REVIEW ARTICLE

Pathophysiological mechanisms associated with sleep disorder breathing and their influence on treatment

J. C. Suri*, M. K. Sen**

*Consultant, Professor, & Head, **Consultant & Associate Professor
Department of Pulmonary, Critical Care & Sleep Medicine, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India

DOI No:10.5958/0974-0155.2014.01104.8 *Indian J Sleep Med 2014; 9.2, 50-58*

Abstract

This article summarizes the anatomical basis as well as the various pathophysiological mechanisms that are considered to be crucial in development of sleep-disordered breathing. The anatomic factors that predispose to the occurrence of pharyngeal collapse are considered. The collapsible tube model for understanding the behavior of human pharyngeal airway, transmural pressure, intraluminal pressure, surrounding tissue pressure, closing pressure of pharyngeal airway, and critical closing pressure are discussed. The role of nose in snoring and obstructive sleep apnea (OSA) is also touched on. The role of obesity on upper airway is outlined. These include the mechanical consequences of fat deposition within the maxillomandibular enclosure on pharyngeal collapsibility and possible influences of visceral fat on OSA. An overview of pharyngeal anatomy and musculature, pharyngeal muscle activity during wake/sleep, and neural regulation of sleep and breathing is given. Factors pertaining to the loss of pharyngeal dilator muscle activation, change in central respiratory drive, and OSA-induced neuropathy/myopathy are discussed. Abnormalities of central neuronal output and control of breathing are explained. The impact of end-expiratory lung volume on upper airway resistance is also discussed. The use of computational modeling to predict responses to upper airway surgery in OSA is discussed. Novel methods such as manipulation of the arousal threshold and measures to reduce a high loop gain (oxygen therapy, acetazolamide) are also briefly discussed.

Introduction

Obstructive sleep 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 population[1,2]. In India, the prevalence of SDB has been found to be 4.6% among adults and 4.8% among school-going children[3,4]. Also, SDB was estimated to afflict 10.3% of the elderly population and 9.5% of pregnant subjects in studies conducted by the author[5,6].

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

Address for correspondence
Dr. J. C. Suri
Consultant, Professor, & Head
Department of Pulmonary, Critical Care & Sleep Medicine, Vardhman Mahavir Medical College & Safdarjang Hospital, New Delhi, India.
Email: docjcsuri@gmail.com

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[7]. 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[8–11].

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[12–23]. The postpubertal male pharynx has a longer length than its female counterpart, and therefore is also more collapsible.[13,14] 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[15].

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[16,17]. 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[18].

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.[22]

Fat deposition within the pharynx

Deposition of fat within the maxillomandibular enclosure increases P_{tissue} and thus encourages pharyngeal narrowing.[19] Tongue volume and lateral pharyngeal volume are independent risk factors for OSA.[23] The fat content in the posterior region of the tongue is higher than in its other regions.[24] Tongue volume is not always greater in patients with OSA, and it does not reduce after weight reduction.[19,25] 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.[26] This is often reversible with continuous positive airway pressure (CPAP) therapy.[27] 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.[19,28,29] The volume of excess soft tissue associated with the development of OSA differs between races and in those with craniofacial abnormalities.[29,30] Even a small reduction in upper airway fat volume (17 cm^3) that may be brought about by weight reduction has been shown to be associated with significant

(31%) reduction in apnea–hypopnea index (AHI) in Caucasian patients with OSA.[31]

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_{tissue} 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.[32] The caudal displacement of soft tissue also elongates the upper airway and may compensate for the upper airway anatomical imbalance by decreasing P_{tissue} and increasing longitudinal pharyngeal wall tension in accordance with the tube law referred to earlier[19].

A predominantly central deposition of visceral fat may reduce lung volumes and thereby longitudinal tension of the pharyngeal wall, predisposing to upper airway collapse.[19] Central obesity has been associated with the male preponderance of OSA; peripherally distributed obesity may protect women from developing the disorder.[33] 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.[38–41]

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.[50,51] 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.[61] 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.[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[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[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.[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_{tm}) being the difference between intraluminal pressure and tissue pressure ($P_{tm} = P_{lumen} - P_{tissue}$). P_{lumen} is the lateral wall pressure acting on the luminal surface of the tube and P_{tissue} being the tissue pressure exerted on its outside surface. The tube may collapse if (a) P_{tissue} increases (e.g., fat deposition surrounding the airway), (b) P_{lumen} decreases, or (c) longitudinal traction of pharyngeal airway decreases thus making it more compliant (e.g., reduction in lung volume). The P_{crit} (critical closing pressure) is determined by considering this pharyngeal collapsible tube model as a Starling resistor. It would collapse when P_{tissue} exceeds P_{lumen}.[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.[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.[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.[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.[62,69] The length of duration of an arousal has been seen to be proportional to the severity of the obstructive events.[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.[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.[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.[73–75] Those patients who have a preexisting high arousal threshold would not be suitable for such a therapeutic strategy.[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.[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.[65] 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.[78–81] 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 $PaCO_2$ levels below the apnea threshold during the ensuing sleep cycle, leading to cyclical breathing.[65]

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_{crit}).[82]

Lung volume

As alluded to earlier, the volume of lung has a direct bearing and dependence on upper airway caliber and its mechanical properties.[83–88] This dependence of the upper airway lumen on volume of lung is more apparent in patients with OSA both during wakefulness and sleep.[88] Caudal traction of trachea exerted by increasing lung volumes on the upper airway may prevent it from collapse.[89–94] 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[95–97].

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 ("Tube Law")
e. Deposition of fat within the pharynx
f. Change in the type of muscle fibers of pharyngeal dilators from type IIa to type IIb
g. Central deposition of visceral fat
h. Racial and other variations craniopharyngeal 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.[98] 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.[65,99–101]

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

1. **Young T**, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea—A population health perspective. *Am J respire Crit Care Med* 2002; 165: 1217–39.
2. **Jennum P**, Riha RL. Epidemiology of sleep apnea/hypopnea syndrome and sleep-disordered breathing. *Eur Respir J* 2009; 33: 907–14.
3. **Suri JC**, Sen MK, Adhikari T. Epidemiology of sleep disorders in the adult population of Delhi-a questionnaire based study. *Indian J Sleep Med* 2008; 3.4: 128–37.
4. **Suri JC**, Sen MK, Adhikari T. Epidemiology of sleep disorders in schoolchildren of Delhi-a questionnaire based study. *Indian J Sleep Med* 2008; 3(2): 42–50.
5. **Suri JC**, Sen MK, Ojha UC, Adhikari T. Epidemiology of sleep disorders in the elderly-a questionnaire based study. *Indian J Sleep Med* 2009; 4(1): 12–18.
6. **Suri JC**, Sen MK, Suri J, Vaidya S, Adhikari T. Epidemiology of sleep disorders in pregnant subjects – A questionnaire based study. *Indian J Sleep Med* 2009; 4(1): 12–18.
7. **Shepard JW Jr**, Geffer WB, Guilleminault C, et al. Evaluation of the upper airway in patients with obstructive sleep apnea. *Sleep* 1991; 14: 361–71.
8. **Tangel DJ**, Mazzanotte WS, Sandberg EJ, White DP. The influence of sleep on the activity of tonic postural versus inspiratory phasic muscles in normal man. *J Appl Physiol* 1992; 73: 1053–66.
9. **Tangel DT**, Mezzanottle WS, White DP. The influence of sleep on tensor palatine EMG and upper airway resistance in normal subjects. *J Appl Physiol* 1991; 70: 2574–81.
10. **Onal E**, Lopata M, O'Conner T. Diphragmatic and genioglossal electromyogram responses to isocapnic hypoxia in humans. *Am Rev Respir Dis* 1981; 124: 215–17.
11. **Ona LE**, Lopata M, O'Connor T. Diaphragmatic and genioglossal electromyogram responses to CO2 rebreathing in humans. *J Appl Physiol* 1981; 50: 1052–5.
12. **Owens RL**, Eckert DJ, Yeh SY, Malhotra A. Upper airway function in the pathogenesis of obstructive sleep apnea: A review of the current literature. *Curr Opin Pulm Med* 2008; 14(6): 519–24.
13. **Ronen O**, Malhotra A, Pillar G. Influence of gender and age on upper-airway length during development. *Pediatrics* 2007; 120(4): e1028–34.
14. **Kirkness JP**, Schwartz AR, Schneider H, et al. Contribution of male sex, age, and obesity to mechanical instability of the upper airway during sleep. *J Appl Physiol* June 2008; 104(6): 1618–24.
15. **Marcus CL**, Lutz J, Hamer A, Smith PL, Schwartz A. Developmental changes in response to subatmospheric pressure loading of the upper airway. *J Appl Physiol* 1999; 87: 626–33.
16. **Iftikhar I**, Ahmed M, Tarr S, Zyzanski SJ, Blankfield RP. Comparison of obstructive sleep apnea patients with and without leg edema. *Sleep Med* 2008; 9(8): 890–3.
17. **Beecroft JM**, Hoffstein V, Pierratos A, Chan CT, McFarlane PA, Hanly PJ. Pharyngeal narrowing in end-stage renal disease: Implications for obstructive sleep apnoea. *Eur Respir J* 2007; 30: 965–71.
18. **Dickman R**, Green C, Fass SS, et al. Relationships between sleep quality and ph monitoring findings in persons with gastroesophageal reflux disease. *J Clin Sleep Med* 2007; 3(5): 505–13.
19. **Isono S**. Obesity and obstructive sleep apnoea: Mechanisms for increased collapsibility of the passive pharyngeal airway. *Respirology* 2012; 17(1): 32–42.
20. **Isono S**, Remmers JE, Tanaka A, Sho Y, Sato J, Nishino T. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. *J Appl Physiol* 1997;82: 1319–26.
21. **Watanabe T**, Isono S, Tanaka A, Tanzawa H, Nishino T. Contribution of body habitus and craniofacial characteristics to segmental closing pressures of the passive pharynx in patients with sleep-disordered breathing. *Am J Respir Crit Care Med* 2002; 165: 260–5.

22. **Georgalas C**. The role of the nose in snoring and obstructive sleep apnoea: An update. *Eur Arch Otorhinolaryngol* 2011; 268: 1365–73.
23. **Schwab RJ**, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. *Am J Respir Crit Care Med* 2003; 168: 522–30.
24. **Nashi N**, Kang S, Barkdull GC, Lucas J, Davidson TM. Lingual fat at autopsy. *Laryngoscope* 2007; 117: 1467–73.
25. **Welch K**, Foster G, Ritter C, et al. A novel volumetric magnetic resonance imaging paradigm to study upper airway anatomy. *Sleep* 2002; 25: 532–42.
26. **Pae EK**, Wu J, Nguyen D, Monti R, Harper RM. Geniohyoid muscle properties and myosin heavy chain composition are altered after short-term intermittent hypoxic exposure. *J Appl Physiol* 2005; 98: 889–94.
27. **Carrera M**, Barbé F, Sauleda J,. Effects of obesity upon genioglossus structure and function in obstructive sleep apnoea. Eur Respir J 2004 23:425-429
28. Iida-Kondo C, Yoshino N, Kurabayashi T, Mataki S, Hasegawa M, Kurosaki N. Comparison of tongue volume/oral cavity volume ratio between obstructive sleep apnea syndrome patients and normal adults using magnetic resonance imaging. *J Med Dent Sci* 2006; 53: 119–26.
29. **Saigusa H**, Suzuki M, Higurashi N, Kodera K. Three-dimensional morphological analyses of positional dependence in patients with obstructive sleep apnea syndrome. *Anesthesiology* 2009; 110: 885–90.
30. **Tsuiki S**, Isono S, Ishikawa T, Yamashiro Y, Tatsumi K, Nishino T. Anatomical balance of the upper airway and obstructive sleep apnea. *Anesthesiology* 2008; 108: 1009–15.
31. **Sutherland K**, Lee RW, Phillips CL, et al. Effect of weight loss on upper airway size and facial fat in men with obstructive sleep apnoea. *Thorax* 2011; 66: 797–803.
32. **Tagaito Y**, Isono S, Tanaka A, Ishikawa T, Nishino T. Sitting posture decreases collapsibility of the passive pharynx in anesthetized paralyzed patients with obstructive sleep apnea. *Anesthesiology* 2010; 113(4): 812–8.
33. **Schwartz AR**, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and obstructive sleep apnea: Pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc* 2008 February 15; 5(2): 185–92.
34. **Sutherland K**, Lee RWW, Cistulli PA. Obesity and craniofacial structure as risk factors for obstructive sleep apnoea: Impact of ethnicity. *Respirology* 2012; 17(2): 213–22.
35. **Schwartz AR**, Patil SP, Squier S, Schneider H, Kirkness JP, Smith PL. Obesity and upper airway control during sleep. *J Appl Physiol* February 2010; 108 (2): 430–5.
36. **Hensrud DD**, Klein S. Extreme obesity: A new medical crisis in the United States. *Mayo Clin Proc* 2006; 81(10 Suppl): S5–10.
37. **Wang Y**, Beydoun MA. The obesity epidemic in the United States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: A systematic review and meta-regression analysis. *Epidemiol Rev* 2007; 29: 6–28.
38. **Jia WP**, Wang C, Jiang S, Pan JM. **Characteristics of obesity and its related disorders in China.** *Biomed Environ Sci* 2010; **23:** 4–11.
39. **de Onis M**, Blössner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. *Am J Clin Nutr* 2010; 92: 1257–64.
40. **James WP**. The epidemiology of obesity: The size of the problem. *J Intern Med* 2008; 263(4): 336–52.
41. **Rush EC**, Freitas I, Plank LD. Body size, body composition and fat distribution: Comparative analysis of European, Maori, Pacific Island and Asian Indian adults. *Br J Nutr* 2009; 102: 632–41.
42. **Jayan B**, Prasad BNBM, Kotwal A, Kharbanda OP, Chowdhury SK, Gupta SH. The role of cephalometic analysis in obese and non-obese urban Indian adults with obstructive sleep apnea syndrome: A pilot study. *Indian J Sleep Med* 2007; 2(2): 59–63.
43. **Liu Y**, Lowe AA, Zeng X, Fleetham JA. Cephalometric comparisons between Chinese and Caucasian patients with obstructive sleep apnea. *Am J Orthod Dentofacial Orthop* 2000; 117(4): 479–85.
44. **Li KK**, Powell NB, Kushida C, Riley RW, Adornato B, Guilleminault C. A comparison of Asian and white patients with obstructive sleep apnea syndrome. Laryngoscope 1999; 109(12): 1937–40.
45. **Ping-Ying Chiang R**, Lin CM, Powell N, Chiang YC, Tsai YJ. Systematic analysis of cephalometry in obstructive sleep apnea in Asian children. Laryngoscope 2012; 122(8): 1867–72.
46. **Hsu PP**, tan AK, Chan YH, Lu PK, Blair RL. Clinical predictors in obstructive sleep apnea patients with calibrated cephalometyric analysis—a new approach. *Clin Otolaryngol* 2005; 30(3): 234–41.
47. **Takai Y**, Yamashiro Y, Satoh D, Isobe K, Sakamot S, Homma S. Cephalometric assessment of craniofacial morphology in Japanese male patients with obstructive sleep apnea-hypopnea syndrome. *Sleep Biol Rhythms* 2012; 10(3): 162–8.
48. **Lee RW**, Vasudavan S, Hui DS, et al. Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. *Sleep* 2010; 33(8): 1075–80.
49. **White DP**. Pathophysiology of obstructive sleep apnea. *Thorax* 1995; 50: 797–804.
50. **Weiganel DA**, Lat B, Zwillich CW, Wiegand L. Geniohyoid muscle activity in normal man during wakefulness and sleep. *J Appl Physiol* 1992; 69: 1262–9.
51. **Tangel DJ**, Mazzanotte WS, Sandberg EJ, White DP. The influence of sleep on the activity of tonic postural versus inspiratory phasic muscles in normal man. *J Appl Physiol* 1992; 73: 1053–66.
52. **Tangel DT**, Mezzanottle WS, White DP. Influence of sleep on tensor palatine EMG and upper airway resistance in normal subjects. *J Appl Physiol* 1991; 70: 2574–81.
53. **Onal E**, Lopata M, O'Conner T. Diphragmatic and genioglossal electromyogram responses to isocapnic hypoxia in humans. *Am Rev Respir Dis* 1981; 124: 215–17.

54. **Ona LE**, Lopata M, O'Connor T. Diaphragmatic and genioglossal EMG responses to CO2 rebreathing in humans. *J Appl Physiol* 1981; 50: 1052–5.

55. **Horner RL**, Innes JA, Murphy K, Guy A. Evidence for reflex upper airway dilator muscle activation by sudden negative airway pressure in man. *J Physiol* (Loud) 1991; 436: 15–29.

56. **Wheatley JR**, Mezzanotte WS, Tangel DJ, White DP. Influence of sleep on genioglossal muscle activation by negative pressure in normal men. *Am Rev Respir Dis* 1993; 148: 597–605.

57. **Horner RL**, Innes JA, Holden HB, Guy A. Afferent pathways for pharyngeal dialator reflex to negative pressure in man: A study using upper airway anaesthesia. *J Physiol (loud)* 1991; 436: 31–44.

58. **Haponik E**, Smith P, Bohlman M, Allan R, Goldman S, Bleecher E. Computerized tomography in obstructive sleep apnea: Correlation of airway size with physiology during sleep and wakefulness. *Am Rev Respir Dis* 1983; 127: 221–6.

59. **Rivlin J**, Hoffstein V, Klabfleisch J, McNiciholas W, Zamel N, Bryan AC. Upper airway morphology in patients with idiopathic obstructive sleep apnea. *Am Rev Respir Dis* 1984; 129: 335–60.

60. **Stauffer JL**, Zwillich CW, Cadieux RJ, et al. Pharyngeal size and resistance in obstructive sleep apnea. *Am Rev Respri Dis* 1987; 136: 623–27.

61. **Mezzanotte WS**, Tangel DJ, White DP. Waking genioglossal EMG in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). *J Clin Invest* 1992; 89: 1571–9.

62. **Remmers JE**, DeGroot WJ, SauerLand EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol* 1978; 44: 931–8.

63. **Kubota K**, Tanaka R. The fusimotor activity and natural sleep in the cat. *Brain Res* 1966; 3: 198–201.

64. **Eckert DJ**, Mc Evoy RD, George KE, Thomson KJ, Catche side PG. Genioglossus reflex inhibition to upper-airway negative-pressure stimuli during wakefulness and sleep in healthy males. *J Physiol* 2007; 581: 1193–205.

65. **Eckert DJ**, Malhotra A. Pathophysiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008; 5: 144–53.

66. **Eckert DJ**, Saboisky JR, Jordan AS. Upper airway myopathy is not important in the pathophysiology of obstructive sleep apnea. *J Clin Sleep Med* 2007; 3: 570–3.

67. **Kimoff RJ**. Upper airway myopathy is important in the pathophysiology of obstructive sleep apnea. *J Clin Sleep Med* 2007; 3: 567–9.

68. **Dunteary M**, Bradford A, O'Halloran KD. Oxidative stress impairs upper airway muscles endurance in an animal model of sleep disordered breathing. *Adv Exp Med Biol* 2008; 605: 458–62.

69. **Phillipson EA**, Sullivan CE. Arousal: The forgotten response to respiratory stimuli. *Am Rev Respir Dis* 1978; 118: 807–9.

70. **Nigro CA**, Rhodius EE. Variation in the duration of arousal in obstructive sleep apnea. *Med Sci Monit* 2005; 11: CR188-CR192.

71. **Younes M**. Role of arousals in the pathogenesis of obstructive sleep apnea. *Am J Respir Crit Care Med* 2004; 169: 623–33.

72. **Jordan AS**, Wellman A, Heinzer RC et al. Mechanisms used to restore ventilation after partial upper airway collapse during sleep in humans. *Thorax* 2007; 62: 861–7.

73. **Younes M**, Ostrowski M, Atkar R. Mechanisms of breathing instability with obstructive sleep apnea. *J Appl Physiol* 2007; 103: 1929–41.

74. **Younes M**, Park E, Horner RL. Peutobarbital sedation increases genioglossus respiratory activity in sleeping rats. *Sleep* 2007; 30: 478–88.

75. **White DP**. Sleep apnea. *Proc Am Thorac Soc* 2006; 3: 124–8.

76. **Dyken Me**, Yamada T, Glenn CL, Berger HA. Obstructive sleep apnea associated with cerebral hypoxemia and death. *Neurology* 2004; 62: 491–3.

77. **Khoo MC**, Kronauer RE, Strohl KP, Slutsky AS. Factors inducing periodic breathing in humans: A general model. *J Appl Physiol* 1982; 53: 644–59.

78. **Younes M**. Proportional assist ventilation, a new approach to ventilatory support. *Am Rev Respir Dis* 1992; 145: 114–20.

79. **Wellman A**, Jordan AS, Malhotra A et al. Ventilatory control and airway anatomy in obstructive sleep apnea. *Am J Respir Crit Care Med* 2004; 170: 1225–32.

80. **Meza S**, Mendez M, Ostrowski M, Younes M. Susceptibility to periodic breathing with assisted ventilation during sleep in normal subjects. *J Appl Physiol* 1998; 85: 1929–40.

81. **Younes M**, Ostrowski M, Thompson W, Leslie C, Shewchuk W. Chemical control stability in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2001; 163: 1181–90.

82. **Ibrahim LH**, Patel Sr, Modarres M et al. A measure of ventilatory variability at wake sleep transition predicts sleep apnea severity. *Chest* 2008; 134: 73–8.

83. **Series F**, Cormier Y, Desmeules M. Influence of passive changes of lung volume on upper airways. *J Appl Physiol* 1990; 68: 2159–64.

84. **Begle RL**, Badr S, Skatrud JB, Dempsey JA. Effect of lung inflation on pulmonary resistance during NREM sleep. *Am Rev Respir Dis* 1990; 141: 854–60.

85. **Series F**, Marc I. Influence of lung volume dependence of upper airway resistance during continuous negative airway pressure. *J Appl Physiol* 1994; 77: 840–4.

86. **Burger CD**, Stanson AW, Daniels BK, Sheedy PF II, Shepard JW Jr. Fast-CT evaluation of the effect of lung volume on upper airway size and function in normal men. *Am Rev Respir Dis* 1992; 146: 335–9.

87. **Stanchina ML**, Malhotra A, Fogel RB et al. The influence of lung volume on pharyngeal mechanics, collapsibility, and genioglossus activation during sleep. *Sleep* 2003; 26: 851–56.

88. **Hoffstein V**, Zamel N, Phillipson EA. Lung volume dependence of pharyngeal cross-sectional area in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1984; 130: 175–8.

89. **Rubinstein I**, Hoffstein V, Bradley TD. Lung volume-related changes in the pharyngeal area of obese females with and without obstructive sleep apnea. *Eur Respir J* 1989; 2: 344–51.

90. **Hudgel DW**, Devadutta P. Decrease in functional residual capacity during sleep in normal humans. *J Appl Physiol* 1984; 57: 1319–22.

91. **Kay A**, Trinder J, Kim Y. Progressive changes in airway resistance during sleep. *J Appl Physiol* 1996; 81: 282–92.

92. **Van deGaceff WB**. Thoracic influence on upper airway patency. *J Appl Physiol* 1988; 65: 2124–31.

93. **Van de Graaff WB**. Thoracic traction on the trachea: Mechanisms and magnitude. *J Appl Physiol* 1991; 70: 1328–36.

94. **Kairaitis K**, Byth K, Parikh R, Stavrinou R, Wheatley JR, Amis TC. Tracheal traction effects on upper airway patency in rabbits: The role of tissue pressure. *Sleep* 2007; 30: 179–86.

95. **Heinzer RC**, Stanchina ML, Malhotra A. Effect of increased lung volume on sleep disordered breathing in patients with sleep apnea. *Thorax* 2006; 61: 435–9.

96. **Heinzer RC**, Stanchina ML, Malhotra A. Lung volume and continuous positive airway pressure requirements in obstructive sleep apnea. *Am J Respir Crit Care Med* 2005; 172: 114–17.

97. **Heinzer R**, White DP, Malhotra A. Effect of positive airway pressure on sleep disordered breathing. *Sleep* 2008; 31: 429–32.

98. **Huang Y**, White DP, Malhotra A. Use of computational modeling to predict responses to upper airway surgery in obstructive sleep apnea. *Laryngoscope* 2007; 117(4): 648–53.

99. **Moraes W**, Poyares D, Sukys-Clandino L. Donepezil improves obstructive sleep apnea in Alzheimer disease: A double-blind, placebo-controlled study. *Chest* 2008; 133: 677–83.

100. **Carley DW**, Olopade C, Ruigt GS. Efficacy of mirtazapine in obstructive sleep apnea syndrome. *Sleep* 2007; 30: 35–41.

101. **Heinzer RC**, White DP, Jordan AS et al. Trazodome increases arousal threshold in obstructive sleep apnea. *Eur Respir J* 2008;31: 1308–12.