Using the pathophysiology of obstructive sleep apnea to teach cardiopulmonary integration

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Levitzky MG. Using the pathophysiology of obstructive sleep apnea to teach cardiopulmonary integration. Adv Physiol Educ 32: 196–202, 2008; doi:10.1152/advan.90137.2008.—Obstructive sleep apnea (OSA) is a common disorder of upper airway obstruction during sleep. The effects of intermittent upper airway obstruction include alveolar hypoventilation, altered arterial blood gases and acid-base status, and stimulation of the arterial chemoreceptors, which leads to frequent arousals. These arousals disturb sleep architecture and cause hypersomnolence. Chronic intermittent alveolar and systemic arterial hypoxia-hypercapnia can cause pulmonary and systemic hypertension, with effects on the right and left ventricles, and even the renal system. The pathophysiology of OSA can therefore be used to review and integrate many topics in pulmonary and cardiovascular physiology in the context of problem-based learning, a guided discussion, or a formal lecture. The discussion begins with a case scenario, followed by a definition of the disorder, the common symptoms and signs of OSA, and a description of an apneic event. These are related to the physiology of the upper airway in OSA, normal alterations in the respiratory system during sleep, the effects of apnea on gas exchange and arterial blood gases, and the cardiovascular consequences of alterations in alveolar and systemic arterial Po2 and Pco2. The treatment of OSA, particularly how the use of continuous positive airway pressure relates to the pathophysiology of the disorder, is discussed briefly.

mechanics of breathing; alveolar hypoventilation; pulmonary hypertension; systemic hypertension

OBSTRUCTIVE SLEEP APNEA (OSA) is a common disorder characterized by numerous brief occlusions of the upper airway that occur during sleep. These occlusions, which occur during inspiratory efforts, result in alveolar hypoventilation that leads to decreased arterial Po2 and increased arterial Pco2. Stimulation of arterial chemoreceptors by these altered blood gases causes repeated arousal responses that disturb sleep architecture and may result in hypersomnolence during daily activity. Chronic intermittent alveolar and systemic arterial hypoxia-hypercapnia can cause pulmonary and systemic hypertension, with effects on the right and left ventricles, and even affect the renal system. The pathophysiology of OSA can therefore be used to review and integrate many aspects of pulmonary and cardiovascular physiology in the context of problem-based learning, a guided discussion, or a formal lecture. The common symptoms and signs of OSA can be related to the effects of the disorder on the mechanics of breathing in the upper airway; the effects of alveolar hypoventilation on arterial blood gases, oxygen and carbon dioxide transport by the blood, and acid-base status; pulmonary blood flow and hypoxic pulmonary vasoconstriction; the control of breathing and how normal sleep affects the control of breathing and respiratory muscles; and the effects of repeated episodes of hypoventilation on pulmonary and systemic blood vessels, right and left ventricular mechanics, the electrocardiogram, and cardiac effects on urine formation. OSA can also be used to review the physiology of sleep and the electroencephalogram, but they are outside the scope of this article (and the author’s knowledge).

OSA Case Scenario

A 61-yr-old professor comes to the family physician because he feels tired all the time. He often falls asleep when he attends lectures, seminars, or boring meetings. Although he says he sleeps through the night (except to get up to urinate), his wife says he snores loudly and often seems to stop breathing and gasp for breath. He is restless and thrashes around in bed. He almost always wakes up with a headache, and for the past year he has been having trouble remembering things. He is 5 ft 7 in. tall and weighs 250 lb. His heart rate is 80 beats/min, his blood pressure is 135/95 mmHg, and his respiratory rate is 15 breaths/min. His electrocardiogram, chest radiograph, and echocardiogram strongly suggest pulmonary hypertension.

Definition and Epidemiology of OSA

OSA is usually defined as 15 or more apneas (and/or hypopneas) per hour during sleep, caused by collapse of the upper airway (21, 25). An apnea is usually defined in this context as 10 s or more without airflow (12, 21, 25). It is important to note that as much as 40–70% of the resistance to airflow normally resides in the upper airway, even when a person is awake. Note that unlike central sleep apnea, obstruction occurs in OSA despite the central drive to breathe and inspiratory muscle activity (12). OSA occurs in ∼9% of middle-aged men and 4% of middle-aged women in the United States, although estimates of its prevalence have a very wide range; one source stated that 85% of people with OSA are undiagnosed (21, 26). The prevalence of OSA increases with age and body weight; it is increased among pregnant women. There is also a high prevalence in 3- to 5-yr-old children, among whom it may be as high as 5% (26).

Symptoms and Signs of OSA

A symptom is usually defined as a problem reported by the patient, yet people with OSA may be unaware that they show many of the most common “symptoms” (1, 12) of the disorder and may not know (or be willing to acknowledge) that there is...
anything wrong (25). The most frequently occurring symptom, loud snoring, is often reported by the person’s bed partner, especially if the bed partner is aware of the periods of obstructive apnea indicated by no snoring and the gasping that accompanies arousals. Snoring is almost always a feature of OSA, but not everyone who snores has OSA. Hypersomnolence (also known as excessive daytime sleepiness) is usually a symptom, often accompanied by depressed mentation. Changes in personality may be noted by people close to the person with OSA. People with OSA often have headaches upon waking and frequently report nocturia. The signs of OSA include systemic hypertension; polycythemia; right axis deviation on the electrocardiogram, indicating right ventricular hypertrophy secondary to pulmonary hypertension; and signs of cor pulmonale. Bradycardia may occur during the apneic event, with tachycardia after airflow is restored. There is usually no respiratory abnormality while the person with OSA is awake, but the arterial blood gases may show metabolic alkalosis.

**Description of a Sleep Apnea Event**

Several factors predispose to obstruction of the upper airway during sleep. Altered body position, decreased tone of the pharyngeal muscles, depression of the respiratory drive, and depression of respiratory protective reflexes all occur in normal people during normal nonrapid eye movement (NREM) sleep, as discussed in greater detail below. Incomplete intermittent obstruction of the upper airway, usually involving the soft palate, results in snoring; periods of complete obstruction lasting 10 s or more are considered a sleep apnea. As shown in Fig. 1, an apnea of 10 s or more will result in a significant increase in arterial PCO₂ and a significant decrease in arterial PO₂ (16). Even small increases in arterial PCO₂ stimulate increased activity in arterial chemoreceptors, as shown in Fig. 2, and eventually in central chemoreceptors; much larger decreases in PCO₂ are necessary to stimulate increased activity. Increased arterial chemoreceptor activity results in increased respiratory drive and inspiratory muscle activity, but, as discussed below, this is likely to exacerbate the obstruction of the upper airway. Chemoreceptor stimulation, probably mainly due to increased arterial PCO₂, and possibly stimulation of mechanoreceptors in the upper airway, lead to arousal from sleep, resulting in a nearly immediate decrease in upper airway resistance and restoration of airflow. The arousal response has not been well defined, but it does not usually cause complete awakening (the person with OSA is usually unaware of it). The increased respiratory drive that occurs during the apneic period may result in a brief period of hyperventilation after airflow patency is restored.

**Diagnosis of OSA: Polysomnography**

Polysomnography is a diagnostic test used in the evaluation of sleep disorders (4, 7, 12). Various physiological sensors are connected to the patient, and data are collected while the patient sleeps. The tests are usually done overnight in a dedicated sleep laboratory, and the data are displayed simultaneously on a polysomnogram or polysomnograph. Physiological data that may be collected during a sleep study of a person suspected of having OSA include electroencephalograms and electrooculograms, to monitor the person’s sleep state; electromyograms of muscles involved in breathing; airflow at the nose or mouth, usually determined with a thermistor; end-tidal carbon dioxide, as an indicator of alveolar ventilation; chest and abdominal motion, usually determined by impedance plethysmography; electrocardiograms and blood pressure; and pulse oximetry. Esophageal pressure (as an indicator of intrapleural pressure) and autonomic nervous system activity, as determined by a finger tonometer, are collected far less commonly. Figure 3 shows an idealized normal polysomnogram; Fig. 4 shows an idealized polysomnogram from a person with OSA.

In the normal polysomnogram (Fig. 3), chest and abdominal motion are in phase and hemoglobin oxygen saturation, as determined by a pulse oximeter, is nearly constant as airflow is normal. There are no changes in heart rate or blood pressure.
There are two sleep apnea events in the polysomnogram drawn to represent one from a person with OSA (Fig. 4). Oxygen saturation decreases as each apnea continues, while blood pressure increases and heart rate decreases. Respiratory efforts continue during the apneas, but there is no airflow. (In people with central sleep apnea there is no drive to breathe during the apneas, so there is no chest or abdominal motion.) Chest and abdominal motion are not in phase. After arousal, airflow is restored, oxygen saturation increases, blood pressure falls, and heart rate increases.

Pathophysiology of OSA

During normal eupneic inspiration, air moves from the external environment through the resistance of the airways into the alveoli because alveolar pressure is made less than the atmospheric pressure (by convention, 0 cmH₂O) by the actions of inspiratory muscles. Because there is a gradient from the negative (<0 cmH₂O) pressure in the alveoli to the atmospheric pressure at the nose or mouth, the pressure in the upper airway must be negative during inspiration (15). During normal quiet breathing, alveolar pressure may be only −1 or −2 cmH₂O, but it can be much more negative with a greater inspiratory effort, as shown in Fig. 5. During a Mueller maneuver, intrapleural pressure can fall as low as −30 cmH₂O (2); pressures as low as −80 cmH₂O during episodes of complete airway obstruction in OSA are possible. Negative pressure in the upper airway during a large inspiratory effort can easily be demonstrated by a strong rapid inspiration through the nose; the nose is pulled inward and resistance to airflow increases. Small reinforced adhesive butterfly bandages to place over the nose to prevent collapse during inspiration are sold in drug stores. They can often be seen on athletes during sporting events. The most common causes of upper airway collapse during inspiration appear to be the tongue or the soft palate adhering to the wall of the pharynx, as shown in Fig. 6 (4, 7, 22, 25). As the airway begins to collapse because of negative pressure in the upper airway, the person with OSA makes greater inspiratory efforts, thus making upper airway pressure even more negative, exacerbating the problem until arousal occurs (see Fig. 4).

Collapse of the upper airway during normal inspiration is believed to be prevented by contraction of the pharyngeal dilator muscles (4). As many as 20 muscles may be included in the pharyngeal dilator group, including the genioglossis, which pulls the tongue forward to prevent upper airway obstruction; the geniohyoid, sternohyoid, and thyrohyoid, which move the hyoid bone forward to enlarge and stabilize the pharyngeal airway; and the tensor palatini, which pulls the palate away from the posterior wall of the pharynx (2, 4). (Similarily, the alae nasi muscles dilate the anterior nares during inspiration.) The activity of all of these dilator muscles appears to be centrally coordinated with the activity of the diaphragm. It is also known that experimentally induced negative pressure in the upper airway causes a reflex contraction of the pharyngeal dilator muscles (pharyngeal dilator reflex).

Factors That May Contribute to the Development of OSA

Many factors can contribute to the development of OSA in different patients (4, 14, 22, 25). Although the disorder is usually associated with middle-aged and older obese men, as discussed previously, it is not limited to them. People with short thick necks (especially when the neck is flexed or they are in the supine position); people with nasal congestion, obstruction, or polyps; people with enlarged tonsils and adenoids (especially in 3- to 5-yr-old children) or uvulas; people with large tongues (macroglossia), short jaws (retrognathia), or craniofacial abnormalities; people with very compliant (“floppy”) pharynxes or soft palates; and people with fat deposition or submucosal edema in the lateral walls of the pharynx or pharyngeal dilator muscles may be prone to the development of OSA. Decreased function of the pharyngeal dilator muscles, decreased effectiveness of the pharyngeal dilator reflex, decreased chemoreceptor response, or an impaired arousal response may lead to OSA; all of these may be impaired by the...
person’s use of ethanol or depressant drugs. Central sleep apnea and OSA are often mixed, so a depressed central drive may also be present in a person with OSA.

Why Obstruction Occurs During Sleep

Significant changes in the mechanics and control of breathing occur during normal sleep in people that do not have OSA (23). The most obvious is a result of altered body position. When a person is in the supine position gravity pulls the tongue toward the back wall of the pharynx, as shown in Fig. 6. The control of breathing is altered during NREM sleep by removal of the component of respiratory drive known as the “wakeness” drive (23). Minute volume decreases by ~16% and arterial PCO₂ increases by 4–6 mmHg; arterial oxygen saturation decreases by as much as 2% (2, 23). The tone of the pharyngeal muscles is decreased and the pharyngeal dilator

![Fig. 5. Representation of alveolar, intrapleural, and upper airway pressure at end expiration (left) and during a strong inspiratory effort (right). Note the potential collapse of the upper airway during the strong inspiratory effort.]

![Fig. 6. Common sites of upper airway obstruction during OSA events (right).]
reflex, as well as other protective respiratory reflexes, is depressed. The response to arterial hypoxia is depressed as well. REM sleep decreases the tone of the intercostal and accessory muscles, but it has less effect on diaphragm. The depression of minute volume and the increase in arterial PCO₂ are not as great as occur during NREM sleep, but the depression of the response to arterial hypoxia is greater. These changes in the mechanics and control of breathing that occur during sleep in people that do not have OSA predispose those with OSA to obstruction during sleep.

Pathophysiology of Other Symptoms and Signs of OSA

Metabolic alkalosis when the patient is awake. Chronic repeated upper airway obstructions during sleep cause carbon dioxide retention and therefore respiratory acidosis. This leads to the compensatory renal retention of bicarbonate ions and excretion of hydrogen ions. The upper airway is not obstructed when the patient is awake and arterial PCO₂ may return to normal levels. The elevated bicarbonate levels cause a metabolic alkalosis (19).

Pulmonary hypertension, polycythemia, right ventricular hypertrophy, right-axis deviation, and cor pulmonale. Upper airway obstructions during sleep cause alveolar hypoxia and hypercapnia. Hypoxic pulmonary vasoconstriction occurs in response to the hypoxia and hypercapnia, as shown in Fig. 7. This constriction of pulmonary blood vessels in response to alveolar hypoxia increases pulmonary vascular resistance and causes pulmonary hypertension (10). Repeated episodes of pulmonary hypertension due to obstruction-induced hypoxic pulmonary vasoconstriction may lead to vascular remodeling, resulting in chronic pulmonary hypertension that persists even during unobstructed awake states. Chronic alveolar hypoxia during the episodes of upper airway obstruction leads to hypoxemia (low arterial PO₂), which causes renal release of erythropoietin. Erythropoietin acts on the bone marrow to produce more red blood cells, which may eventually increase the hematocrit. As the hematocrit increases, the viscosity of the blood increases, as shown in Fig. 8. The increased pulmonary artery pressure and increased blood viscosity chronically increase the afterload of the right ventricle, producing right ventricular hypertrophy, which can be seen as a right-axis deviation in the electrocardiogram. As the pulmonary hypertension and increased viscosity progress, the hypertrophied right ventricle may not be able to meet the increased work load, leading to cor pulmonale, which is defined as right ventricular failure secondary to pulmonary hypertension (10, 17).

Systemic hypertension. Repeated increases in sympathetic tone and systemic blood pressure during arousals may cause vascular remodeling and changes in endothelial function, causing systemic hypertension that may persist when the patient is awake with no upper airway obstruction (2, 6, 20).

Morning headache. Arterial hypoxemia and hypercapnia during episodes of upper airway obstruction cause increased cerebral blood flow, presumably caused by dilatation of cerebral blood vessels (5, 8). Figure 9 shows that the effect of hypercapnia is much greater near the normal range for arterial PCO₂ than is the effect of hypoxemia near the normal range for arterial PO₂.
arterial PO2. The repeated dilatations of cerebral blood vessels during sleep are the likely cause of the morning headaches commonly experienced by people with OSA.

Bradyarrhythmia during obstruction and tachycardia after airflow is restored. Stimulation of arterial chemoreceptors usually increases heart rate because it increases tidal volume. This increase in heart rate is believed to be a reflex initiated by stimulation of stretch receptors in the small airways, possibly the same receptors involved in the Hering-Breuer inflation reflex. The afferent pathway of this lung inflation reflex includes the vagus nerves. On the other hand, stimulation of arterial chemoreceptors when tidal volume cannot increase, for example, in a patient on a mechanical ventilator, causes bradycardia (2, 18). During the episodes of obstruction, inspiratory efforts against the obstructed airway do not result in much of an increase in lung volume even though the arterial chemoreceptors are stimulated. After arousal leads to the restoration of airflow, large tidal volumes stretch the lungs and cause tachycardia via the lung inflation reflex. The person with OSA may hyperventilate immediately after arousal and then hypoventilate until arterial PCO2 is restored to levels sufficient to stimulate arterial chemoreceptors again.

Nocturia. As noted above, hypoxic pulmonary vasoconstriction, increased blood viscosity, and pulmonary hypertension increase the right ventricular afterload. The increased afterload leads to increased right ventricular end-diastolic pressure and volume. The increased right ventricular end-diastolic pressure and volume lead to increased right atrial volume, which increases the secretion of atrial natriuretic peptide from atrial myocytes, increasing sodium excretion. The increased atrial volume also stretches receptors that suppress antidiuretic hormone secretion from the posterior pituitary gland and increases urine volume (6).

Hypersomnolence or excessive daytime sleepiness. The repeated arousals precipitated by upper airway obstruction, which may occur as many as hundreds of times per night, interfere with normal sleep architecture, especially REM sleep. Abnormal sleep architecture leads to daytime somnolence, decreased attentiveness, blunted mentation, depression, and personality changes; hypersomnolence greatly increases the risk of motor vehicle accidents (9, 11, 13, 25).

Ethanol consumption exacerbates OSA. Ethanol depresses the respiratory responses to hypoxia and hypercapnia as well as depressing the activity and tone of the genioglossal and pharyngeal dilator muscles (10). Ethanol also depresses other protective respiratory reflexes, which can lead to aspiration and other problems not directly related to OSA. Ethanol consumption may also interfere with normal sleep architecture.

Treatment of OSA

OSA can be treated a number of ways, depending on the cause and severity of the problem in the individual patient and whether or not the patient is compliant with the treatment. Lifestyle changes. Because the supine position predisposes upper airway obstruction, changing to another body position during sleep may decrease or eliminate obstructions. Simple solutions such as sewing a tennis ball into the back of the patient’s pajama top, body belts that make the supine position uncomfortable, or the use of special pillows may prevent patients from assuming the supine position during sleep. Weight loss can help patients for whom adipose tissue around the upper airway is a contributing factor to upper airway obstruction during sleep. Decreased consumption of ethanol will help many OSA patients for the reasons described above.

Fig. 10. Representation of the effects of continuous positive airway pressure (CPAP) in opposing upper airway obstruction in OSA.
Oral appliances. Devices designed to be placed in the oral cavity to maintain airway patency may be effective in patients that can tolerate them (3). These include mandibular advancement devices that are custom made for the individual patient.

Continuous positive airway pressure. Continuous positive airway pressure is positive pressure in the airway during both inspiration and expiration administered to a spontaneously breathing patient. Air is usually delivered to a mask covering the nose via a tube from an electrically powered blower. The mask, which is attached to the head by adjustable straps, has a one-way valve to prevent exhaled air from being inhaled and to allow air to flow though the mask so all of the air flow does not enter the patient’s airway. The positive pressure prevents the upper airway from collapsing during inspiration, as shown in Fig. 10. Continuous positive airway pressure can be very effective in preventing upper airway collapse during sleep, but many patients cannot tolerate it because the mask may be uncomfortable and may irritate the skin. Some patients say they feel claustrophobic with the mask on or that it dries their upper airway mucosa. Many report difficulty exhaling against the positive pressure or that air is forced down the esophagus. The apparatus may also be noisy and is cumbersome to bring when traveling.

Surgery. Surgical treatment of patients with OSA who are unable to alleviate sleep-related upper airway obstruction by lifestyle change, oral appliances, or positive airway pressure is aimed at removing anatomic sites of obstruction in the naso-, oro-, or hypopharynx (24). Procedures include nasal reconstruction, tonsillectomy, uvulopalatopharyngoplasty (removing the uvula and part of the posterior palate and reorienting the anterior and posterior pharyngeal pillars), and other patient-specific corrective measures (24). Tracheotomy to completely bypass the upper airway is considered a last resort.

Summary

OSA is a common disorder of upper airway obstruction during sleep. Discussion and explanation of the pathophysiology of the disorder and its symptoms and signs involves many aspects of pulmonary and cardiovascular physiology and can be used to demonstrate the integration of the cardiovascular and respiratory systems. Topics that can be discussed include the mechanics of breathing, alveolar ventilation, pulmonary blood flow, oxygen transport by the blood, acid-base balance, control of breathing, systemic and pulmonary hypertension, right ventricular hypertrophy, and cor pulmonale. Sleep physiology, renal physiology, interpretation of electrocardiograms, and lifestyle and social issues can be added to the discussion, particularly in the context of problem-based learning.

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REFERENCES


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