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Hypoventilation Syndromes

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Overview

Background

Alveolar hypoventilation is caused by several disorders that are collectively referred as hypoventilation syndromes. Alveolar hypoventilation is defined as insufficient ventilation leading to hypercapnia, which is an increase in the partial pressure of carbon dioxide as measured by arterial blood gas analysis (PaCO2).[1] (See Etiology.)

Patients who hypoventilate may develop clinically significant hypoxemia, and the presence of hypoxemia along with hypercapnia aggravates the clinical manifestations seen with hypoventilation syndromes. Alveolar hypoventilation may be acute or chronic and may be caused by several mechanisms. (See Etiology and Presentation.)

The specific hypoventilation syndromes discussed in this article include the following (See Etiology, Presentation, Workup, Treatment, and Medication):

- Central alveolar hypoventilation
- Obesity-hypoventilation syndrome (OHS)
- Chest wall deformities
- Neuromuscular disorders
- Chronic obstructive pulmonary disease (COPD)

Central alveolar hypoventilation

The phrase "central alveolar hypoventilation" is used to describe patients with alveolar hypoventilation secondary to an underlying neurologic disease. Causes of central alveolar hypoventilation include drugs and central nervous system (CNS) diseases such as cerebrovascular accidents, trauma, and neoplasms.

Obesity-hypoventilation syndrome

OHS is another well-known cause of hypoventilation. Abnormal central ventilatory drive and obesity contribute to the development of OHS. OHS is defined as a combination of obesity and a body mass index greater than or equal to 30kg/m2 with awake chronic hypercapnia (PaCO2 >45 mm Hg). Other disorders that may cause hypoventilation should be ruled out first. Approximately 90% of patients with OHS also have obstructive sleep apnea (OSA).[2] Hypoventilation is worse during rapid eye movement (REM) sleep than during non-REM sleep.

Chest wall deformities

Chest wall deformities such as kyphoscoliosis, fibrothorax, and those occurring postthoracoplasty are associated with alveolar hypoventilation leading to respiratory insufficiency and respiratory failure.

Neuromuscular disorders

Neuromuscular diseases that can cause alveolar hypoventilation include myasthenia gravis, amyotrophic lateral sclerosis, Guillain-Barré syndrome, and muscular dystrophy. Patients with neuromuscular disorders have rapid, shallow breathing secondary to severe muscle weakness or abnormal motor neuron function.

The central respiratory drive is maintained in patients with neuromuscular disorders. Thus, hypoventilation is secondary to respiratory muscle weakness. Patients with neuromuscular disorders have nocturnal desaturations that are most prevalent in the REM stage of sleep. The degree of nocturnal desaturation is correlated with the degree of diaphragm dysfunction. The nocturnal desaturations may precede the onset of daytime hypoventilation and gas exchange abnormalities.

Chronic obstructive pulmonary disease

Hypoventilation is not uncommon in patients with severe COPD. Alveolar hypoventilation in COPD usually does not occur unless the forced expiratory volume in 1 second (FEV1) is less than 1L or 30% of the predicted value. However, many patients with severe airflow obstruction do not develop hypoventilation. Therefore, other factors, such as abnormal control of ventilation, genetic predisposition, and respiratory muscle weakness, are likely to contribute.

Respiratory physiology

The respiratory control system tightly regulates ventilation. Alveolar ventilation (VA) is under the control of the central respiratory centers, which are located in the ventral aspects of the pons and medulla. The control of ventilation has metabolic and voluntary neural components. The metabolic component is spontaneous and receives chemical and neural stimuli from the chest wall and lung parenchyma and receives chemical stimuli from the blood levels of carbon dioxide and oxygen.

Metabolism rapidly generates a large quantity of volatile acid (carbon dioxide) and nonvolatile acid in the body. The metabolism of fats and carbohydrates leads to the formation of a large amount of carbon dioxide, which combines with water to form carbonic acid (H2 CO3). The lungs excrete the volatile fraction via ventilation. Therefore, acid accumulation does not occur. PaCO2 is tightly maintained in a range of 39-41 mm Hg in normal states.

Ventilation is influenced and regulated by chemoreceptors for PaCO2, PaO2, and pH, located in the brainstem; by neural impulses from lung stretch receptors; and by impulses from the cerebral cortex. Failure of any of these mechanisms results in a state of hypoventilation and hypercapnia.

Hypoventilation and sleep

Hypoventilation and oxygen desaturation deteriorate during sleep secondary to a decrement in ventilatory response to hypoxia and increased PaCO2. In addition, diminished muscle tone develops during REM sleep, which further exacerbates hypoventilation secondary to insufficient respiratory effort.

Etiology

The respiratory system serves a dual purpose: delivering oxygen to the pulmonary capillary bed from the environment and eliminating carbon dioxide from the bloodstream by removing it from the pulmonary capillary bed. Metabolic production of carbon dioxide occurs rapidly. Thus, a failure of ventilation promptly increases PaCO2.

Hypoventilation may be secondary to several mechanisms, including central respiratory drive depression, neuromuscular disorders, chest wall abnormalities, obesity hypoventilation, and COPD. The specific causes can be summarized as follows:

- COPD
- Neuromuscular disorders[3] - Amyotrophic lateral sclerosis, muscular dystrophies (Duchenne and Becker dystrophies), diaphragm paralysis, Guillain-Barré syndrome, myasthenia gravis
- Chest wall deformities - Kyphoscoliosis, fibrothorax, thoracoplasty
- Central respiratory drive depression - Drugs (narcotics, benzodiazepines, barbiturates), neurologic disorders (encephalitis, brainstem disease, trauma, poliomyelitis, multiple sclerosis), primary alveolar hypoventilation
- Obesity-hypoventilation syndrome (OHS)
- Carotid body resection and/or injury
- Myxedema (severe hypothyroidism)

Gas exchange abnormalities

The alveoli are perfused by venous blood flow from the pulmonary capillary bed and participate in gas exchange. This gas exchange includes delivery of oxygen to the capillary bed and elimination of carbon dioxide from the bloodstream. The continued removal of carbon dioxide from the blood is dependent on adequate ventilation.

The relationship between ventilation and PaCO2 can be expressed as $PaCO_2 = (k)(VCO_2)/VA$, in which VCO2 is the metabolic production of carbon dioxide (ie, venous carbon dioxide production), k is a constant, and VA is alveolar ventilation. Therefore, in alveolar hypoventilation, PaCO2 increases as the VA decreases. Because the alveolus is a limited space, an increase in PaCO2 leads to a decrease in oxygen, with resultant hypoxemia.

VA also can be reduced when an increase in physiologic dead-space ratio (ie, the dead-space gas volume-to-tidal gas volume [VD/VT] ratio) occurs. Physiologic dead space occurs when an increase in ventilation to poorly perfused alveoli occurs. An increase in physiologic dead space results in a ventilation-perfusion mismatch, which, in classic presentation, occurs in patients with COPD.

The effect of physiologic dead space on alveolar hypoventilation can be expressed in the equation $PaCO_2 = (k)(VCO_2)/VE(1 - VD/VT)$, in which VE (ie, expired volume) is the total expired ventilation and 1 - VD/VT measures the portion of ventilation directly involved in gas exchange. An increase in the physiologic dead space without an augmentation in ventilation leads to alveolar hypoventilation and an increased PaCO2.

Primary and central alveolar hypoventilation

Patients with primary alveolar hypoventilation can voluntarily hyperventilate and normalize their PaCO2. These patients are unable to centrally integrate chemoreceptor signals, although the peripheral chemoreceptors appear to function normally.

Congenital central hypoventilation syndrome

Hypoventilation may be caused by depression of the central respiratory drive. Congenital central hypoventilation syndrome (CCHS), previously known as Ondine curse, is defined as the failure of automatic control of breathing. It generally presents in newborns and, in 90% of the cases, is caused by a polyalanine repeat expansion mutation in the PHOX2B gene. Patients heterozygous for PHOX2B may have milder forms of the disease and live into adulthood.[4]

CCHS may occur in association with Hirschsprung disease. In addition, patients with CCHS are at increased risk for neuroblastoma and ganglioneuroma.[4]

These patients have absent or minimal ventilatory response to hypercapnia and hypoxemia during sleep and wakefulness. Since these individuals do not develop respiratory distress when challenged with hypercapnia or hypoxia, progressive hypercapnia and hypoxemia occurs during sleep. Ventilation in CCHS patients is more stable during rapid eye movement (REM) sleep than in non-REM sleep.[5]

The diagnosis is established after excluding another cause, either pulmonary, cardiac, metabolic, or neurologic, for central hypoventilation. Patients with CCHS require lifelong ventilatory support during sleep, and some may require 24-hour ventilatory support.

Obesity-hypoventilation syndrome

Patients with OHS have a higher incidence of restrictive ventilatory defects when compared with patients who are obese but do not hypoventilate. Studies have shown that patients with OHS have total lung capacities that are 20% lower and maximal voluntary ventilation that is 40% lower than patients who are obese who do not have hypoventilation.[6]

Patients with OHS demonstrate an excessive work of breathing and an increase in carbon dioxide production. Inspiratory muscle strength and resting tidal volumes also are reported to be decreased in patients with obesity hypoventilation. Pulmonary compliance is lower in patients with OHS when compared with patients who are obese who do not have hypoventilation.

Obesity increases the work of breathing because of reductions in chest wall compliance and respiratory muscle strength. An excessive demand on the respiratory muscles leads to the perception of increased breathing effort and could unmask other associated respiratory and heart diseases.

Leptin deficiency or leptin resistance may also contribute to OHS, by reducing ventilatory responsiveness and leading to carbon dioxide retention.[7]

Despite the above-mentioned physiologic abnormalities, the most important factor in the development of hypoventilation in OHS is likely a defect in the central respiratory control system. These patients have been shown to have a decreased responsiveness to carbon dioxide rebreathing, hypoxia, or both.

Chest wall deformities

In patients with chest wall deformities, hypoventilation develops secondary to decreased chest wall compliance, with a resultant decreased tidal volume. Alveolar dead space is unchanged, but the VD/VT ratio is increased due to the reduced tidal volume.

The most common chest wall abnormality to cause hypoventilation is kyphoscoliosis. It is associated with a decrease in vital capacity and expiratory reserve volume, while the residual volume is only moderately reduced. These patients usually are asymptomatic until the late stages of disease, when the most severe deformity of the spine has occurred.

Neuromuscular disorders

Patients with neuromuscular disorders have a reduced vital capacity and expiratory reserve volume secondary to respiratory muscle weakness. The residual volume is maintained.

The reduction in vital capacity is greater than that which would be expected solely from the underlying respiratory muscle weakness, and these patients are likely to also have a significant reduction in lung and chest wall compliance, which further reduces vital capacity. The reduction in lung and chest wall compliance may be secondary to atelectasis and reduced tissue elasticity. In addition, the VD/VT ratio is increased due to the reduced tidal volume, and this further contributes to hypoventilation.

During sleep, ventilation decreases because of a lessening in respiratory center function. During REM sleep, atonia worsens, thus leading to more severe hypoventilation, particularly when diaphragmatic function is impaired. The effects of atonia are amplified by a low sensitivity of the respiratory centers. Nocturnal mechanical ventilation improves nocturnal hypoventilation and daytime arterial blood gases in these patients.

Chronic obstructive lung disease

Hypoventilation in patients with COPD is secondary to multiple mechanisms. As mentioned previously, these patients usually have severe obstruction, with an FEV1 of less than 1 L or 30% of the predicted value.

Patients with COPD who hypoventilate have a decreased chemical responsiveness to hypoxia and hypercapnia. This decreased chemical responsiveness also is observed in relatives of these patients who do not have COPD, leading researchers to believe that a genetic predisposition to alveolar hypoventilation exists.

These patients have a reduced tidal volume and a rapid, shallow breathing pattern, which leads to an increased VD/VT ratio. Patients also may have abnormal diaphragm function secondary to muscular fatigue and muscular mechanical disadvantage from hyperinflation.

Epidemiology

Occurrence in the United States

The frequency of hypoventilation syndromes varies with the underlying cause of hypoventilation. The most common of these disorders is chronic obstructive lung disease, which affects more than 15 million people in the United States.

When the prevalence of hypoventilation was studied in 54 stable, hypercapnic COPD patients without concomitant sleep apnea or morbid obesity, it was found that 43% had sleep-related hypoventilation, which was more severe in REM sleep.

Currently, the prevalence of OHS ranges from 10-20%.[8] Data from the US Centers of Disease Control and Prevention (CDC) show that one third of the adult US population is obese. With an increase in the obesity rate, the prevalence of OHS will likely continue to increase.[9]

Sex-related demographics

Primary alveolar hypoventilation occurs more commonly in male patients than in female patients. COPD also occurs more commonly in men than in women; however, because of increased smoking in women, the incidence is increasing in females. OHS is another condition that occurs more commonly in males, with a 2:1 male-to-female ratio.[2]

Age-related demographics

Most patients with hypoventilation syndromes are older. COPD and obesity increase in prevalence with age. Primary alveolar hypoventilation occurs more commonly in early adulthood, but it also occasionally is diagnosed in infancy. Most patients with OHS are older than 50 years.[10]

Prognosis

The prognosis of patients with hypoventilation syndromes is variable, being dependent on the underlying cause of hypoventilation and the severity of the underlying illness.

The morbidity and mortality rates of patients with hypoventilation syndromes depend on the specific etiology of the hypoventilation. Pulmonary hypertension is more common and more severe in patients with OHS than in those with only obstructive sleep apnea (OSA).

OHS patients have higher rates of ICU admission compared with patients with similar levels of obesity without hypoventilation.[2]

The morbidity and mortality rates of each of the above-mentioned disorders are increased secondary to the presence of respiratory failure and alveolar hypoventilation.

Some of the consequences of hypoventilation, such as cor pulmonale and pulmonary hypertension, may be irreversible.

Studies reported several decades ago showed significant increase in mortality in patients with OHS. This increased mortality is likely secondary to an increased risk of arrhythmias and cardiovascular complications.

Presentation

History

The clinical manifestations of hypoventilation syndromes usually are nonspecific, and in most cases, they are secondary to the underlying clinical diagnosis. Manifestations vary depending on the severity of hypoventilation, the rate of development of hypercapnia, and the degree of compensation for respiratory acidosis that may be present.

Progression

During the early stages of hypoventilation with mild to moderate hypercapnia, patients usually are asymptomatic or have only minimal symptoms.

Patients may be anxious and complain of dyspnea with exertion. As the degree of hypoventilation progresses, patients develop dyspnea at rest. Some patients may have disturbed sleep and daytime hypersomnolence.

As the hypoventilation continues to progress, more patients develop increased hypercapnia and hypoxemia. Therefore, they may have clinical manifestations of hypoxemia, such as cyanosis, and they also may have signs related to their hypercapnia.

Other symptoms of worsening hypoventilation can include the progression of anxiety to delirium. In addition, patients can become increasingly confused, somnolent, and obtunded. This condition occasionally is referred to as carbon dioxide narcosis.

Patients may develop asterixis, myoclonus, and seizures in severe hypercapnia. Papilledema may be seen in some individuals secondary to increased intracranial pressure related to cerebral vasodilation. Conjunctival and superficial facial blood vessel dilation also may be noted.

Patients with respiratory muscle weakness usually display generalized weakness secondary to their underlying neuromuscular disorder. Respiratory muscle weakness also may lead to impaired cough and recurrent lower respiratory tract infections.

With advanced disease, patients may develop respiratory failure and require ventilatory support.

Central alveolar hypoventilation

Patients with central alveolar hypoventilation usually have no respiratory complaints. However, they may have symptoms of sleep disturbance and daytime hypersomnolence. In some patients, the diagnosis of central alveolar hypoventilation is made only after the development of respiratory failure.

Obesity-hypoventilation syndrome

Patients with OHS typically report symptoms of OSA, such as daytime hypersomnolence, fatigue, loud snoring, nocturnal choking, and morning headaches. They may also have pulmonary hypertension and chronic right-sided heart failure (cor pulmonale), with secondary peripheral edema in advanced disease.

Chronic obstructive pulmonary disease

Patients with COPD and hypoventilation usually have severe disease and complain of significant dyspnea. They also may have peripheral edema secondary to pulmonary hypertension with cor pulmonale.

Physical Examination

In patients with alveolar hypoventilation, the findings upon physical examination usually are nonspecific and are related to the underlying illness.

Thoracic examination

Upon thoracic examination, patients with obstructive lung disease have diffuse wheezing, hyperinflation (barrel chest), diffusely decreased breath sounds, hyperresonance upon percussion, and prolonged expiration.

Coarse crackles beginning with inspiration may be heard, and wheezes frequently are heard upon forced and unforced expiration. Cyanosis may be noted if accompanying hypoxia is present. Clubbing may be present.

Pulmonary hypertension

Patients with central alveolar hypoventilation, COPD, and OHS may show evidence of pulmonary hypertension from examination findings. These findings include a narrowly split and loud pulmonary component (P2) of the second heart sound, a large a-wave component in the jugular venous pulse, a left parasternal (right ventricular) heave, and an S4 of right ventricular origin. A diastolic murmur indicative of pulmonic valve regurgitation may be auscultated.

Advanced disease

Patients with advanced disease develop signs of right ventricular failure (cor pulmonale) and may have elevated jugular venous pressure with a prominent V wave, lower-extremity edema, and hepatomegaly. A pulsatile liver develops if tricuspid regurgitation is severe. Ascites may occur but is unusual. The systolic murmur of tricuspid valve regurgitation may be present.

Other

The patient's mental status may be depressed with severe elevations of PaCO2. Patients may have asterixis and papilledema upon examination, and conjunctival and superficial facial blood vessels may be dilated.

DDx

Differential Diagnoses

- ALA Dehydratase Deficiency Porphyria
- Botulism
- Bronchitis
- Chronic Obstructive Pulmonary Disease (COPD)
- Diaphragm Disorders
- Diaphragmatic Paralysis
- Emphysema
- Obesity
- Opioid Abuse
- Respiratory Acidosis
- Sedative, Hypnotic, Anxiolytic Use Disorders

Workup
Workup

Approach Considerations

A diagnosis of lung disease should not be assumed in patients with hypoventilation, because other organ system dysfunction may be the primary cause of the condition. Central and peripheral neurologic disorders and muscular disorders should be considered.

The effects of sedating drugs such as narcotics and benzodiazepines in causing or worsening hypoventilation should always be considered. In patients without an obvious source of hypoventilation, a drug screen should be performed.

Although the differential diagnosis for hypoventilation syndromes is broad, a thorough history, physical examination, and laboratory evaluation should be helpful in limiting it.

Serum chemistries

The most common finding in chronic hypoventilation after chemistry analysis is the presence of a compensatory increase in the serum bicarbonate (HCO_3) concentration secondary to respiratory acidosis. Patients also occasionally may have hypercalcemia and hyperkalemia

Complete blood cell count

Many patients with chronic hypoventilation also are hypoxemic. These patients also may have secondary polycythemia, and a complete blood cell (CBC) count may reveal an elevated hematocrit level.

Thyroid function studies

Hypothyroidism is a potential cause of obesity. Obesity, in turn, can contribute to hypoventilation and OSA. Thyroid function should be evaluated in all patients with alveolar hypoventilation who are suspected of having central etiology or OSA.

Arterial blood gas analysis

Alveolar hypoventilation can be documented by the presence of hypercapnia or elevated $PaCO_2$ (>45 mm Hg). In addition, PaO_2 should be evaluated because hypoxemia may be present and frequently is associated with alveolar hypoventilation.

HCO_3 and pH should be evaluated to determine the presence of acute or chronic acidosis and the degree of compensation.

Transdiaphragmatic pressure

Measurement of transdiaphragmatic pressure is useful in documenting respiratory muscle weakness. This test is performed by placing an esophageal catheter with an esophageal balloon and a gastric balloon. The difference between the pressures measured at the two balloons is the transdiaphragmatic pressure, which is decreased in patients with diaphragmatic dysfunction and paralysis.

Chest Radiography

Perform a chest radiograph to rule out pulmonary disease as a cause of hypoventilation. Findings on chest radiographs that may help to determine the etiology of a hypoventilation syndrome include hyperinflation of lung volumes, diaphragm flattening, and elevation of the hemidiaphragms.

Hyperinflation of lung volumes and diaphragm flattening occur secondary to severe obstructive airway disease. With complicating pulmonary hypertension, the hilar vascular shadows are prominent secondary to

pulmonary artery enlargement, and the cardiac silhouette may become prominent secondary to right ventricular enlargement.

Elevation of the hemidiaphragms may be related to diaphragm weakness or paralysis or to atelectasis.

Evidence of bony thoracic abnormalities, such as severe kyphoscoliosis, also may be present. Patients with mild kyphosis of scoliosis generally do not develop hypercapnia.

Fluoroscopy

The fluoroscopic "sniff test" (in which paradoxical elevation of the paralyzed diaphragm is seen during inspiratory effort against a closed glottis) can confirm chest radiographic findings regarding unilateral diaphragmatic paralysis. This test is less useful in the diagnosis of bilateral diaphragmatic paralysis.

CT Scanning and MRI

Chest CT scanning

Computed tomography (CT) scanning of the chest may be performed for the same reasons as chest radiography. However, a CT scan is more sensitive for detecting disease and may reveal abnormalities not seen on a chest radiograph, having greater sensitivity, for example, in detecting emphysema, diaphragm abnormalities, and skeletal thoracic abnormalities.

Brain CT scanning

Perform imaging of the brain if a central cause of hypoventilation is suspected. Specific etiologies that may be diagnosed by brain CT scan include cerebrovascular accident and CNS tumor or trauma. Pay particular attention to the brainstem for lesions in the pons and medulla.

Brain MRI

If a central cause of hypoventilation is suspected and the initial brain CT scan is negative or inconclusive, consider a magnetic resonance imaging (MRI) scan of the brain. MRI may disclose abnormalities that are not seen on CT scanning. Pay particular attention to the brainstem, as with the CT scan mentioned above.

Echocardiography

Echocardiography is indicated to evaluate patients with hypoventilation syndromes for evidence of pulmonary hypertension and right ventricular enlargement. It also is useful to determine the presence of other potential complicating factors, such as left ventricular dysfunction and valvular dysfunction.[11]

On 2-dimensional (2D) echocardiography, patients with pulmonary artery hypertension have increased thickness of the right ventricle. As pulmonary hypertension becomes severe, a paradoxical bulging of the interventricular septum into the left ventricle occurs during systole. Later, the right ventricle dilates, becomes hypokinetic, and the septum develops diastolic flattening.

Doppler echocardiography is the most reliable method of estimating pulmonary artery pressure (PAP). Patients with pulmonary artery hypertension may have functional tricuspid valve regurgitation. The maximum tricuspid regurgitant (TR) jet velocity is recorded, and the PAP is calculated using a modified Bernoulli

equation: PAP systolic = (4 x TR jet velocity squared) + RAP. RAP is right atrial pressure, estimated from the size of the inferior vena cava (IVC) and respiratory variation in flow in the IVC.

Pulmonary Function Testing

These measurements are required for the diagnosis of obstructive and restrictive lung diseases and for assessment of the severity of disease.

The ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) is reduced in airflow obstruction and is the diagnostic variable. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines obstructive lung disease as an FEV1/FVC ratio of less than 0.70. Others recommend that obstructive lung disease be diagnosed if the FEV1/FVC ratio is below the lower limits of normal. Note that the FEV1/FVC ratio decreases with age; this helps avoid overdiagnosis of obstructive lung disease in elderly patients.[12]

FEV1 is used to evaluate the degree of airflow obstruction. Generally, when the FEV1 drops to less than 30% (very severe COPD), patients may have hypercapnia. Lung volume measurements may document an increase in total lung capacity, functional residual capacity, and residual volume in obstructive pulmonary disease.

Lung volume measurements are also helpful in the diagnosis of restrictive ventilatory defects. When lung volumes are reduced without a reduction in the diffusing capacity for carbon monoxide, this indicates extrathoracic restriction. Obesity and thoracic cage disorders such as severe kyphoscoliosis may cause this.

Measurement of maximal inspiratory and expiratory pressures may be useful in screening for respiratory muscle weakness and neuromuscular disorders.

ECG, EMG, and Nerve Conduction Velocity

Electrocardiography

Electrocardiography (ECG) may show signs of right heart strain, right ventricular hypertrophy, and right atrial enlargement.[2]

Electromyography and nerve conduction velocity

Electromyography (EMG) and nerve conduction velocity study are useful in diagnosing neuromuscular disorders, such as myasthenia gravis, Guillain-Barré syndrome, and amyotrophic lateral sclerosis, that may be the cause of ventilatory muscle weakness. These studies may reveal a neuropathic or myopathic pattern, depending on the etiology.

Polysomnography

Polysomnography should be performed in all patients with OHS because the majority of these individuals also have OSA. Polysomnography involves monitoring of multiple physiologic variables to include respiratory effort, airflow, oxygen saturation, sleep stages, body position, limb movements, and electrocardiogram.[13]

Sleep stages and arousals are monitored by electroencephalogram, to determine brain wave activity; electro-oculogram, to determine eye movement; and submental electromyogram, to detect muscle tone. The electro-oculogram and electromyogram facilitate the determination of the REM sleep stage, which is associated with decreased muscle tone and increased frequency of obstructive apneas.

Respiratory effort is recorded using devices to measure abdominal and chest wall movement. These devices include strain gauges, impedance devices, electromyographic bands, and an esophageal balloon with respiratory inductive plethysmography.

From the collected data, sleep stage distribution, arousals, apneas, and hypopneas can be quantitated and central and obstructive apneas can be differentiated. The apnea index and apnea-plus-hypopnea index (AHI) can be calculated by dividing the total number of apneas or apneas plus hypopneas by the total sleep time. The AHI also is known as the respiratory disturbance index. An AHI is considered abnormal at 5 per hour, and an AHI of 5-15 represents mild OSA.

Treatment

Approach Considerations

The treatment of hypoventilation primarily is directed at correcting the underlying disorder. Use caution when correcting chronic hypercapnia. Rapid correction of the hypercapnia can alkalinize the cerebrospinal fluid, which may cause seizures, and can induce a metabolic alkalosis, placing the patient at risk for cardiac dysrhythmias. Infusion of sodium HCO3 is not indicated for chronic hypoventilation syndromes.

Bronchodilators, such as beta agonists (eg, albuterol, salmeterol), anticholinergic agents (eg, ipratropium bromide), and methylxanthines (eg, theophylline), are helpful in treating patients with obstructive lung disease and severe bronchospasm. Additionally, theophylline may improve diaphragm muscle contractility and stimulate the respiratory center.

Drugs aimed at reversing the effects of certain sedative drugs may be helpful in the event of an overdose. Naloxone (Narcan) may be used to reverse the effects of narcotics, and flumazenil (Romazicon) may be used to reverse the effects of benzodiazepines.

Ventilation

Acute hypoventilation

Treatment of hypoventilation also is aimed at assisting ventilation. Therapies that may be beneficial are noninvasive ventilatory techniques, such as bilevel positive-pressure ventilation (PPV). Ventilatory assistance may be required in patients for the following indications:

- Symptoms of nocturnal hypoventilation, such as daytime hypersomnolence, morning headaches, fatigue, nightmares, and enuresis
- Dyspnea at rest
- Hypoventilation that causes pulmonary hypertension and cor pulmonale
- Nocturnal hypoxia (arterial oxygen saturation < 88%) despite supplemental oxygen

Patients with acute hypoventilation, diagnosed through symptoms and laboratory data, should be started on bilevel PPV urgently. If this fails to improve symptoms and laboratory data within a short period (1-2 h), consideration for intubation and invasive mechanical ventilation should be undertaken. Acute hypercapnia may progress to cardiovascular instability, arrhythmia, cardiac or respiratory arrest, and death if untreated.

Chronic hypoventilation

Noninvasive ventilation using nocturnal bilevel PPV using a mask interface is widely accepted as the ventilatory mode of choice in patients with chronic respiratory failure related to COPD, neuromuscular disease, thoracic deformities, and idiopathic hypoventilation. Nocturnal bilevel PPV acts by reducing nocturnal hypoventilation and increasing carbon dioxide responsiveness.[14] Nocturnal bilevel PPV may obviate the need for tracheotomy and has improved many patient-oriented outcomes. Bilevel PPV is the preferred method of noninvasive ventilation.[15, 16]

The indications for noninvasive bilevel PPV for nocturnal hypoventilation syndromes have been formulated based on the available literature. Patients considered for this therapy should have at least 1 of the following:

- A disease known to cause hypoventilation
- Symptoms and signs of hypoventilation present
- Failure to respond to first-line therapies in mild cases of hypoventilation - ie, treatment of primary underlying disease with bronchodilators, respiratory stimulants, weight loss, supplemental oxygen, or continuous positive airway pressure (CPAP)[17]
- Moderate to severe hypoventilation

Nocturnal bilevel PPV is indicated for use in patients with neuromuscular disorders who exhibit morning headache, daytime hypersomnolence, sleep difficulties, or cognitive dysfunction.

In the absence of symptoms, nocturnal bilevel PPV is recommended when $PaCO_2$ is greater than 45 mm Hg or when PaO_2 is less than 60mm Hg on a morning blood gas measurement.[14]

Daytime ventilation should be used when these patients have $PaCO_2$ greater than 50 mm Hg or less than 88% oxygen saturation.[3]

Studies in patients with OHS have demonstrated that one year of treatment with nocturnal bilevel PPV improves blood gas values.[18]

In patients unable to tolerate noninvasive ventilation or in patients in whom this is not effective, tracheostomy may be required.

Surgery

Surgery associated with hypoventilation includes bariatric procedures to promote weight loss and placement of an electrode on the phrenic nerve for diaphragm pacing. Some patients with thoracic deformities, such as kyphoscoliosis, may be candidates for corrective surgical procedures.

Refractory cases of hypoventilation due to advanced underlying disease, such as neuromuscular disease, chest wall deformities, or even obesity-hypoventilation syndrome, may require tracheostomy and assisted ventilation for optimal management.

Diet

Weight loss is an ideal treatment in obesity-hypoventilation syndrome. Weight loss improves the abnormal physiology and restores normal daytime gas exchange. In some individuals even a modest weight loss of 10 kg improves minute ventilation and normalizes daytime $PaCO_2$. In concomitant obstructive sleep apnea, weight

loss has been shown to decrease the number of sleep-disordered breathing events (apneas and hypopneas) and the severity of hypoxemia.

Deterrence/prevention

Alcohol and many illicit substances are known respiratory depressants. Their use in patients with hypoventilation syndromes may lead to coma and death.[19]

Oxygen Therapy

Because many patients with hypercapnia also are hypoxemic during the day, oxygen therapy may be indicated.

Oxygen therapy is indicated to prevent the sequelae of long-standing hypoxemia. Patients with COPD who meet the criteria for oxygen therapy have a decreased mortality when treated with continuous supplemental oxygen therapy. Oxygen therapy also has been shown to reduce pulmonary hypertension.

Use oxygen therapy with caution because it may worsen hypercapnia in some situations. In patients with COPD, the presence of worsening hypercapnia following oxygen therapy is a consequence of ventilation-perfusion mismatching rather than reduced ventilatory drive secondary to reduction in hypoxia.

Hypercapnia is best avoided by titration of oxygen delivery to maintain oxygen saturations in the range of 90-94% and PaO2 between 60 and 65mm Hg.

Approximately 50% of patients with OHS require oxygen therapy in addition to nocturnal bilevel PPV.[2] However, breathing 100% oxygen may cause worsening hypercapnia in stable patients with obesity-associated hypoventilation, due to a reduction in minute ventilation, resulting in alveolar hypoventilation and an associated increase in the volume of dead space-to-tidal volume ratio. Therefore, oxygen therapy should be administered with caution in patients who are morbidly obese.[20] Oxygen use alone is often an inadequate therapy for OHS.

Patients with neuromuscular disease should not usually be given oxygen therapy without ventilatory support.

Respiratory Stimulants

Respiratory stimulants have been used in alveolar hypoventilation but have limited efficacy. These are generally a last resort and should only be considered with noninvasive pressure ventilation.

Medroxyprogesterone

Medroxyprogesterone increases the central respiratory drive and it has been shown to be effective in obesity-hypoventilation syndrome and central hypoventilation syndromes. Its effectiveness in COPD is not clear. Initial studies documenting a reduction in hypercapnia with treatment with medroxyprogesterone were performed in the 1960s.[21]

More recent studies also have documented a decrease in hypercapnia in patients with obesity-hypoventilation syndrome with associated hypercapnia while receiving total daily doses of 60 mg of medroxyprogesterone in divided doses 2-3 times per day.[22]

However, the drug does not improve apnea frequency or symptoms of sleepiness. In addition, the risk of venous thromboembolism is increased with progestational agents.[9] Many experts do not currently recommend progesterone therapy.

Acetazolamide

Acetazolamide is a diuretic that inhibits carbonic anhydrase, increases HCO3 excretion, and causes metabolic acidosis. The metabolic acidosis subsequently stimulates ventilation. However, this medication must be used with caution. If the patient's respiratory system cannot compensate for the metabolic acidosis it induces, the patient may suffer hyperkalemia and, potentially, a cardiac dysrhythmia.

Theophylline

Theophylline increases diaphragm muscle strength and stimulates the central ventilatory drive. In addition to being a stimulant, theophylline is also a bronchodilator. However, the effectiveness of this medication is limited.

Weight Loss

Weight loss should be encouraged in patients with OHS. Diet regulation and exercise are prudent recommendations, and supervised weight loss programs should be offered to these patients. Unfortunately, many of these patients have numerous comorbidities that prevent them from performing an adequate level of exercise to facilitate significant weight loss.

Bariatric surgical procedures, such as gastric bypass procedures, should be offered to patients who are appropriate surgical candidates and who are willing to accept the risk of the surgical procedure. OHS is associated with a higher operative mortality.[2]

Bariatric Surgery

The numerous surgical options available today can be grouped into two categories based on their weight loss mechanism. Gastric restrictive procedures include vertical banded gastroplasty (VBG), adjustable gastric banding (AGB), and Roux-en-Y gastric bypass (RYGB). The procedures causing malabsorption include biliopancreatic diversion (BPD) and biliopancreatic diversion with duodenal switch (BPD-DS). All of the procedures have been successful in improving comorbidities associated with obesity.

The most commonly performed procedure is RYGB because it has the best short- and long-term results for safety, efficacy, and durability, and it has been shown to be superior to AGB. RYBG is generally performed laparoscopically. All of the procedures require long-term dietary compliance and careful nutritional follow-up.[23]

A National Institutes of Health (NIH) consensus statement addresses the issue of surgical treatment for obesity and obesity with associated comorbid conditions. According to these guidelines, patients who are recommended for surgical treatment include those with a body mass index greater than 40 kg/m2, as well as patients with a body mass index greater than 35 kg/m2 and an obesity-related comorbid condition (including OHS).

Diaphragm Pacing

Diaphragm pacing in appropriate patients with primary alveolar hypoventilation may allow for a more normal lifestyle. In the pacing procedure, an electrode is surgically placed onto the phrenic nerve, which is connected to a subcutaneous receiver. An external, battery-operated transmitter and antenna are placed on the skin over the receiver, and the phrenic nerve is stimulated by electric current, resulting in a diaphragmatic contraction.

The transmitter settings may be adjusted for respiratory rate and to give enough tidal volume to allow for adequate oxygenation and ventilation. Unfortunately, phrenic nerve stimulation results in irreversible injury to the nerve. Thus, over time, pacing of the phrenic nerve becomes ineffective.[24]

Direct pacing of the diaphragm in patients with phrenic nerve paralysis has been of interest. Studies are ongoing to determine the utility of this treatment modality.[25]

ICU Admission

If hypoventilation is severe and leads to respiratory failure, admission to an intensive care unit (ICU) may be required. ICU admission allows for more specialized nursing and respiratory care. Criteria for ICU admission are as follows:

- Confusion
- Lethargy
- Respiratory muscle fatigue
- Worsening hypoxemia
- Hypercapnia
- Respiratory acidosis with a pH of less than 7.3.

All patients requiring immediate tracheal intubation and mechanical ventilation also require ICU admission. Most acute care facilities require that all patients being treated with noninvasive bilevel PPV be admitted to the ICU as well.

Outpatient Care

Home oxygen therapy

In the outpatient setting, continue oxygen treatment in patients who meet the specific criteria for long-term oxygen therapy. These criteria include PaO2 less than 55 mm Hg and PaO2 less than 59 mm Hg with evidence of polycythemia or cor pulmonale.

Re-evaluate patients in 1-3 months after initiating therapy, because some patients may improve and may not require long-term oxygen.

Again, use oxygen therapy with caution in patients with alveolar hypoventilation, because some of these patients may experience worsening of hypercapnia.

Noninvasive ventilation

Noninvasive mechanical ventilation can be continued in the outpatient setting. Bilevel PPV can be used for long-term treatment of patients with a hypoventilation syndrome.

Furthermore, patients with a hypoventilation syndrome improve with nocturnal noninvasive mechanical ventilation only. Clinical studies have shown improvements in hypercapnia and hypoxia after treatment with nocturnal noninvasive bilevel PPV in patients with COPD with associated hypoventilation, a neuromuscular disorder, OHS, or kyphoscoliosis.

Consultations

Consider consultation with experts in certain medical specialties for assistance with evaluation and management of hypoventilation syndromes. The patient's history, physical examination findings, and available laboratory studies should guide the consultation selection.[26] Specialists who should be considered include the following:

- Pulmonary medicine specialist
- Neurologist
- Physical and rehabilitation medicine specialist

Medication

Medication Summary

Several drugs may be used to treat hypoventilation syndromes. Most produce the desired effect by stimulating the central respiratory drive, by reversing the effects of other medications that can depress the central respiratory drive, or by inducing bronchial dilatation.

For example, bronchodilators such as beta-agonists (eg, albuterol), anticholinergic agents (eg, atropine), and methylxanthines (eg, theophylline) are helpful in treating patients with obstructive lung disease and severe bronchospasm. Additionally, theophylline may improve diaphragm muscle contractility and stimulate the respiratory center.

Over the past several years, multiple long-acting beta-2 agonists and long-acting acting anticholinergics have become available for use in COPD. Patients may benefit from long-acting bronchodilators, such as salmeterol, formoterol, vilanterol, or olodaterol or a long-acting anticholinergic such as tiotropium, umeclidinium, or aclidinium. Patients often are started on a combination product with both these medications. Inhaled steroids might help in select COPD patients or for short-term treatment.

Beta2 Agonists

Class Summary

Bronchodilators act to decrease the muscle tone in small and large airways in the lungs, thereby increasing ventilation. These drugs include beta adrenergic agonists, methylxanthines, and anticholinergic agonists.

Albuterol (Proventil HFA, Ventolin HFA, ProAir HFA)

Albuterol is a beta agonist for the reversal of bronchospasm. It relaxes bronchial smooth muscle by its action on beta2 receptors, with little effect on cardiac muscle contractility.

Ipratropium (Atrovent)

Ipratropium is an anticholinergic bronchodilator that is chemically related to atropine.

Theophylline (Elixophyllin Elixir, Theo-24)

Theophylline potentiates exogenous catecholamines, stimulates endogenous catecholamine release, and stimulates diaphragmatic muscular relaxation, which, in turn, stimulates bronchodilation.

The drug's popularity has decreased because of theophylline's narrow therapeutic range and frequent toxicity. The therapeutic range is 10-20 mg/dL, but bronchodilation may require near-toxic (>20 mg/dL) levels. The clinical efficacy is controversial, especially in an acute setting

Opioid Reversal Agents

Class Summary

Opioid abuse, toxicity, and overdose are potential etiologies of hypoventilation. Opioid antagonists can be used to reverse the effects of opiates and to improve ventilation.

Naloxone

Naloxone is a pure opioid antagonist. It prevents or reverses opioid effects (eg, hypotension, respiratory depression, sedation), possibly by displacing opiates from their receptors. The drug is used to reverse opioid intoxication.

Benzodiazepine Toxicity Antidotes

Class Summary

These drugs are used to reverse the CNS-depressant effects of benzodiazepine overdose. Their ability to reverse benzodiazepine-induced respiratory depression is less predictable.

Flumazenil (Romazicon)

Flumazenil reverses the effects of benzodiazepines in an overdose by selectively antagonizing the gamma-aminobutyric acid (GABA)/benzodiazepine receptor complex. If the patient who is overdosed has not responded after 5 minutes of administering a cumulative dose of 5 mg, the cause of sedation is not likely due to benzodiazepines.

Flumazenil is short acting, with a half-life of 0.7-1.3 hours. However, because most benzodiazepines have longer half-lives, multiple doses should be administered to avoid relapse into a sedative state. Flumazenil also has a risk for provoking seizures.

Pulmonary, Other

Class Summary

These agents inhibit the enzyme carbonic anhydrase, which, in turn, increases HCO3 excretion and causes metabolic acidosis. The metabolic acidosis subsequently stimulates ventilation.

Acetazolamide (Diamox Sequels)

Acetazolamide improves symptomatic periodic breathing and hypoxia.

Progestins

Class Summary

These agents stimulate the central respiratory drive and may be beneficial in patients with hypoventilation.

Medroxyprogesterone acetate (Provera, Depo-Provera)

Medroxyprogesterone acetate increases the central respiratory drive and stimulates ventilation. It may increase upper airway muscular tone. For the treatment of hypoventilation, higher doses than usual of medroxyprogesterone acetate are required to induce significant reductions in hypercapnia.

Long acting beta agonists

Class Summary

Most of these are available in a combination product, and have been shown to be beneficial in stable COPD. Examples of these include salmeterol, formoterol, vilanterol, and olodaterol. These are contraindicated in asthmatics without the concomitant use of a long acting asthma control medication.

Long-Acting Muscarinic Agents

Class Summary

These medications interrupt vagal-induced bronchoconstriction, and are also known as long-acting anticholinergics. These are mainly used in COPD.

Tiotropium (Spiriva HandiHaler, Spiriva Respimat)

Tiotropium, a bronchodilator similar to ipratropium, is a once-daily, long-acting anticholinergic medication that has been shown to have significant clinical benefit. A quaternary ammonium compound, it elicits anticholinergic/antimuscarinic effects, with inhibitory effects on M3 receptors on airway smooth muscles, leading to bronchodilation. Tiotropium is the only long-acting muscarinic agent available at this time and has become a first-line therapy in patients with persistent symptoms. Tiotropium is more effective than salmeterol in preventing exacerbations.

Umeclidinium bromide (Incruse Ellipta)

Umeclidinium bromide is a long-acting muscarinic antagonist (LAMA) inhalation powder, often referred to as an anticholinergic. It blocks action of acetylcholine at muscarinic receptors (M1 to M5) in the bronchial airways (M3) by preventing an increase in intracellular calcium concentration, leading to relaxation of airway smooth muscle, improved lung function, and decreased mucus secretion. Umeclidinium dissociates slowly from M3 muscarinic receptors extending its duration of action. It is indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD), including chronic bronchitis and/or emphysema.

Long-Acting Beta Agonists

Class Summary

Most of these are available in a combination product, and have been shown to be beneficial in stable COPD. Examples of these include salmeterol, formoterol, vilanterol, and olodaterol. These are contraindicated in asthmatic patients without the concomitant use of a long-acting asthma control medication.

Formoterol (Perforomist)

Formoterol relaxes the smooth muscles of the bronchioles and relieves bronchospasms. This effect also may facilitate expectoration. It is shown to improve symptoms and morning peak flows. When administered at high or more frequent doses than recommended, incidence of adverse effects is higher. Bronchodilating effect lasts more than 12 hours. It is used in addition to anticholinergic agents.

Salmeterol (Serevent Diskus)

By relaxing the smooth muscles of the bronchioles in conditions associated with bronchitis, emphysema, asthma, or bronchiectasis, salmeterol can relieve bronchospasms. The effect also may facilitate expectoration. It is shown to improve symptoms and morning peak flows. When administered at high or more frequent doses than recommended, incidence of adverse effects is higher. Bronchodilating effect lasts more than 12 hours. It is used on a fixed schedule in addition to regular use of anticholinergic agents.

Vilanterol/fluticasone furoate inhaled (Breo Ellipta)

LABA and corticosteroid combination inhaler indicated for long-term, once-daily, maintenance treatment of airflow obstruction with COPD, including chronic bronchitis and/or emphysema. It is also approved to reduce COPD exacerbations. The product contains fluticasone fumarate, which has shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times that of fluticasone propionate.

Olodaterol inhaled (Striverdi Respimat)

Olodaterol is a once-daily LABA inhaler indicated for maintenance bronchodilator treatment in patients with COPD, including chronic bronchitis and/or emphysema in patients who are experiencing airflow obstruction. LABAs activate specific β2-adrenergic receptors on the surface of smooth muscle cells, which increases intracellular cAMP and smooth muscle relaxation.

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