hyoid planes. All these findings may actually be a result of rather than causative factors for the upper airway anatomical imbalance. The caudal displacement of soft tissue also elongates the upper airway and may compensate for the upper airway anatomical imbalance by decreasing $P_{\text{intra}}$ and increasing longitudinal pharyngeal wall tension in accordance with the tube law referred to earlier.39

A predominantly central deposition of visceral fat may reduce lung volumes and thereby longitudinal tension of the pharyngeal wall, predisposing to upper airway collapse.39 Central obesity has been associated with the male preponderance of OSA; peripherally distributed obesity may protect women from developing the disorder.35 Although a clear association between OSA and obesity has been observed, the cause and effect relationship seems to be less clearly explicable, and may be as a result of several factors.34 Obesity may alter the functional control of the upper airway through its neurochemical effects over metabolic and inflammatory consequences.35 Direct effects of obesity on pharyngeal collapsibility and upper airway lumen have been discussed earlier. Ethnic variations exist in the pattern of obesity. Extreme obesity in the USA is predominantly existent in African-Americans.36,37 Central or abdominal fat deposition, which is more common and occurs at a lower overall body mass index (BMI) among Asian populations, predisposes to OSA.38-44

The role of upper airway anatomy that is independent of obesity is thus highlighted in several studies among Asians in general and patients from the Indian subcontinent in particular.42-48 In a case control study conducted in the author's experience of 40 patients with obstructive sleep apnea–hypopnea syndrome (Unpublished data), it was observed that retrognathia, was common in OSA and increased neck circumference, increased hyoid-mandibular distance, shorter mandible and longer soft palate correlated significantly with severity of OSA.

### Decrease in pharyngeal dilator muscle function

The segment of the pharynx extending from the choanae up to the larynx has no bony structure to support its walls. Hence, the caliber of the lumen of this part depends, to a large extent, on the activity of the pharyngeal dilator muscles. In a subject with an anatomically small pharyngeal airway lumen, even small decrements in the tone of these dilator muscles can result in a significant compromise in the patency of the pharynx. Till the time these muscles are active, this collapsible segment of the pharynx is kept dilated. There are three major groups of such muscles.49 The first group comprises muscles influencing the hyoid bone position (geniohyoid, sternohyoid, etc.), the second group consists of the muscles of the tongue (genioglossus), and the third group controls the palate (tensor palatini, levator palatini, etc.). Functionally, most of these muscles contract vigorously during inspiration and oppose the normal collapsing influence of negative inspiratory forces present during inspiration, thereby stiffening and dilating the airway.50,52 Such muscles (such as genioglossus) are principally under the influence of central respiratory neurons and are known as phasic muscles. Other muscles (such as tensor palatini) show a constant level of activity during the entire respiratory cycle, with no inspiratory phasic variation. These muscles are termed as tonic muscles and are mainly controlled by tonic or postural neurons.52

The inspiratory phasic and tonic muscle groups are under the influence of respiratory chemical stimuli (hypercapnia and hypoxia) as well as negative inspiratory pressure forces that tend to result into inspiratory collapse of this pharyngeal segment.53-56 The latter stimulus can be diminished or abolished by pharyngeal anesthesia.57

There are sleep-induced decrements in the activity of tonic pharyngeal dilator muscles (levator palatini) even in normal individuals, leading to a decreased airway patency. This may be inconsequential in normal subjects. However, in patients with OSA, there is a structurally small airway (due to micrognathia, tonsillar hypertrophy, fat deposition in the neck, etc.) as evidenced by the various methods cited earlier.58-60 During wakefulness, there is a tight control of the pharyngeal dilator muscle activity to maintain airway patency, mainly driven by the negative pressure reflex response.61 In patients with OSA, who have an inherently small-volume pharynx, there is an augmented activity of these muscles that tends to overcome this anatomical handicap.62 This augmented neuromuscular activity, which serves as a "compensation
for an anatomically small airway," has been noticed to reduce to normal levels with the application of CPAP.\textsuperscript{31,61} This enhanced tone of the pharyngeal dilator (genioglossus) is crucial in the maintenance of upper airway patency during wakefulness. During sleep, due to loss of this negative pressure reflex of upper airway, this enhanced genioglossus activity is also lost. This, in turn, leads to a significant reduction of the upper airway lumen. Although the phasic activity of genioglossus remains unaffected during sleep, this alone is unable to maintain the patency of the anatomically small upper airway.\textsuperscript{49,62,63} A loss of activity of tonic pharyngeal dilators (e.g., tensor palatini) during sleep also contributes to an additional compromise in the upper airway lumen. Recent studies have also shown a pronounced state-dependent reflex inhibition (rather than loss of excitation) that may mediate diminished pharyngeal reflex responses during sleep.\textsuperscript{64,65}

**Collapsible tube model of pharynx**

The structure of the pharynx has been compared to an artificial model of a collapsible tube in a rigid chamber as it is inherently collapsible during sleep, when the tone of the dilator muscles also decreases.\textsuperscript{19} Also, it is surrounded by several soft tissues (tongue, soft palate, tonsils, fat pads) and is enclosed within bony structures (mandible, maxilla, and cervical spine). The cross-sectional area of this tube is governed by the "tube law"—the transmural pressure ($P_{\text{tm}}$) being the difference between intraluminal pressure and tissue pressure ($P_{\text{tm}} = P_{\text{lumen}} - P_{\text{tissue}}$). $P_{\text{lumen}}$ is the lateral wall pressure acting on the luminal surface of the tube and $P_{\text{tissue}}$ being the tissue pressure exerted on its outside surface. The tube may collapse if (a) $P_{\text{tissue}}$ increases (e.g., fat deposition surrounding the airway), (b) $P_{\text{lumen}}$ decreases, or (c) longitudinal traction of pharyngeal airway decreases thus making it more compliant (e.g., reduction in lung volume). The $P_{\text{crit}}$ (critical closing pressure) is determined by considering this pharyngeal collapsible tube model as a Starling resistor. It would collapse when $P_{\text{tissue}}$ exceeds $P_{\text{lumen}}$.\textsuperscript{19}

The role of an abnormally collapsible pharynx in the pathogenesis of OSA is evidenced by the demonstration of a higher pharyngeal closing pressure in the patients with OSA than in age- and BMI-matched subjects without OSA under conditions of general anesthesia and muscle paralysis.\textsuperscript{20} A pharyngeal closing pressure greater than atmospheric exclusively in the retropalatal region is found in obese patients with OSA and in both retropalatal and retroglossal segments in OSAS associated with craniofacial abnormalities.\textsuperscript{21}

**Myopathy-like dysfunction in the pathogenesis of OSA**

It is often argued that the decreased response of pharyngeal dilator muscles results from myopathy due to recurrent muscular injury from vibration or oxidative stress and hypoxia.\textsuperscript{66–68} A compensatory increase in signaling to these myopathic muscles, which occurs during wakefulness, is lost during sleep. This has been hypothesized to result into a sleep-linked loss of upper airway pharyngeal dilator muscle activity.

**Other factors**

**Arousal**

It is a well known observation that obstructive respiratory events in sleep (apnea and hypopnea) are terminated by an arousal. Arousal, in fact, has been presumed to be a protective mechanism that is involved in restoration of upper airway patency after such an event.\textsuperscript{62,69} The length of duration of an arousal has been seen to be proportional to the severity of the obstructive events.\textsuperscript{70} Recent studies have, however, shown that restoration of upper airway patency and resumption of ventilation after an obstructive event in patients with OSA can occur even without cortical arousals and, at least some of the time, to a lesser extent than in healthy individuals challenged with respiratory loading.\textsuperscript{71,72} It has been proposed that an arousal-free restoration of airflow can be achieved by a compensatory recruitment of upper airway dilator muscles (genioglossus) only if the sleep state can be continued for a sufficient duration after such an event and respiratory stimuli such as carbon dioxide and negative pressure are allowed to build up.\textsuperscript{65,73}

Therefore, increasing the arousal threshold, thereby preventing arousal from sleep, may be beneficial in patients who awaken easily in response to respiratory loads during sleep.\textsuperscript{73–75} Those patients who have a preexisting high arousal threshold would not be suitable for such a therapeutic strategy.\textsuperscript{76}

**Ventilatory control and loop gain**

The role of ventilatory control has been surmised to be extremely important in pathogenesis of OSA. “Loop gain” is a term borrowed from engineering parlance and has been used in relation to ventilatory control.\textsuperscript{77} It describes the stability of any system that is influenced by feedback loops. Loop gain of ventilatory control reflects the stability of the respiratory system, its responsiveness...
to changes in breathing patterns (during arousal, etc.), and portrays the tendency of the respiratory control system to show fluctuations in ventilatory output (during periodic breathing, etc.). Chemo-responsiveness of the center to hypoxia and hypercapnia is also termed as controller gain. Capability to ventilate and wash out carbon dioxide is often labeled as plant gain. Delayed circulation time, as seen in congestive heart failure, is often termed as mixing gain. These are the essential three components of the “loop gains” of the ventilatory control system. A high loop gain system (i.e., hyperactive ventilatory response to a stimulus) is considered to be unstable. Using proportional assist ventilation to measure loop gain, it has been observed that patients with OSA are commonly associated with an elevated loop gain system and ventilatory instability. A high loop gain system would increase central ventilatory output and pharyngeal obstruction is expected to occur when such output to the pharyngeal dilator muscles is at its minimum. Also, an elevated loop gain system would enhance the ventilatory response to arousal and may excessively wash out carbon dioxide, which would bring down the PaCO₂ levels below the apnea threshold during the ensuing sleep cycle, leading to cyclical breathing.

The contribution of ventilatory instability toward the pathogenesis of OSA is significant. Ventilatory instability or variability has been seen to correlate with AHI, even after normalizing for covariant factors such as anatomical tendency toward obstruction (lower \( P_{\text{crit}} \)).

**Lung volume**

As alluded to earlier, the volume of lung has a direct bearing and dependence on upper airway caliber and its mechanical properties. This dependence of the upper airway lumen on volume of lung is more apparent in patients with OSA both during wakefulness and sleep. Caudal traction of trachea exerted by increasing lung volumes on the upper airway may prevent it from collapse. A reduction in lung volume leads to loss of this caudal traction of the upper airway, thus rendering it more vulnerable to collapse. Although increasing functional residual capacity of lung during sleep decreases the CPAP level required to prevent pharyngeal collapse, other non-mechanical factors also contribute toward preservation of lung volumes during sleep state.

**Summary of pathogenetic factors**

In summary, several factors may singularly or jointly contribute to a variable extent to the pathogenesis of OSA. They commonly include the following:

a. Male gender
b. Gastro-esophageal reflux
c. Nasal obstruction
d. An abnormally collapsible pharynx (“Tubal Law”)
e. Deposition of fat within the pharynx
f. Change in the type of muscle fibers of pharyngeal dilators from type Ila to type Ilb
g. Central deposition of visceral fat
h. Racial and other variations cranio-pharyngeal anatomy that renders the pharynx more conducive to the occurrence of OSA

i. Sleep-induced loss of augmented neuromuscular activity of pharyngeal dilator muscles (which serves as a “compensation for an anatomically small airway” during wakefulness)

j. Sleep-induced reflex inhibition (rather than loss of excitation) that may mediate diminished pharyngeal reflex responses during sleep

k. Pharyngeal dilator muscles myopathy due to recurrent muscular injury from vibration or oxidative stress and hypoxia

l. Low threshold for arousals

m. An elevated loop gain system and unstable ventilatory control

n. Low lung volumes leading to loss of caudal traction of upper airway

An anatomically predisposed upper airway characterized by reduction in the dimensions of pharynx and lowered muscle tone and/or dysfunction of pharyngeal dilator muscles is influenced by multiple pathophysiological disturbances such as a reduced arousal threshold and heightened instability of ventilatory control. A progressively increasing respiratory effort is associated with hypoxia with/without hypercapnia. This quickly leads to an arousal in an attempt to restore ventilation. An increased ventilatory response to hypoxia/hypercapnia, in turn, now results in hyperventilation, often leading to excessive washing out of carbon dioxide and return to sleep. With restoration of sleep, there is again a reduction in lung volume tethering, decrease in pharyngeal dilator activity, and upper airway collapse. Thus, OSA is perpetuated.
**Therapeutic implications**

As evident from the aforementioned discussion, OSA is a heterogeneous disorder that has a multifactorial pathogenetic mechanism. It would seem prudent to determine the specific phenotype upfront to focus on a particular therapeutic strategy. Although several pathophysiological mechanisms have been recognized, it is a difficult to predict the success of a particular therapy (CPAP/oral appliance/surgery) in a given patient. Novel methods involving computational modeling have been designed to predict responses to upper airway surgery in OSA. Using MRI as a tool, experimentally measured upper airway dilator muscle activities, and finite elements analysis, a two-dimensional (2D) and a partial 3D model of the upper airway showed that both velopharynx and the retroglossal airway need to be targeted surgically to be most successful. Other novel strategies include use of oxygen therapy to stabilize ventilatory control and high loop gain; use of sedative/hypnotic and other drugs (donepezil, mirtazapine, trazodone, etc.) in patients with a low arousal threshold, use of acetazolamide, exercise training; and making ongoing efforts to search for agents that may lead to increase in pharyngeal dilator muscle activity.

Future research needs to directly address some such issues related to refining therapeutic modalities based on pathophysiological aspects of upper airway anatomy in relation to OSA.

**REFERENCES**


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