David S. Warner, M.D., and Mark A. Warner, M.D., Editors

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Obstructive Sleep Apnea of Obese Adults

Pathophysiology and Perioperative Airway Management

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Collapsible pharyngeal airway size is determined by interaction between structural properties of the pharyngeal airway and neural regulation of the pharyngeal dilating muscles. Obesity seems to have two distinct mechanical influences on the pharyngeal airway collapsibility. First, obesity increases soft tissue surrounding the pharyngeal airway within limited maxillomandible enclosure occupying and narrowing its space (pharyngeal anatomical imbalance). Second, obesity, particularly central obesity, increases visceral fat volume decreasing lung volume. Pharyngeal wall collapsibility is increased by the lung volume reduction, possibly through decreased longitudinal tracheal traction (lung volume hypothesis). Neural compensation for functioning structural abnormalities operating during wakefulness is lost during sleep, leading to pharyngeal obstruction. Instability of the negative feedback of the respiratory system may accelerate cycling of pharyngeal closure and opening. Improvement of the pharyngeal anatomical imbalance and maintenance of lung volume are the keys for safe perioperative airway managements of obese patients with obstructive sleep apnea.

OBSTRUCTIVE sleep apnea (OSA) is a common disordered breathing during sleep in humans. Polysomonographic recordings of sleep stages, respiration, and oxygenation reveal characteristics of OSA (fig. 1). Complete cessation of airflow for more than 10 s (apnea) or airflow reduction more than 50% (hypopnea) despite continuing breathing efforts results in hypoxemia and hypercapnia. This obstructive apnea or hypopnea is caused by complete or partial closure of the pharyngeal airway.[1] The apnea or hypopnea is usually terminated in association with cortical arousal, opening the pharyngeal airway. Breathing is reestablished with loud snoring, normalizing oxygenation, and often overshooting ventilation. OSA patients repeat the obstructive apnea or hypopnea, resulting in blood gas oscillation and sleep fragmentation. Clinical diagnosis of OSA is made when frequency of apnea and/or hypopnea per hour of sleep (apnea–hypopnea index [AHI]) is greater than five in adults. Severity of OSA is determined by the AHI: mild OSA = AHI 6–20 h^{-1}, moderate OSA = AHI 21–40 h^{-1}, and severe OSA = AHI > 40 h^{-1}.

Recent growing evidence indicates that OSA is an independent risk factor for development of hypertention,[2] cardiovascular morbidity and mortality,[3,4] and sudden death.[5] Daytime sleepiness, a common clinical symptom in OSA patients, can result in increased risk of motor vehicle accident.[6] Although presence of daytime sleepiness could have a significant impact on outcome of anesthesia and surgery, our major interest, here, is perioperative pharyngeal obstruction in OSA patients. Accordingly, anesthesiologists should consider OSA as a risk factor for perioperative pharyngeal obstruction regardless of daytime sleepiness symptom. Prevalence of OSA without daytime sleepiness in general adult population in the United States was reported to be 24% of middle-aged males and 9% of middle-aged females more than a decade ago.[7] Obesity is a common feature of OSA patients. The National Health and Nutrition Examination Survey for 2003–2004, a nationally representative sample of the US population, indicates that the prevalences of overweight (body mass index [BMI] > 25 kg/m^2), obesity (BMI > 30 kg/m^2), and morbid obesity (BMI > 40 kg/m^2) are 71, 31, and 3%, respectively, in adult males and 62, 33, and 7% in adult females.[8] The prevalence of obesity has been significantly increasing for several decades in all developed countries, while the picture is less apparent outside the United States.[9,10] More importantly, the prevalence of clinically severe obesity is increasing much faster than that of moderate obesity, and the number of morbidly obese patients quadrupled between 1986 and 2000, whereas the prevalence of obesity approximately doubled during the period[11] (fig. 2).

The increasing prevalence of obesity has lead to an increase in the prevalence of OSA in the general population.[12,13] Individual weight gain or loss significantly influences the severity of OSA.[14] Although there seems to be close causal linkages between obesity and OSA, neither conclusive evidence nor an explanation for the causality has been provided to date. Obese patients with OSA are at a greater risk for both difficult mask ventila-

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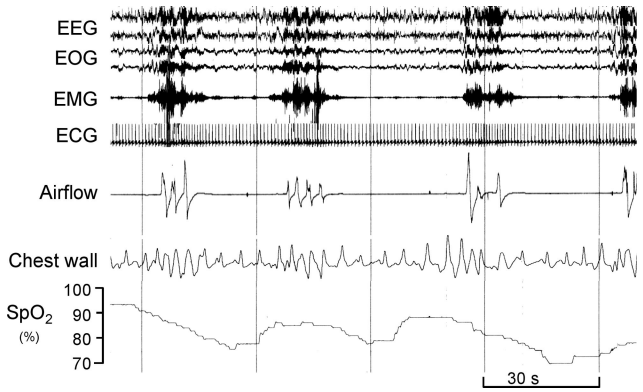

Fig. 1. Polysomnograph record from an obese obstructive sleep apnea patient (48-yr-old man, body mass index = 41.5 kg/m^2, apnea–hypopnea index = 123 h^{-1}). The patient is in non–rapid eye movement sleep stage. Typical repetitive pattern of obstructive apnea, desaturation, and cortical arousal with reestablishment of airflow is seen. Airflow = nasal pressure recording of airflow; chest wall = movement of chest wall; ECG = electrocardiogram; EEG = electroencephalogram; EMG = submental electromyogram; EOG = electro-occulogram; Spo_2 = percutaneous arterial oxygen saturation.

tion during anesthesia induction and postoperative upper airway obstruction.[15,16] This review article discusses pathophysiology and perioperative airway management of obese adult patients with OSA based on currently available evidences.

Collapsibility of the Pharyngeal Airway in OSA Patients

The *pharynx* is a collapsible tube that has a variety of physiologic functions, such as speaking, eating, swallowing, and breathing. Coordination of more than 20 pairs of pharyngeal muscles surrounding the collapsible conduit modulates its size and stiffness under the supervision of neural control mechanisms. An obvious but important feature of pharyngeal obstruction is state dependency, in which the pharynx narrows or closes when the neural control mechanisms are depressed during sleep or general anesthesia. Collapsibility of the pharyngeal airway is not homogeneous and varies among subjects. Numerous studies measuring pharyngeal airway cross-sectional area with computed tomography and magnetic resonance imaging during wakefulness demonstrated a narrower pharyngeal airway in OSA patients.[17,18] Interaction between neural and anatomical mechanisms during wakefulness, however, complicates interpretation of the airway imaging data.

By eliminating the neural control mechanisms during general anesthesia and total paralysis, Isono *et al.*[19] revealed that OSA patients have structurally narrower and more collapsible pharyngeal airways than age- and BMI-matched non-OSA patients. The closing pressures of the passive pharynx in OSA patients were above atmospheric pressure (0.6 ± 1.5 cm H_2O for mild OSA, 2.2 ± 3.0 cm H_2O for moderate to severe OSA), whereas those in non-OSA subjects were below atmospheric pressure (−4.4 ± 4.2 cm H_2O). Within the pharyngeal airway, positive closing pressures were demonstrated in almost 100% of OSA patients at the retropalatal airway but in only 50% at the retroglossal airway. In a subsequent study, Watanabe *et al.*[20] revealed that obesity was a prominent feature in OSA patients with positive closing pressures exclusively at the retropalatal airway, whereas craniofacial abnormalities such as small maxilla and mandible were evident in OSA patients with positive closing pressures at both the retropalatal and retroglossal airways.

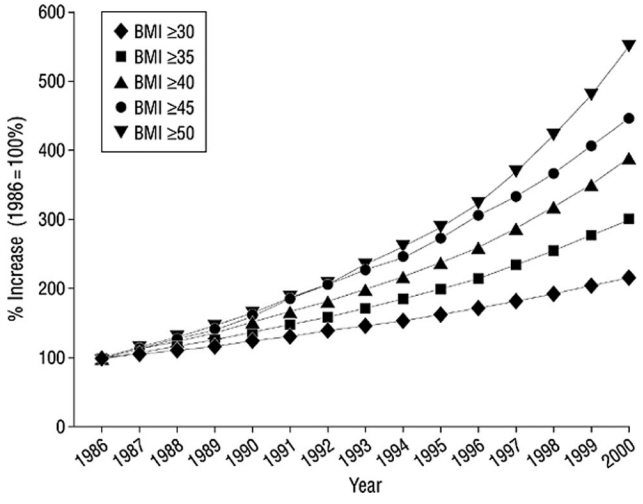

Fig. 2. Prevalence growth by severity of obesity. Calculations are based on the Behavioral Risk Factor Surveillance Survey. BMI = body mass index. Note that the prevalence of clinically severe obesity is increasing much faster than obesity. From Sturm[11]: Arch Intern Med 2003; 163(18):2146–8; reprinted with permission. Copyright © 2003 American Medical Association. All rights reserved.

Obesity and OSA

Fat distribution is not homogenous among obese persons. BMI represents overall increase in body weight for a person's height and has a significant but weak correlation with OSA severity. Neck circumference represents regional obesity near pharyngeal airway and has stronger correlation to OSA severity than to BMI.[21] The volume of adipose tissue deposited adjacent to the pharyngeal airway is related to the presence of OSA and OSA severity.[22–24] More importantly, obese OSA patients accumulated more visceral adipose tissue than BMI-matched non-OSA persons.[25] Recently, Schafer *et al.*[26] reported that OSA severity is more significantly correlated with fat accumulation of the intraabdominal region than of the neck region. These are in agreement with the finding that waist circumference is a better predictor for OSA than neck circumference or BMI.[27] Both neck fat deposits surrounding the pharyngeal airway and intraabdominal fat deposits away from the pharyngeal airway are likely

to be involved in the pathogenesis of OSA, although probably through different mechanisms, as discussed below.

Role of Leptin in Controlling Body Weight and Breathing

Leptin is an adipose-derived hormone that is responsible for signaling the appetite center receptors at the hypothalamus that the body has had enough to eat, and it regulates energy intake, body weight, and fat distribution.[28] Evidence of a higher serum leptin level in obese persons suggests the potential of leptin resistance in the development of obesity. Interestingly, OSA patients are reported to have higher leptin levels than BMI-matched non-OSA persons. Chin *et al.*[29] demonstrated the reduction of serum leptin levels in response to short-term nasal continuous positive airway pressure (CPAP) treatment, which suggests potential OSA contribution to development of leptin resistance in obese OSA patients. OSA, *per se*, seems to play a role in the resistance of these patients to weight loss.

Leptin-deficient obese mice (ob/ob mice) have higher resting arterial carbon dioxide level and depressed ventilatory response to hypercapnia than lean wild-type mice during wakefulness and sleep.[30] Interestingly, leptin infusion in leptin-deficient mice reduced the resting arterial carbon dioxide and improved hypercapnic ventilatory response independent of weight changes, whereas it did not influence ventilation in wild-type mice, suggesting an important role of leptin in respiratory control in obesity. Recent extensive researches reveal interesting interaction between lipid metabolism and control of breathing. Excessive visceral adipose tissue linking to both metabolic syndrome and OSA secretes a number of hormones and proinflammatory cytokines, and these possibly influence breathing in obese OSA patients.[31] A breakthrough for OSA pathogenesis is expected from this new area in the future.

A Local Structural Mechanism (Upper Airway Obesity): Excessive Upper Airway Soft Tissue

Whereas OSA patients have increased total fat volume surrounding the pharyngeal airway, fat accumulation on a more specific region, such as the parapharyngeal fat pad or tongue, was not consistently associated with the presence of OSA, which could be due to either necessity of diffuse rather than localized accumulation of adipose tissue or necessity of total soft tissue volume including both adipose and nonadipose tissue surrounding the pharyngeal airway for OSA development. Schwab *et al.*[32] beautifully demonstrated by use of three-dimensional volumetric analysis that the volume of the tongue and lateral walls independently increases risk of sleep apnea.

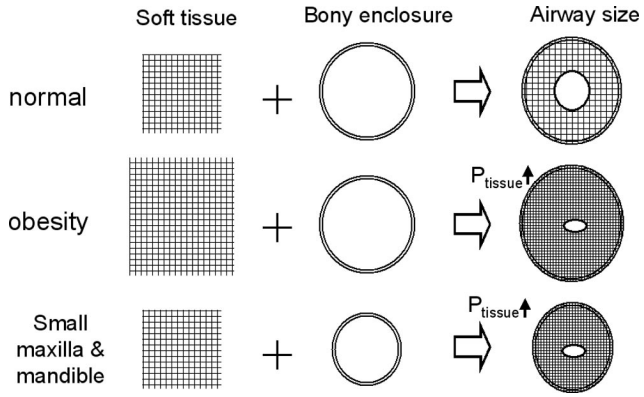

Fig. 3. Schematic explanations for interaction between soft tissue surrounding the pharyngeal airway and craniofacial bony enclosure. The airway size is determined by the balance between amount of soft tissue and bony enclosure size. P_{tissue} = tissue pressure. From Watanabe *et al.*[20]; reprinted with permission.

The question that arises here is whether absolute volume of the upper airway soft tissue is a determinant of OSA development.

A Local Structural Mechanism: Upper Airway Anatomical Balance

Structurally, the pharyngeal airway is a space inside rigid craniofacial bony enclosure formed by the cervical vertebrae, maxilla, and mandible. Within the bony enclosure, the airway shares its space with soft tissue such as the tongue and soft palate. According to this mechanical simplification of the anatomical structures surrounding the pharyngeal airway, the balance between the craniofacial bony enclosure size and the amount of soft tissue is considered to determine the airway space (fig. 3).[20] Either an increase in amount of the soft tissue within the bony enclosure or a decrease in the bony enclosure size would result in limitation of space available for the airway and, consequently, a narrowing of the airway.

Tsuiki *et al.*[33] recently tested this concept by comparing the upper airway anatomical balance between OSA and craniofacial dimension–matched non-OSA subjects. Using lateral cephalograms, they measured the tongue cross-sectional area as an index for the soft tissue volume surrounding the pharyngeal airway and the lower craniofacial cross-sectional area as an index for the craniofacial bony enclosure size. As clearly presented in figure 4,[33] the tongue was greater in non-OSA persons with greater lower craniofacial size, suggesting optimal tongue size for a given craniofacial dimension. OSA patients, however, demonstrated a significantly greater tongue for a given craniofacial dimension than non-OSA persons, indicating the importance of anatomical imbalance for development of OSA rather than absolute soft tissue volume of the upper airway alone.

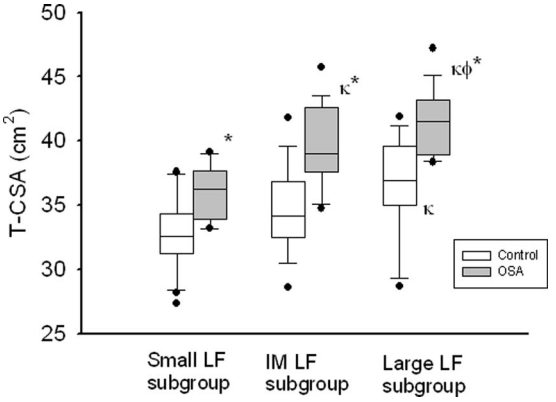

Fig. 4. Box plots showing differences of the tongue cross-sectional area (T-CSA) between non–obstructive sleep apnea subjects (control) and patients with obstructive sleep apnea (OSA) for each of three subgroups defined based on the lower face cage (LF) cross-sectional area. *Lower* and *upper boundaries* indicate 25th and 75th percentages. A *solid line within the box* marks the median, and *vertical lines* indicate the 10th and 90th percentages. *Solid circles* are outliers. Definitions of the subgroups: small LF subgroup, LF-CSA < 65 cm^2; intermediate (IM) LF subgroup, 65 cm^2 < LF-CSA < 71 cm^2; large LF subgroup, LF-CSA > 71 m^2. * $P < 0.05$ *versus* control. κ $P < 0.05$ *versus* small LF subgroup. Φ $P < 0.05$ *versus* IM LF subgroup. From Tsuiki *et al.*[33]; reprinted with permission.

A Structural Mechanism from a Distance: Lung Volume Hypothesis

Obesity is associated with significant reduction of lung volume such as functional residual capacity (FRC) and expiratory residual volume due to diminished chest wall compliance, and total lung capacity and vital capacity are only impaired by extreme obesity.[34] Whereas FRC reduction accounts for development of severe hypoxemia during obstructive events in obese OSA patients, lung volume decrease, *per se*, is indicated to contribute to pharyngeal airway obstruction. Hoffstein *et al.*[35] hypothesized significant lung volume dependence of pharyngeal airway patency as an important factor in the pathophysiology of OSA based on the finding that obese OSA patients demonstrated significantly greater reduction of the smaller pharyngeal cross-sectional area in response to slow exhalation from total lung capacity to residual volume than obese non-OSA persons during wakefulness (54 ± 6 *vs.* 30 ± 5%).

A Structural Mechanism from a Distance: Lung Volume and OSA

Series *et al.*[36] first reported an obese OSA patient who presented decreased frequency of obstructive events and improved sleep architecture in response to a 0.5-l increase of FRC by applying a constant negative extrathoracic pressure during sleep. Interestingly, the same investigators failed to support the lung volume hypothesis in nine mildly obese OSA patients (124% of ideal body weight) despite using the same protocol for changing FRC during sleep.[37] Heinzer *et al.*,[38] however, recently demonstrated that 0.77- and 1.3-l increases of FRC during sleep significantly decreased AHI from 62.3 events/h to 37.2 and 31.2 events/h, respectively, improving sleep quality in 12 more obese OSA patients than those studied by Series *et al.* (mean BMI = 34.9 kg/m^2). Although the discrepant results from two clinical investigations including only 22 OSA patients do not provide conclusive evidence for the lung volume hypothesis, the difference in the severity of obesity between the studies is worthy of note, while the discrepancy is explainable by the difference in study protocols and populations. It is possible that the influence of lung volume is greater in more obese OSA patients, because Heinzer *et al.*[38] found a trend toward a correlation between the extent of AHI reduction during lung inflation and the BMI (correlation coefficient = 0.53, $P = 0.077$, n = 12) in their study population.

Structural Mechanisms: Potential Mechanisms of Lung Volume Dependency of Pharyngeal Airway Collapsibility

Although the lung locates at a distance from the pharyngeal airway, the mechanical influence of lung inflation on the pharyngeal airway resistance was demonstrated in both anesthetized animals and nonobese sleeping persons without sleep-disordered breathing.[39–41] Reduction of the genioglossal muscle activity and upper airway resistance during lung inflation indicates primarily structural mechanisms of lung volume dependency of the pharyngeal airway patency. The trachea moves caudally by approximately 0.5 and 1.0 cm during small (0.5 l) and large (1.0 l) tidal breathing, respectively, in supine adults.[42] The caudal tracheal traction during lung inflation is considered to increase longitudinal tension of the pharyngeal airway wall, thereby unfolding the pharyngeal mucosa and stiffening the airway.[43,44] Interestingly, the magnitude of tracheal traction seems to be the sum of forces associated with a mediastinal shift during lung inflation and intrathoracic pressure swing with and without lung inflation, which is suggestive of a tracheal tug during pharyngeal obstruction, leading to the reestablishment of pharyngeal airway patency.[43]

In an elegant study by Heinzer *et al.*[45] regarding significant lung volume dependence of pharyngeal patency in obese sleeping OSA patients (mean BMI = 31.9 kg/m^2), it was revealed that the CPAP needed to prevent flow limitation increased from 11.9 to 17.1 cm H_2O in response to lung volume reduction of 0.6 l. Tagaito *et al.*[46] found a significant reduction of retropalatal airway closing pressure of 1.2 cm H_2O by an increase in lung volume of 0.7 l in anesthetized, paralyzed OSA patients (median BMI = 26 kg/m^2). Considering the 5- to 7-cm H_2O dif-

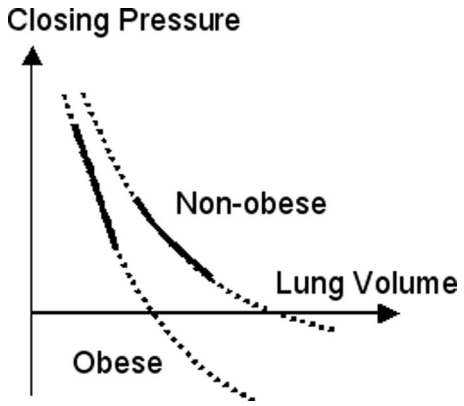

Fig. 5. Schematic illustration of hypothetical mechanism of different lung volume dependence of pharyngeal closing pressure between obese and nonobese obstructive sleep apnea (OSA) patients. *Thick lines* represent working ranges of the relation. The alinear relation of lung volume and pharyngeal closing pressures may change its position and shape with changing body mass index. The relation curve of obese OSA patients may locate left to that of nonobese OSA patients, being steeper than that of nonobese OSA patients. Because closing pressure before lung inflation is expected to be greater in obese OSA patients, the lung volume dependency of pharyngeal closing pressure may be more evident in obese OSA patients than in nonobese OSA patients. From Tagaito *et al.*[46]; modified with permission.

ferences of the pharyngeal closing pressure between normal and OSA patients and the study of Heinzer *et al.* of obese OSA patients, the observed closing pressure changes seem to be small in the study population. Notably, improvement of the retropalatal closing pressure during lung inflation was directly associated with BMI.[46] In response to 0.5-l changes of lung volume, retropalatal closing pressure was roughly estimated to change by 2 cm H_2O in OSA patients with BMI of 32 kg/m^2, whereas it was estimated to change by 0.5 cm H_2O in those with BMI of 25 kg/m^2, suggesting that the lung volume dependence of pharyngeal closing pressure may differ between obese and nonobese OSA patients, as illustrated in figure 5.[46] Because of different awake lung volumes between obese and nonobese apneics—*i.e.*, different tracheal traction during wakefulness between them—lung volume reduction during sleep or anesthesia could result in different magnitude of the mechanical influence on pharyngeal closing pressure and therefore greater lung volume dependence of pharyngeal patency in obese OSA patients.

Neural Responses to Anatomical Abnormalities of the Pharynx

Obstructive sleep apnea is a state-dependent disease possibly caused by complicated neuroanatomical interaction. Mezzanotte *et al.*[47] reported that OSA patients have significantly greater basal genioglossal muscle activity than age- and BMI-matched non-OSA subjects during wakefulness. They further demonstrated that the augmented genioglossal activity was reduced by application of CPAP in OSA patients, whereas CPAP application had no effect on the genioglossal activity in non-OSA subjects.[47] This is considered for compensating the structurally narrower and more collapsible pharyngeal airway. Sleep, however, significantly depresses this neural compensatory mechanism, and OSA develops only during sleep. The genioglossal muscle activity physiologically decreases at sleep onset in both non-OSA subjects and OSA patients.[48,49] Although the pharyngeal airway of non-OSA persons may narrow, airway space is maintained in response to depression of the neural control mechanisms. However, this neural depression is crucial for OSA patients who heavily rely on their airway patency to the neural mechanisms. Depression of the neural control mechanisms at sleep onset is subject to sequential neural activation responses such as airway reflexes and chemical and arousal responses. Therefore, it is possible to hypothesize the development of OSA to deficiency of the neural compensatory mechanisms for the structural abnormalities. Regretfully, no researcher has succeeded in testing or proving the hypothesis, primarily because of the complexity of the neuroanatomical interaction; however, recent extensive research in this field has significantly increased our understanding of the complexity, as is discussed below.

Sequential Neuroanatomical Interaction

Figure 6 illustrates sequential neuroanatomical interaction during OSA. Reflexive increase of pharyngeal dilator muscles is an instantaneous response to pharyngeal narrowing or obstruction. Mechanoreceptors in the upper airway mucosa sense the increased negative pressure, which triggers the ascension of the neural signal to hypoglossal motor neurons through the superior laryngeal or glossopharyngeal nerves and nucleus of the solitary tract. An early report indicated abolishment of the negative pressure reflex during non–rapid eye movement (NREM) sleep in non-OSA subjects.[50] However,

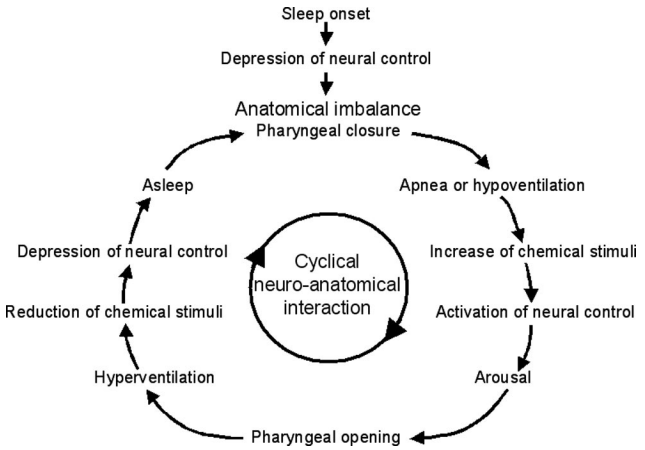

Fig. 6. Cyclical neuroanatomical interaction during obstructive sleep apnea.

recent human and animal studies support depression but preservation of the negative pressure reflex during NREM sleep and light anesthesia, whereas the reflex was significantly depressed during rapid eye movement sleep and deep anesthesia.[51,52] In normal adults, Malhotra *et al.* demonstrated that the magnitude of the genioglossal muscle activation is directly associated with inspiratory negative airway pressure during both wakefulness and NREM sleep, whereas the slope of the association was greater during wakefulness than NREM sleep.[53] Interestingly, elimination of inspiratory pump muscle contraction using iron lung attenuated the negative pressure reflex, suggesting modulation of the reflex by the central pattern generator.[54]

Persistence of pharyngeal obstruction despite the negative pressure reflex leads to hypercapnia and hypoxemia, increasing chemical stimuli to both inspiratory pump muscles and pharyngeal dilator muscles, although with differing responses. Whereas chemical stimuli progressively increase diaphragm activity, activation of the genioglossal muscle occurred only below threshold hypoxemia or above threshold hypercapnia in animal experiments.[55,56] Greater increase of inspiratory collapsing forces compared with the pharyngeal dilating forces favors pharyngeal narrowing[1]; therefore, chemical control of the pharyngeal muscles had been considered to only slightly contribute to reversal of pharyngeal airway patency. However, it was recently demonstrated that application of the combination of inspiratory resistive loading and hypercapnia increased basal genioglossal activity and elicited progressively augmenting genioglossal activation with increasing chemical stimuli in normal individuals during NREM sleep, suggesting the importance of chemical control of the pharyngeal muscles under mechanical loading such as pharyngeal obstruction.[57]

Development of hypoxemia, hypercapnia, and increased negative thoracic pressure during persistent pharyngeal obstruction plays a role in inducing arousal from sleep, a final stage of the neural mechanisms, restoring patent pharyngeal airway. The arousal response has long been believed to be the most important survival response because its impairment indicates persistence of the pharyngeal obstruction and development of severe hypoxemia, and eventual brain damage and death.[58] However, Younes *et al.* recently proposed a different perspective in which arousal is probably an incidental event that interferes with the underling neural compensatory mechanisms for restoration of pharyngeal patency without arousal.[59] In fact, OSA patients did not require cortical arousal for increasing inspiratory flow in response to experimentally induced severe inspiratory flow limitation in 39% of the trials during NREM sleep, and frequency of the flow response without arousal increased with delta power of electroencephalogram (deeper sleep).[59] Accordingly, it is speculated that delay in arousal response by hypnotics may be beneficial for some, although certainly not all, OSA patients, allowing completion of the neural compensatory mechanisms either by chemical stimuli or by other neural excitatory influences on the pharyngeal muscle tone.[60] Furthermore, arousal from sleep in response to pharyngeal obstruction is associated with a burst of the pharyngeal muscle activation and hyperventilation. Although these brisk respiratory responses aid in instantaneous reestablishment of patent pharyngeal airway and reoxygenation, these often lead to unnecessary reduction of the central respiratory drive to both pump muscle and pharyngeal dilator muscles during sleep inclination, predisposing destabilizing breathing and subsequent pharyngeal obstruction.

Cyclical Neuroanatomical Interaction: Higher Loop Gain of the Respiratory System

Multiple negative feedback loops of the respiratory system aim to control and stabilize breathing by adjusting arterial blood gas tensions. The respiratory chemical control loops of OSA patients, however, do not maintain a constant blood gas level during sleep, leading to cyclical chemical stimuli in association with periodic OSA events. In addition, waxing and waning–type breathing instability continues even after tracheostomy in OSA patients, suggesting an inherent unstable nature of the respiratory feedback system in these patients.[61] Stability of the respiratory system is determined by magnitude of the loop gain (fig. 7).[62] The unstable system with a high loop gain overly responds to occurrence of abnormal breathing and starts cycling OSA events increasing AHI. In contrast, the system with a low loop gain is stable but possibly fails to correct the abnormal breathing, prolong-

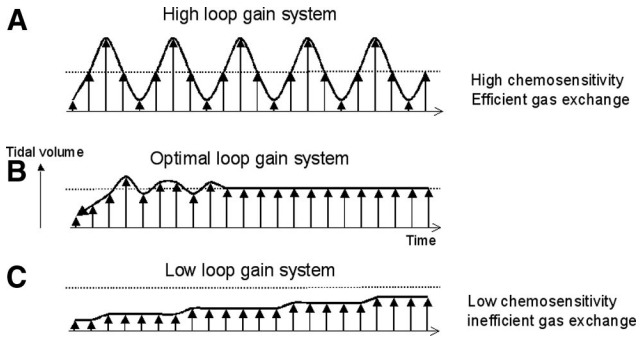

Fig. 7. Influences of different magnitude of respiratory loop gain on breathing stability. Different ventilatory responses to reduced tidal volume are illustrated. *Height of an arrow* represents tidal volume. *Dotted line* represents optimal ventilation level. An individual with a high respiratory loop gain (*A*) will instantaneously respond to the abnormal breathing but overshoot the ventilatory response, resulting in rapid decline in the ventilation. Waxing and waning pattern of unstable breathing continues in this person. In contrast, an individual with low respiratory loop gain (*C*) will slowly respond to the abnormal breathing and fail to establish a desired ventilation level. Breathing stability can be accomplished in an individual with an optimal loop gain (*B*).

ing apnea. In fact, Younes *et al.*[63] demonstrated that severe OSA patients have higher loop gain during sleep than do mild OSA patients, suggesting importance of ventilatory instability for increasing AHI. Interestingly, Wellman *et al.*[64] found a significant association between the loop gain and AHI in an OSA subgroup with closing pressure near atmospheric pressure, whereas the closing pressure was significantly associated with AHI in the whole group of OSA patients.

Among the various components of the respiratory loop gain, controller gain predominantly determined by chemoresponsiveness, such as hypoxic and hypercapnic ventilatory responses, influences breathing instability contributing to pathogenesis of OSA. Chemoresponsiveness, however, varies among OSA patients, and majority of them have normal or blunted chemoresponsiveness during wakefulness.[65,66] Notably, Verbraecken *et al.*[67] found that hypercapnic ventilatory response was increased in eucapnic OSA patients, whereas the response was blunted in chronic hypercapnic OSA patients. Makinodan *et al.*[68] found significant direct association between hypercapnic ventilatory response and serum leptin level in non-OSA persons and eucapnic OSA patients, although age- and BMI-matched chronic hypercapnic OSA patients had higher serum leptin level and lower hypercapnic ventilatory response. Furthermore, Wang *et al.*[69] recently reported a significant association between hypercapnic ventilatory response and AHI in asymptomatic nonobese OSA patients. These results suggest a contribution of increased hypercapnic ventilatory response to nocturnal breathing instability and OSA pathogenesis in OSA patients with higher serum leptin level and hypercapnic ventilatory response. Oxygen therapy for OSA, *i.e.*, desensitization of peripheral chemosensitivity, is reported to decrease loop gain and AHI by a half in OSA patients with higher loop gain before oxygen administration, suggesting some role of hypoxic ventilatory response in OSA pathogenesis.[70] Changes of chemosensitivity upon arousal from sleep to wakefulness may further facilitate the breathing instability.

Plant gain is another important component of the respiratory loop gain and is determined by efficacy of gas exchange for a given ventilatory change. For example, changes of arterial carbon dioxide tension per unit of ventilation are greater at lower lung volume because of less buffering capacity of total lung carbon dioxide stores.[71] Low FRC, low dead space, low metabolic rate, low cardiac output, and high arterial carbon dioxide increase efficacy of the gas exchange, and all combined theoretically increase plant gain, producing an unstable respiratory system.[62,63] It is of note that these are common particularly in obese patients with severe OSA. Although no study has assessed contribution of these conditions to nocturnal breathing instability in OSA patients, increased plant gain of the respiratory feedback system may be also involved in the OSA pathogenesis.

Higher respiratory loop gain may play a role in initiating and cycling the neuroanatomical interaction (respiratory negative feedback loop) in OSA patients (fig. 6). In addition to increase of frequency of the cycling (AHI), it should be noted that the higher loop gain of the respiratory negative feedback system possibly exaggerates each step of the neuroanatomical interaction, amplifying ventilatory oscillation (fig. 6). Central respiratory drive should also project to hypoglossal motor neurons, and therefore, one would expect similar augmenting and decrementing changes of pharyngeal dilator muscles to inspiratory pump muscles. Accordingly, amplification of the neuroanatomical interaction possibly minimizes activity of the pharyngeal dilator muscles at the nadir of the cycling, increasing pharyngeal collapsibility. Certainly, contribution of breathing instability to OSA is an interesting and promising hypothesis; however, further extensive research is required in this area.

Perioperative Airway Management

Although we still do not fully understand the mechanisms of pharyngeal obstruction during sleep, anatomical imbalance surrounding the pharyngeal airway, lung volume reduction, and breathing instability seem to significantly contribute to development and deterioration of OSA in obese persons, as summarized in figure 8. Development of a safe and appropriate anesthetic management strategy of obese OSA patients should be based on the understanding of the OSA pathogenesis. No standard airway management strategy, however, has been established and validated to date despite the recent release of practical guidelines for perioperative OSA managements.[72] Below are my personal opinions based on the OSA pathophysiology and my limited clinical experience.

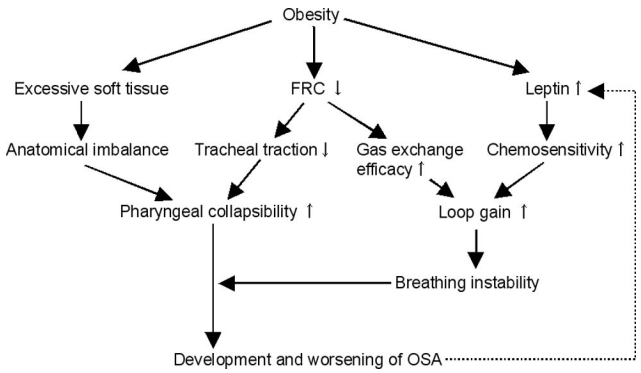

Fig. 8. Hypothetical neuroanatomical linkage between obesity and obstructive sleep apnea (OSA). Anatomical imbalance surrounding the pharyngeal airway, lung volume reduction, and breathing instability may significantly contribute to development and deterioration of OSA in obese persons. FRC = functional residual capacity.

Preoperative OSA Assessment and Airway Management

The first and most important recognition necessary for anesthesiologists is high prevalence of undiagnosed OSA in the surgical patient population (more than 24%).[73] All obese persons undergoing surgery should be suspected of having OSA preoperatively. In addition to an OSA questionnaire, including typical clinical symptoms such as habitual Snoring, Tiredness or daytime sleepiness, Observed apnea, and high blood Pressure (STOP),[74] a variety of clinical assessments of anatomical balance surrounding the pharyngeal airway are helpful. The modified Mallampati score assesses relative tongue size within the limited oral cavity, and classes 3 and 4 suggest the anatomical imbalance and presence of OSA.[75] Excessive soft tissue for the limited maxillomandibular enclosure expands to the submandible space, and therefore, excessive submandible soft tissue on the profile of OSA patients would indicate anatomical imbalance. Tsui *et al.*[76] reported that cricomental space, defined as the perpendicular distance from a line between the cricoid cartilage and the inner mentum to the skin of the neck, of more than 1.5 cm excluded OSA patients with a negative predictive value of 100%. Notably, the profile of OSA patients resembles that of patients with difficult tracheal intubation characterized by increased submandible angle.[77] The caudal soft tissue displacement shifts the mobile hyoid bone caudally, increasing distance between the mandible and hyoid bone, which is easily identified by lateral head and neck radiograph such as the cephalogram for assessment of craniofacial dimensions, and presence of OSA should be strongly suspected when the distance is greater than 20 mm.[33,78] It should be noted that tracheal intubation is difficult in patients with both shorter and longer thyromental distance[79] and that a low hyoid bone was associated with difficult tracheal intubation, suggesting common anatomical abnormalities between OSA and difficult tracheal intubation but probably through different structural mechanisms.[80,81]

After diagnosis of OSA and OSA severity with polysomnography, portable sleep monitoring, or nocturnal pulse oximetry, preoperative prescription of nasal CPAP may be beneficial, particularly in severe OSA patients, as suggested by the American Society of Anesthesiologists guideline. Although few data support routine preoperative use of nasal CPAP, preoperative acclimation of the device is a key for successful postoperative use. In addition, 1 week of nasal CPAP treatment can improve pharyngeal collapsibility and increase pharyngeal cross-sectional area.[82] Nasal CPAP treatment possibly improves leptin resistance and facilitates weight reduction before surgery. Anesthesiologists should also recognize that untreated OSA patients, particularly asymptomatic OSA patients, do not easily accept CPAP treatment. Appropriate timing of the surgery should be discussed among the anesthesiologist, surgeon, and patient, considering the expected advantage of the preoperative OSA treatments and disadvantage of delaying the surgery. In long-term successful CPAP users, there is little reason for the surgery to be delayed or cancelled unless there is necessity for treatment of comorbidities. Although choosing regional anesthesia seems preferable for avoiding perioperative respiratory complications in obese OSA patients for superficial procedures or surgery for extremities as recommended by the American Society of Anesthesiologists guideline, potential failure or difficulty of regional anesthesia, such as spinal or epidural anesthesia, should be always included in planning of perioperative airway management.

Airway Management during Anesthesia Induction

Obstructive sleep apnea is a risk factor for both difficult mask ventilation and tracheal intubation. Langeron *et al.*[15] reported that age older than 55 yr, BMI greater than 26 kg/m^2, snoring, beard, and lack of teeth are independent risk factors for difficult mask ventilation. The first three factors may relate to OSA. Considering high closing pressure of the pharyngeal airway in OSA patients, there would be no doubt in the strong linkage between OSA and difficult mask ventilation.

High prevalence of OSA was reported among patients with difficult tracheal intubation.[83,84] Tracheal intubation with direct laryngoscopy was demonstrated to be more difficult in OSA patients than in non-OSA persons (21.9 and 16.7% *vs.* 2.6 and 3.3%), but BMI was not matched between the groups in these studies.[85,86] Within the OSA group, severe OSA patients had a higher prevalence of difficult tracheal intubation than mild and moderate OSA patients.[86] Both obesity and craniofacial abnormalities possibly contribute to difficult tracheal intubation in OSA patients. Difficult tracheal intubation in obese persons is controversial.[87–89] Voyagis *et al.*[87] found that direct laryngoscopy was more difficult in obese persons than in nonobese persons (20.2 *vs.* 7.6%). Difficult tracheal intubation in obese persons was confirmed by Juvin *et al.*,[88] but prevalence of OSA patients was higher in the obese group than in the lean group. In contrast, Ezri *et al.*[89] found no difference of laryngeal view during direct laryngoscopy between obese and nonobese groups, whereas a history of OSA was associated with difficult laryngoscopy. Unfortunately, no study has compared difficulty in direct laryngoscopy between obese and nonobese subjects while controlling presence and severity of OSA and craniofacial characteristics. Interestingly, a high Mallampati score and large neck circumference were associated with difficult tracheal intubation within obese persons, suggesting potential involvement of anatomical imbalance in difficult tracheal intubation.[90]

Kheterpal *et al.*[16] identified five risk factors—limited or severely limited mandibular protrusion, thick/obese neck anatomy, sleep apnea, snoring, and BMI > 30 kg/m^2—as independent predictors of difficult or impossible and difficult tracheal intubation during anesthesia induction. This suggests that obese OSA patients with limited mandible protrusion are in the highest risk group for potentially fatal airway complications. It should be noted that except for limited mandibular protrusion, the risk factors for airway disaster overlap those identified for difficult mask ventilation and tracheal intubation. Advancement of the mandible is a key structural arrangement for airway maintenance maneuver during mask ventilation as well as tracheal intubation with direct laryngoscopy.[91,92] Mobility of the mandible could be a key structural property for safe anesthesia induction and is worthy of future investigations.

During anesthesia induction, potential difficult or impossible mask ventilation should always be considered in obese patients with OSA and without preoperative OSA assessment.[15,16] The obese OSA patients are to be placed in the sniffing or ramped position with elevation of torso and head combined with the semiupright position.[93] These head and body positions decrease pharyngeal closing pressure by improving the pharyngeal anatomical balance and increasing lung volume in addition to improvement of laryngeal view during direct laryngoscopy. Inhalation of pure oxygen for more than 3 min with a tightly fitted anesthesia mask can increase apnea tolerance time despite potential development of pulmonary atelectasis,[94] and application of CPAP or bilevel positive-pressure ventilation (intermittent positive-pressure ventilation with positive end-expiratory pressure) improves oxygenation and prevents airway obstruction during anesthesia induction.[95–97] Triple airway maneuvers, including mandible advancement, neck extension, and mouth opening, should be performed by use of two hands, as Safar *et al.* originally proposed.[98–100] Responses to mechanical interventions in obese persons differ from those in nonobese persons. Isono *et al.*[101] demonstrated that mandible advancement significantly decreased the retropalatal closing pressures in nonobese persons but not in obese persons. In contrast, the retroglossal airway never failed to respond to mandible advancement in both nonobese and obese persons, indicating an advantage of intermittent positive-pressure ventilation through an oral airway during anesthesia induction by opening the mouth, particularly in obese OSA patients.[100,101] Certainly, mouth opening alone decreases the mandible enclosure size and increases closing pressures,[102] and the advantage of nasal ventilation was recently reported in nonobese subjects without airway maneuvers.[103] However, mouth opening allows establishment of the oral airway route and adequate mask ventilation by avoiding breathing through the most collapsible and difficult retropalatal airway, which is part of the nasal airway route.[93,100]

Although timing of administration of muscle relaxants is controversial,[104] use of muscle relaxants during anesthesia induction may be beneficial for pharyngeal airway maintenance, although various factors need to be considered. Inspiratory negative airway pressure acts as a collapsing force. Muscle relaxants can eliminate unfavorable strong negative airway pressure induced by increased chemical drive during difficult mask ventilation. Intravenous anesthetics rapidly and significantly decrease inspiratory negative airway pressure by depressing the chemical drive and may be an appropriate induction drug. Among them, ketamine has a less depressant effect on pharyngeal dilating muscle activity while it increases pharyngeal secretion and possibly offsets the beneficial effect.[105] Slow induction with spontaneous breathing is not recommended in these patients. Failure of airway maintenance with strong negative intrathoracic pressure can induce pulmonary edema.[106] Maintenance of positive airway pressure is a key for successful airway maintenance regardless of using or not using muscle relaxants. Clearly, use of succinylcholine also does not ensure recovery of either muscle function or pharyngeal patency before development of severe hypoxemia in these patients with decreased FRC.[107] When an airway disaster occurs during anesthesia induction with nondepolarizing muscle relaxant, administration of high-dose sugammadex can rapidly reverse its action, particularly rocuronium-induced paralysis, but sugammadex is currently only available in European countries. But again, this may not ensure reversal of patent pharyngeal airway without recovery of consciousness.[108] Reversal of both muscle paralysis and consciousness level is necessary for restoring airway patency in the situation. Insertion of supralaryngeal airways without delay is strongly recommended for airway disasters.

Gastroesophageal reflux is common in both obese persons and OSA patients with lower esophageal sphincter hypotonia.[109] Although pulmonary aspiration during anesthesia induction is relatively rare, it is an important cause of anesthesia-related mortality.[110] Rapid sequence induction with succinylcholine is often chosen in obese persons. Although this induction technique may be appropriate for obese persons with symptomatic gastroesophageal reflux and full stomach, its benefits should be weighed against risks of rapid development of severe desaturation and difficulty in both tracheal intubation and mask ventilation in obese OSA patients with no other risk of pulmonary aspiration.[111]

Awake intubation should be considered when any element of the triple airway maneuver, including mandible advancement, neck extension, and mouth opening, is disturbed in obese patients with severe OSA. In fact, limited mandible advancement is an independent risk factor for impossible mask ventilation.[16] Limited neck

mobilization due to cervical spine pathology and halo traction can significantly impair the performance of the airway maintenance maneuvers during mask ventilation as well as tracheal intubation. Preservation of the neural compensatory mechanisms is a key for airway maintenance during awake fiberoptic intubation. Although adequate regional airway anesthesia is mandatory, it should be recognized that the upper airway anesthesia alone could block the mechanical receptors on the mucosa for the negative pressure reflex, narrowing the cross-sectional area of the pharynx.[112] Conscious sedation is preferable if needed and is to be achieved by titrating the sedative with caution. Deep sedation should be avoided, and the Ramsey sedation score should be maintained above 4. A sitting position or semiupright position increases airway space behind the epiglottis and improves endoscopic view during the tracheal intubation.

Emergence from Anesthesia and Tracheal Extubation

Regardless of intraoperative body position, a semiupright position or lateral position is recommended for every obese OSA patient at the end of surgery for better oxygenation and pharyngeal airway maintenance. Residual inhalation anesthetics and paralysis are capable of depressing peripheral chemosensitivity, which leads to decreased hypoxic ventilatory response and increased arousal threshold.[113–115] Selective impairment of pharyngeal muscle contraction was demonstrated during partial paralysis and augmented by subanesthetic inhalation anesthetic.[116] Complete reversal of neuromuscular block should be confirmed by neuromuscular monitor.[117,118] Reversal with sugammadex seems to be preferable for restoration of pharyngeal dilator muscles to neostigmine, but sugammadex is currently unavailable in United States.[119] Full awakening after establishment of spontaneous breathing is strongly recommended upon trachea extubation.[120] External stimuli, such as suctioning, nasal airway insertion, and even patient care surrounding the head and neck, can cause vigorous coughing and hemodynamic instability and, therefore, should be performed before or after emergence from anesthesia. Use of β blockers and antihypertensive drugs may be beneficial for preventing hemodynamic instability during emergence from anesthesia and extubation in OSA patients with cardiovascular diseases.[121] Emergence agitation in these patients is extremely dangerous, possibly resulting in accidental extubation and injuries in addition to losing signals from cardiorespiratory monitors.

Incidence of claims for death or brain damage during anesthesia induction significantly decreased after release of the practice guideline for management of the difficult airway from the American Society of Anesthesiologists.[122,123] The incidence at tracheal extubation, however, did not decrease during the decade,[123] and regretfully, the extubation strategy recommended by the task force has not been revised in the 2003 guideline.[124] Severe pharyngeal edema developed during upper airway surgery in severe OSA patients can result in choking immediately after endotracheal extubation.[125,126] A high incidence of severe respiratory compromises (6.1%: 19 in 311) including one death and six reintubations after anterior cervical spine surgery was also attributable to pharyngeal edema.[127] Even modest pharyngeal swelling caused by laryngoscopy and excessive fluid infusion during surgery may possibly have significant influences on pharyngeal airway maintenance immediately after surgery.[128] Development of a technique for prediction of upper airway patency immediately after extubation would significantly increase safety of extubation procedure in patients with difficult airways, such as obese OSA patients. Anesthesiologists should recognize occurrence of pharyngeal obstruction even without loud snoring and be able to diagnose airway patency immediately after extubation by assessing synchrony of thoracoabdominal movements.

Postoperative Analgesia

Considering the high prevalence of cardiovascular comorbidities in OSA patients, adequate pain relief is of great importance. Postoperative analgesia, however, cannot be achieved without risks of respiratory depression and development of severe hypoxemia, particularly in obese OSA patients. Opioids, the most common analgesics after surgery, decrease both hypoxic and hypercapnic ventilatory responses when administered either intravenously or intrathecally,[129,130] suggesting possible impairment of the sequential neural control mechanisms during OSA and failure or delay of pharyngeal opening (fig. 6). In fact, Catley *et al.*[131] reported a high prevalence of OSA with severe hypoxemia within 16 h after surgery in patients receiving morphine for analgesia (456 episodes in 10 of 16 patients), whereas use of regional analgesia resulted in less frequency of such events (0 episode in 16 patients). Routes (intravenous, intramuscular, intrathecal, or epidural) and techniques (patient controlled or nurse controlled) of the opioid administration for postoperative analgesia do not seem to influence the risk of respiratory complications.[132,133] The American Society of Anesthesiologists guideline recommends exclusion of opioids from neuraxial postoperative analgesia in OSA patients if possible. However, adequate analgesia for a major surgery is often difficult to achieve without use of opioids, and there is no consensus regarding individual determination of an optimal opioid dose. Importantly, Brown *et al.*[134] recently demonstrated increased opioid sensitivity in severe OSA children. Future investigation on opioid sensitivity in adult OSA patients

Table 1. Personal Recommendation of Postoperative Patient Care and Monitoring for an Obese Patient with Severe Obstructive Sleep Apnea

	Ward with No Monitoring	Ward with Pulse Oximetry	PACU or ICU with Pulse Oximetry
CPAP (+)			
Opioid (−)	Acceptable	Desirable	Unnecessary
Opioid (+)	Not recommended	Acceptable	Desirable
CPAP (−)			
Opioid (−), nasal airway (+)	Acceptable	Desirable	Desirable
Opioid (−), nasal airway (−)	Not recommended	Not recommended	Desirable
Opioid (+)	Not recommended	Not recommended	Desirable

For example, postanesthesia care unit (PACU) or intensive care unit (ICU) management with cardiorespiratory monitoring is desirable and management in the ward is not recommended if the patient is unable to use continuous positive airway pressure (CPAP) and use of opioid is planned for postoperative analgesia.

is necessary for the development of a safe postoperative analgesia strategy for OSA patients.

Because of potential postoperative respiratory depression or OSA deterioration by residual general anesthetics, paralysis, and opioids, respiration and oxygen saturation should be continuously monitored in all OSA patients receiving opioid analgesia at least for 24 h after surgery.[135,136] The level of postoperative patient care and monitoring would significantly depend on compliance of nasal CPAP and use of opioids for postoperative analgesia in addition to severity of OSA and obesity and invasiveness of surgery[72,137] (table 1).

Postoperative Airway Management

All obese OSA patients should be optimally positioned postoperatively. A sitting position or lateral position is advantageous over a supine position.[138] Use of a pillow to produce the sniffing position is beneficial for airway maintenance.[139] These positional interventions are not sufficient to prevent pharyngeal obstruction in moderate to severe OSA patients. Nasal CPAP with oxygen should immediately be applied in the postanesthetic care unit or ward if the patients accept the treatment. A CPAP machine designed to automatically determine the optimal CPAP level is preferable after surgery. A bilevel positive-pressure machine is necessary for OSA patients with obesity hypoventilation syndrome. Although the literature suggests the usefulness of postoperative CPAP,[140,141] OSA patients, particularly new CPAP users, do not always wear the mask postoperatively. It is not known whether a single postoperative event of pharyngeal obstruction can result in severe fatal hypoxemia. Although oxygen administration is not a fundamental treatment for OSA, it is beneficial for mild OSA patients or OSA patients with CPAP failure as an alternative to CPAP treatment.[142] Continuous oxygen therapy is recommended while opioids are used for postoperative analgesia.[143]

In conclusion, improvement of the pharyngeal anatomical imbalance and maintenance of lung volume are the keys for safe perioperative airway management of obese patients with OSA.

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References

1. Remmers JE, deGroot WJ, Sauerland EK, Anch AM: Pathogenesis of upper airway occlusion during sleep. J Appl Physiol 1978; 44:931–8
2. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG: Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study: Sleep Heart Health Study. JAMA 2000; 283:1829–36
3. Marin JM, Carrizo SJ, Vicente E, Agusti AG: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. Lancet 2005; 365:1046–53
4. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V: Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005; 353:2034–41
5. Gami AS, Howard DE, Olson EJ, Somers VK: Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med 2005; 352:1206–14
6. Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J: The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. N Engl J Med 1999; 340:847–51
7. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S: The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328:1230–5
8. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM: Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006; 295:1549–55
9. Schokker DF, Visscher TL, Nooyens AC, van Baak MA, Seidell JC: Prevalence of overweight and obesity in the Netherlands. Obes Rev 2007; 8:101–8
10. Pacific Cohort Studies Collaboration: The burden of overweight and obesity in the Asia-Pacific region. Obes Rev 2007; 8:191–6
11. Sturm R: Increases in clinically severe obesity in the United States, 1986–2000. Arch Intern Med 2003; 163:2146–8
12. Young T, Peppard PE, Taheri S: Excess weight and sleep-disordered breathing. J Appl Physiol 2005; 99:1592–9
13. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T: Progression and regression of sleep-disordered breathing with changes in weight: The Sleep Heart Health Study. Arch Intern Med 2005; 165:2408–13
14. Smith PL, Gold AR, Meyers DA, Haponik EF, Bleecker ER: Weight loss in mildly to moderately obese patients with obstructive sleep apnea. Ann Intern Med 1985; 103:850–5
15. Langeron O, Masso E, Huraux C, Guggiari M, Bianchi A, Coriat P, Riou B: Prediction of difficult mask ventilation. ANESTHESIOLOGY 2000; 92:1229–36
16. Kheterpal S, Han R, Tremper KK, Shanks A, Tait AR, O'Reilly M, Ludwig TA: Incidence and predictors of difficult and impossible mask ventilation. ANESTHESIOLOGY 2006; 105:885–91
17. Haponik EF, Smith PL, Bohlman ME, Allen RP, Goldman SM, Bleecker ER: Computerized tomography in obstructive sleep apnea: Correlation of airway size with physiology during sleep and wakefulness. Am Rev Respir Dis 1983; 127:221–6
18. Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA, Pack AI: Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing: Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med 1995; 152:1673–89
19. 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
20. 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

21. Martinez-Rivera C, Abad J, Fiz JA, Rios J, Morera J: Usefulness of truncal obesity indices as predictive factors for obstructive sleep apnea syndrome. Obesity (Silver Spring) 2008; 16:113–8

22. Horner RL, Mohiaddin RH, Lowell DG, Shea SA, Burman ED, Longmore DB, Guz A: Sites and sizes of fat deposits around the pharynx in obese patients with obstructive sleep apnoea and weight matched controls. Eur Respir J 1989; 2:613–22

23. Shelton KE, Woodson H, Gay S, Suratt PM: Pharyngeal fat in obstructive sleep apnea. Am Rev Respir Dis 1993; 148:462–6

24. Mortimore IL, Marshall I, Wraith PK, Sellar RJ, Douglas NJ: Neck and total body fat deposition in nonobese and obese patients with sleep apnea compared with that in control subjects. Am J Respir Crit Care Med 1998; 157:280–3

25. Shinohara E, Kihara S, Yamashita S, Yamane M, Nishida M, Arai T, Kotani K, Nakamura T, Takemura K, Matsuzawa Y: Visceral fat accumulation as an important risk factor for obstructive sleep apnoea syndrome in obese subjects. J Intern Med 1997; 241:11–8

26. Schafer H, Pauleit D, Sudhop T, Gouni-Berthold I, Ewig S, Berthold HK: Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. Chest 2002; 122:829–39

27. Grunstein R, Wilcox I, Yang TS, Gould Y, Hedner J: Snoring and sleep apnoea in men: Association with central obesity and hypertension. Int J Obes Relat Metab Disord 1993; 17:533–40

28. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM: Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995; 269:543–6

29. Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakamura T, Nakao K, Ohi M: Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. Circulation 1999; 100:706–12

30. O'donnell CP, Schaub CD, Haines AS, Berkowitz DE, Tankersley CG, Schwartz AR, Smith PL: Leptin prevents respiratory depression in obesity. Am J Respir Crit Care Med 1999; 159:1477–84

31. Alam I, Lewis K, Stephens JW, Baxter JN: Obesity, metabolic syndrome and sleep apnoea: All pro-inflammatory states. Obes Rev 2007; 8:119–27

32. Schwab RJ, Pasirstein M, Pierson R, Mackley A, Hachadoorian R, Arens R, Maislin G, Pack AI: 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

33. 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

34. Bedell GN, Wilson WR, Seebohm PM: Pulmonary function in obese persons. J Clin Invest 1958; 37:1049–60

35. 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

36. Series F, Cormier Y, Lampron N, La Forge J: Increasing the functional residual capacity may reverse obstructive sleep apnea. Sleep 1988; 11:349–53

37. Series F, Cormier Y, Lampron N, La Forge J: Influence of lung volume in sleep apnoea. Thorax 1989; 44:52–7

38. Heinzer RC, Stanchina ML, Malhotra A, Jordan AS, Patel SR, Lo YL, Wellman A, Schory K, Dover L, White DP: Effect of increased lung volume on sleep disordered breathing in patients with sleep apnoea. Thorax 2006; 61:435–9

39. Van de Graaff WB. Thoracic influence on upper airway patency. J Appl Physiol 1988; 65:2124–31

40. 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

41. Stanchina ML, Malhotra A, Fogel RB, Trinder J, Edwards JK, Schory K, White DP: The influence of lung volume on pharyngeal mechanics, collapsibility, and genioglossus muscle activation during sleep. Sleep 2003; 26:851–6

42. van der Weide L, van Sornsen de Koste JR, Lagerwaard FJ, Vincent A, van Triest B, Slotman BJ, Senan S: Analysis of carina position as surrogate marker for delivering phase-gated radiotherapy. Int J Radiat Oncol Biol Phys 2008; 71: 1111–7

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

44. Thut DC, Schwartz AR, Roach D, Wise RA, Permutt S, Smith PL: Tracheal and neck position influence upper airway airflow dynamics by altering airway length. J Appl Physiol 1993; 75:2084–90

45. Heinzer RC, Stanchina ML, Malhotra A, Fogel RB, Patel SR, Jordan AS, Schory K, White DP: Lung volume and continuous positive airway pressure requirements in obstructive sleep apnea. Am J Respir Crit Care Med 2005; 172:114–7

46. Tagaito Y, Isono S, Remmers JE, Tanaka A, Nishino T: Lung volume and collapsibility of the passive pharynx in patients with sleep-disordered breathing. J Appl Physiol 2007; 103:1379–85

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

48. Mezzanotte WS, Tangel DJ, White DP: Influence of sleep onset on upper-airway muscle activity in apnea patients *versus* normal controls. Am J Respir Crit Care Med 1996; 153:1880–7

49. Worsnop C, Kay A, Pierce R, Kim Y, Trinder J: Activity of respiratory pump and upper airway muscles during sleep onset. J Appl Physiol 1998; 85:908–20

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

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

52. Eikermann M, Malhotra A, Fassbender P, Zaremba S, Jordan AS, Gautam S, White DP, Chamberlin NL: Differential effects of isoflurane and propofol on upper airway dilator muscle activity and breathing. ANESTHESIOLOGY 2008; 108: 897–906

53. Malhotra A, Pillar G, Fogel RB, Beauregard J, Edwards JK, Slamowitz DI, Shea SA, White DP: Genioglossal but not palatal muscle activity relates closely to pharyngeal pressure. Am J Respir Crit Care Med 2000; 162:1058–62

54. Fogel RB, Trinder J, Malhotra A, Stanchina M, Edwards JK, Schory KE, White DP: Within-breath control of genioglossal muscle activation in humans: Effect of sleep-wake state. J Physiol 2003; 550:899–910

55. Parisi RA, Neubauer JA, Frank MM, Edelman NH, Santiago TV: Correlation between genioglossal and diaphragmatic responses to hypercapnia during sleep. Am Rev Respir Dis 1987; 135:378–82

56. Horner RL, Liu X, Gill H, Nolan P, Liu H, Sood S: Effects of sleep-wake state on the genioglossus *versus* diaphragm muscle response to CO(2) in rats. J Appl Physiol 2002; 92:878–87

57. Stanchina ML, Malhotra A, Fogel RB, Ayas N, Edwards JK, Schory K, White DP: Genioglossus muscle responsiveness to chemical and mechanical stimuli during non-rapid eye movement sleep. Am J Respir Crit Care Med 2002; 165: 945–9

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

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

60. Park E, Younes M, Liu H, Liu X, Horner RL: Systemic *versus* central administration of common hypnotics reveals opposing effects on genioglossus muscle activity in rats. Sleep 2008; 31:355–65

61. Onal E, Lopata M: Periodic breathing and the pathogenesis of occlusive sleep apneas. Am Rev Respir Dis 1982; 126:676–80

62. Khoo MC, Gottschalk A, Pack AI: Sleep-induced periodic breathing and apnea: A theoretical study. J Appl Physiol 1991; 70:2014–24

63. 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

64. Wellman A, Jordan AS, Malhotra A, Fogel RB, Katz ES, Schory K, Edwards JK, White DP: Ventilatory control and airway anatomy in obstructive sleep apnea. Am J Respir Crit Care Med 2004; 170:1225–32

65. Gold AR, Schwartz AR, Wise RA, Smith PL: Pulmonary function and respiratory chemosensitivity in moderately obese patients with sleep apnea. Chest 1993; 103:1325–9

66. Sin DD, Jones RL, Man GC: Hypercapnic ventilatory response in patients with and without obstructive sleep apnea: Do age, gender, obesity, and daytime PaCO(2) matter? Chest 2000; 117:454–9

67. Verbraecken J, De Backer W, Willemen M, De Cock W, Wittesaele W, Van de Heyning P: Chronic CO2 drive in patients with obstructive sleep apnea and effect of CPAP. Respir Physiol 1995; 101:279–87

68. Makinodan K, Yoshikawa M, Fukuoka A, Tamaki S, Koyama N, Yamauchi M, Tomoda K, Hamada K, Kimura H: Effect of serum leptin levels on hypercapnic ventilatory response in obstructive sleep apnea. Respiration 2008; 75:257–64

69. Wang D, Grunstein RR, Teichtahl H: Association between ventilatory response to hypercapnia and obstructive sleep apnea-hypopnea index in asymptomatic subjects. Sleep Breath 2007; 11:103–8

70. Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP: Effect of oxygen in obstructive sleep apnea: Role of loop gain. Respir Physiol Neurobiol 2008; 162:144–51

71. Hudgel DW, Gordon EA, Thanakitcharu S, Bruce EN: Instability of ventilatory control in patients with obstructive sleep apnea. Am J Respir Crit Care Med 1998; 158:1142–9

72. Gross JB, Bachenberg KL, Benumof JL, Caplan RA, Connis RT, Cote CJ, Nickinovich DG, Prachand V, Ward DS, Weaver EM, Ydens L, Yu S: American Society of Anesthesiologists Task Force on Perioperative Management: Practice guidelines for the perioperative management of patients with obstructive sleep apnea: A report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. ANESTHESIOLOGY 2006; 104:1081–93

73. Chung F, Ward B, Ho J, Yuan H, Kayumov L, Shapiro C: Preoperative identification of sleep apnea risk in elective surgical patients, using the Berlin questionnaire. J Clin Anesth 2007; 19:130–4

74. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM: STOP questionnaire: A tool to screen patients for obstructive sleep apnea. ANESTHESIOLOGY 2008; 108:812–21

75. Nuckton TJ, Glidden DV, Browner WS, Claman DM: Physical examination:

Mallampati score as an independent predictor of obstructive sleep apnea. Sleep 2006; 29:903–8

76. Tsai WH, Remmers JE, Brant R, Flemons WW, Davies J, Macarthur C: A decision rule for diagnostic testing in obstructive sleep apnea. Am J Respir Crit Care Med 2003; 167:1427–32

77. Suzuki N, Isono S, Ishikawa T, Kitamura Y, Takai Y, Nishino T: Submandible angle in nonobese patients with difficult tracheal intubation. ANESTHESIOLOGY 2007; 106:916–23

78. Ferguson KA, Ono T, Lowe AA, Ryan CF, Fleetham JA: The relationship between obesity and craniofacial structure in obstructive sleep apnea. Chest 1995; 108:375–81

79. Benumof JL: Both a large and small thyromental distance can predict difficult intubation (letter). Anesth Analg 2003; 97:1543

80. Chou HC, Wu TL: Mandibulohyoid distance in difficult laryngoscopy. Br J Anaesth 1993; 71:335–9

81. Isono S: Difficult tracheal intubation and a low hyoid (letter). ANESTHESIOLOGY 2009; 110:431

82. Corda L, Redolfi S, Taranto Montemurro L, La Piana GE, Bertella E, Tantucci C: Short- and long-term effects of CPAP on upper airway anatomy and collapsibility in OSAH. Sleep Breath 2008 Sep 25 [Epub ahead of print]

83. Hiremath AS, Hillman DR, James AL, Noffsinger WJ, Platt PR, Singer SL: Relationship between difficult tracheal intubation and obstructive sleep apnoea. Br J Anaesth 1998; 80:606–11

84. Chung F, Yegneswaran B, Herrera F, Shenderey A, Shapiro CM: Patients with difficult intubation may need referral to sleep clinics. Anesth Analg 2008; 107:915–20

85. Siyam MA, Benhamou D: Difficult endotracheal intubation in patients with sleep apnea syndrome. Anesth Analg 2002; 95:1098–102

86. Kim JA, Lee JJ: Preoperative predictors of difficult intubation in patients with obstructive sleep apnea syndrome. Can J Anaesth 2006; 53:393–7

87. Voyagis GS, Kyriakis KP, Dimitriou V, Vrettou I: Value of oropharyngeal Mallampati classification in predicting difficult laryngoscopy among obese patients. Eur J Anaesthesiol 1998; 15:330–4

88. Juvin P, Lavaut E, Dupont H, Lefevre P, Demetriou M, Dumoulin JL, Desmonts JM: Difficult tracheal intubation is more common in obese than in lean patients. Anesth Analg 2003; 97:595–600

89. Ezri T, Medalion B, Weisenberg M, Szmuk P, Warters RD, Charuzi I: Increased body mass index *per se* is not a predictor of difficult laryngoscopy. Can J Anaesth 2003; 50:179–83

90. Brodsky JB, Lemmens HJ, Brock-Utne JG, Vierra M, Saidman LJ: Morbid obesity and tracheal intubation. Anesth Analg 2002; 94:732–6

91. Isono S, Tanaka A, Sho Y, Konno A, Nishino T: Advancement of the mandible improves velopharyngeal airway patency. J Appl Physiol 1995; 79: 2132–8

92. Kitamura Y, Isono S, Suzuki N, Sato Y, Nishino T: Dynamic interaction of craniofacial structures during head positioning and direct laryngoscopy in anesthetized patients with and without difficult laryngoscopy. ANESTHESIOLOGY 2007; 107:875–83

93. Isono S: Optimal combination of head, mandible and body positions for pharyngeal airway maintenance during perioperative period: Lesson from pharyngeal closing pressures. Semin Anesth Periop Med Pain 2007; 26:83–93

94. Baraka AS, Taha SK, Aouad MT, El-Khatib MF, Kawkabani NI: Preoxygenation: Comparison of maximal breathing and tidal volume breathing techniques. ANESTHESIOLOGY 1999; 91:612–6

95. Rusca M, Proietti S, Schnyder P, Frascarolo P, Hedenstierna G, Spahn DR, Magnusson L: Prevention of atelectasis formation during induction of general anesthesia. Anesth Analg 2003; 97:1835–9

96. Cressey DM, Berthoud MC, Reilly CS: Effectiveness of continuous positive airway pressure to enhance pre-oxygenation in morbidly obese women. Anaesthesia 2001; 56:680–4

97. El-Khatib MF, Kanazi G, Baraka AS: Noninvasive bilevel positive airway pressure for preoxygenation of the critically ill morbidly obese patient. Can J Anaesth 2007; 54:744–7

98. Safar P, Escarraga LA, Elam JO: A comparison of the mouth-to-mouth and mouth-to-airway methods of artificial respiration with the chest-pressure arm-lift methods. N Engl J Med 1958; 258:671–7

99. Safar P, Aguto-Escarraga L, Drawdy L, McMahon MC, Norris AH, Redding J: The resuscitation dilemma. Anesth Analg 1959; 38:394–405

100. Isono S: One hand, two hands, or no hands for maximizing airway maneuvers? ANESTHESIOLOGY 2008; 109:576–7

101. Isono S, Tanaka A, Tagaito Y, Sho Y, Nishino T: Pharyngeal patency in response to advancement of the mandible in obese anesthetized persons. ANESTHESIOLOGY 1997; 87:1055–62

102. Isono S, Tanaka A, Tagaito Y, Ishikawa T, Nishino T: Influences of head positions and bite opening on collapsibility of the passive pharynx. J Appl Physiol 2004; 97:339–46

103. Liang Y, Kimball WR, Kacmarek RM, Zapol WM, Jiang Y: Nasal ventilation is more effective than combined oral–nasal ventilation during induction of general anesthesia in adult subjects. ANESTHESIOLOGY 2008; 108:998–1003

104. Calder I, Yentis SM: Could "safe practice" be compromising safe practice? Should anaesthetists have to demonstrate that face mask ventilation is possible before giving a neuromuscular blocker? Anaesthesia 2008; 63:113–5

105. Rothstein RJ, Narce SL, DeBerry-Borowiecki B, Blanks RH: Respiratory-related activity of upper airway muscles in anesthetized rabbit. J Appl Physiol 1983; 55:1830–6

106. Oswalt CE, Gates GA, Holmstrom MG: Pulmonary edema as a complication of acute airway obstruction. JAMA 1977; 238:1833–5

107. Benumof JL, Dagg R, Benumof R: Critical hemoglobin desaturation will occur before return to an unparalyzed state following 1 mg/kg intravenous succinylcholine. ANESTHESIOLOGY 1997; 87:979–82

108. Puhringer FK, Rex C, Sielenkamper AW, Claudius C, Larsen PB, Prins ME, Eikermann M, Khuenl-Brady KS: Reversal of profound, high-dose rocuronium-induced neuromuscular blockade by sugammadex at two different time points: An international, multicenter, randomized, dose-finding, safety assessor-blinded, phase II trial. ANESTHESIOLOGY 2008; 109:188–97

109. Sabate JM, Jouet P, Merrouche M, Pouzoulet J, Maillard D, Harnois F, Msika S, Coffin B: Gastroesophageal reflux in patients with morbid obesity: A role of obstructive sleep apnea syndrome? Obes Surg 2008; 18:1479–84

110. Ng A, Smith G: Gastroesophageal reflux and aspiration of gastric contents in anesthetic practice. Anesth Analg 2001; 93:494–513

111. Freid EB: The rapid sequence induction revisited: Obesity and sleep apnea syndrome. Anesthesiol Clin North Am 2005; 23:551–64

112. Gozal D, Burnside MM: Increased upper airway collapsibility in children with obstructive sleep apnea during wakefulness. Am J Respir Crit Care Med 2004; 169:163–7

113. Knill RL, Gelb AW: Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. ANESTHESIOLOGY 1978; 49:244–51

114. Wyon N, Joensen H, Yamamoto Y, Lindahl SG, Eriksson LI: Carotid body chemoreceptor function is impaired by vecuronium during hypoxia. ANESTHESIOLOGY 1998; 89:1471–9

115. Bowes G, Townsend ER, Kozar LF, Bromley SM, Phillipson EA: Effect of carotid body denervation on arousal response to hypoxia in sleeping dogs. J Appl Physiol 1981; 51:40–5

116. Isono S, Kochi T, Ide T, Sugimori K, Mizuguchi T, Nishino T: Differential effects of vecuronium on diaphragm and geniohyoid muscle in anaesthetized dogs. Br J Anaesth 1992; 68:239–43

117. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS, Nisman M: Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. ANESTHESIOLOGY 2008; 109:389–98

118. Eriksson LI: Evidence-based practice and neuromuscular monitoring: It's time for routine quantitative assessment. ANESTHESIOLOGY 2003; 98:1037–9

119. Eikermann M, Zaremba S, Malhotra A, Jordan AS, Rosow C, Chamberlin NL: Neostigmine but not sugammadex impairs upper airway dilator muscle activity and breathing. Br J Anaesth 2008; 101:344–9

120. Asai T, Koga K, Vaughan RS: Respiratory complications associated with tracheal intubation and extubation. Br J Anaesth 1998; 80:767–75

121. Dyson A, Isaac PA, Pennant JH, Giesecke AH, Lipton JM: Esmolol attenuates cardiovascular responses to extubation. Anesth Analg 1990; 71:675–8

122. Practice guidelines for management of the difficult airway: A report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. ANESTHESIOLOGY 1993; 78:597–602

123. Peterson GN, Domino KB, Caplan RA, Posner KL, Lee LA, Cheney FW: Management of the difficult airway: A closed claims analysis. ANESTHESIOLOGY 2005; 103:33–9

124. American Society of Anesthesiologists Task Force on Management of the Difficult Airway: Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. ANESTHESIOLOGY 2003; 98:1269–77

125. Riley RW, Powell NB, Guilleminault C, Pelayo R, Troell RJ, Li KK: Obstructive sleep apnea surgery: Risk management and complications. Otolaryngol Head Neck Surg 1997; 117:648–52

126. Fairbanks DNF: Uvulopalatopharyngoplasty complications and avoidance strategies. Otolaryngol Head Neck Surg 1990; 102:239–45

127. Sagi HC, Beutler W, Carroll E, Connolly PJ: Airway complications associated with surgery on the anterior cervical spine. Spine 2002; 27:949–53

128. Tanaka A, Isono S, Ishikawa T, Sato J, Nishino T: Laryngeal resistance before and after minor surgery: Endotracheal tube *versus* laryngeal mask airway. ANESTHESIOLOGY 2003; 99:252–8

129. Weil JV, McCullough RE, Kline JS, Sodal IE: Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. N Engl J Med 1975; 292:1103–6

130. Bailey PL, Lu JK, Pace NL, Orr JA, White JL, Hamber EA, Slawson MH, Crouch DJ, Rollins DE: Effects of intrathecal morphine on the ventilatory response to hypoxia. N Engl J Med 2000; 343:1228–34

131. Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG: Pronounced, episodic oxygen desaturation in the postoperative period: Its association with ventilatory pattern and analgesic regimen. ANESTHESIOLOGY 1985; 63:20–8

132. Ostermeier AM, Roizen MF, Hautkappe M, Klock PA, Klafta JM: Three sudden postoperative respiratory arrests associated with epidural opioids in patients with sleep apnea. Anesth Analg 1997; 85:452–60

133. Etches RC: Respiratory depression associated with patient-controlled analgesia: A review of eight cases. Can J Anaesth 1994; 41:125–32

134. Brown KA, Laferriere A, Lakheeram I, Moss IR: Recurrent hypoxemia in children is associated with increased analgesic sensitivity to opiates. ANESTHESIOLOGY 2006; 105:665–9

135. Taylor S, Kirton OC, Staff I, Kozol RA: Postoperative day one: A high risk period for respiratory events. Am J Surg 2005; 190:752–6

136. Etches RC: Respiratory depression associated with patient-controlled analgesia: A review of eight cases. Can J Anaesth 1994; 41:125–32

137. Turner K, VanDenkerkhof E, Lam M, Mackillop W: Perioperative care of patients with obstructive sleep apnea: A survey of Canadian anesthesiologists. Can J Anaesth 2006; 53:299–304

138. Isono S, Tanaka A, Nishino T: Lateral position decreases collapsibility of the passive pharynx in patients with obstructive sleep apnea. ANESTHESIOLOGY 2002; 97:780–5

139. Isono S, Tanaka A, Ishikawa T, Tagaito Y, Nishino T: Sniffing position improves pharyngeal airway patency in anesthetized patients with obstructive sleep apnea. ANESTHESIOLOGY 2005; 103:489–94

140. Rennotte MT, Baele P, Aubert G, Rodenstein DO: Nasal continuous positive airway pressure in the perioperative management of patients with obstructive sleep apnea submitted to surgery. Chest 1995; 107:367–74

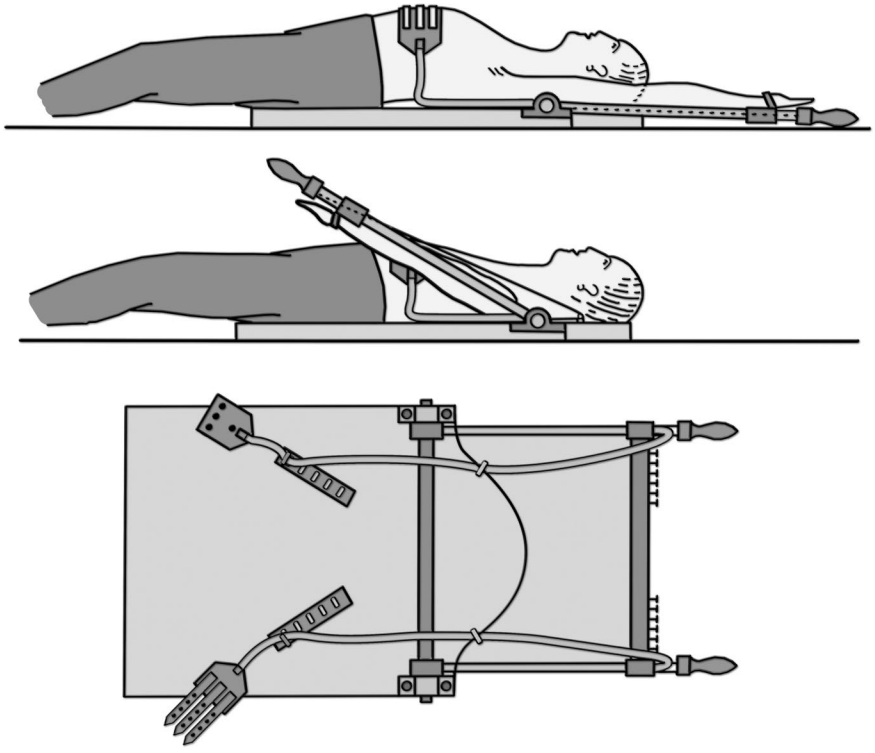
141. Gupta RM, Parvizi J, Hanssen AD, Gay PC: Postoperative complications in patients with obstructive sleep apnea syndrome undergoing hip or knee replacement: A case-control study. Mayo Clin Proc 2001; 76:897–905

142. Rosenberg-Adamsen S, Lie C, Bernhard A, Kehlet H, Rosenberg J: Effect of oxygen treatment on heart rate after abdominal surgery. ANESTHESIOLOGY 1999; 90:380–4

143. Jones JG, Jordan C, Scudder C, Rocke DA, Barrowcliffe M: Episodic postoperative oxygen desaturation: The value of added oxygen. J R Soc Med 1985; 78:1019–22

ANESTHESIOLOGY REFLECTIONS

Fries Apparatus for Artificial Respiration



Swedish citizen K. A. E. Fries of Stockholm filed in 1911 for a U.S. Patent on his "Apparatus for Producing Artificial Respiration." He hoped to resuscitate individuals "nearly drowned or suffocated by smoke, gas, or steam, or who for some other reason are in need of artificial respiration." Patterned loosely after the supine method of Silvester, the Fries approach shifted the victim's arm positions to exert "pressure on a proper part of the person's chest." Using the Fries Apparatus (as depicted above, from the Wood Library-Museum Archives) "one person, even an inexperienced one," could "without exertion perform the same amount of work for a long time as two or more practiced persons . . .." Granted in 1913, US Patent 1,057,633 mentioned that the Fries Apparatus might "also be used for gymnastic purposes." (Copyright © the American Society of Anesthesiologists, Inc. This image appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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