found to have normal respiratory muscle strength, normal pulmonary function, and normal alveolar-arterial P_{O_2} difference. Hypoventilation is more marked during sleep in patients with respiratory drive defects, and polysomnography often reveals central apneas, hypopneas, or hypoventilation. Brain imaging (CT scan or magnetic resonance imaging [MRI]) can sometimes identify structural abnormalities in the pons or medulla that result in hypoventilation. Chronic narcotic use or significant hypothyroidism can depress the central respiratory drive and lead to chronic hypercapnia as well.

Respiratory muscle weakness has to be profound before lung volumes are compromised and hypercapnia develops. Typically physical examination reveals decreased strength in major muscle groups prior to the development of hypercapnia. Measurement of maximum inspiratory and expiratory pressures or forced vital capacity (FVC) can be used to monitor for respiratory muscle involvement in diseases with progressive muscle weakness. These patients also have increased risk for sleep-disordered breathing, including hypopneas, central and obstructive apneas, and hypoxemia. Nighttime oximetry and capnometry during polysomnography are helpful in better characterizing sleep disturbances in this patient population.

TREATMENT HYPOVENTILATION

Nocturnal noninvasive positive-pressure ventilation (NIPPV) has been used successfully in the treatment of hypoventilation and apneas, both central and obstructive, in patients with neuromuscular and chest wall disorders. Nocturnal NIPPV has been shown to improve daytime hypercapnia, prolong survival, and improve health-related quality of life when daytime hypercapnia is documented. ALS guidelines recommend consideration of nocturnal NIPPV if symptoms of hypoventilation exist *and* one of the following criteria is present: Pa_{CO_2} ≥45 mmHg; nocturnal oximetry demonstrates oxygen saturation ≤88% for 5 consecutive min; maximal inspiratory pressure <60 cmH_2O; FVC <50% predicted; or sniff nasal pressure <40 cmH_2O. However, at present, there is inconclusive evidence to support preemptive nocturnal NIPPV use in all patients with neuromuscular and chest wall disorders who demonstrate nocturnal but not daytime hypercapnia. Nevertheless, at some point, the institution of full-time ventilatory support with either pressure or volume-preset modes is required in progressive neuromuscular disorders. There is less evidence to direct the timing of this decision, but ventilatory failure requiring mechanical ventilation and chest infections related to ineffective cough are frequent triggers for the institution of full-time ventilatory support.

Treatment of chronic hypoventilation from lung or neuromuscular diseases should be directed at the underlying disorder. Pharmacologic agents that stimulate respiration, such as medroxyprogesterone and acetazolamide, have been poorly studied in chronic hypoventilation and should not replace treatment of the underlying disease process. Regardless of the cause, excessive metabolic alkalosis should be corrected, because plasma bicarbonate levels elevated out of proportion for the degree of chronic respiratory acidosis can result in additional hypoventilation. When indicated, administration of supplemental oxygen is effective in attenuating hypoxemia, polycythemia, and pulmonary hypertension. However, in some patients, supplemental oxygen can worsen hypercapnia.

Phrenic nerve or diaphragm pacing is a potential therapy for patients with hypoventilation from high cervical spinal cord lesions or respiratory drive disorders. Prior to surgical implantation, patients should have nerve conduction studies to ensure normal bilateral phrenic nerve function. Small case series suggest that effective diaphragmatic pacing can improve quality of life in these patients.

HYPOVENTILATION SYNDROMES

OBESITY HYPOVENTILATION SYNDROME

The diagnosis of OHS requires body mass index (BMI) ≥30 kg/m² and chronic daytime alveolar hypoventilation, defined as Pa_{CO_2} ≥45 mmHg at sea level in the absence of other known causes of hypercapnia. In almost 90% of cases, the sleep-disordered breathing is in the form of OSA. Several international studies in different populations confirm that the overall prevalence of OSA syndrome, defined by an apnea-hypopnea index (AHI) ≥5 *and* daytime sleepiness, is approximately 3–4% in middle-aged men and 2% in middle-aged women. Thus, the population at risk for the development of OHS continues to rise as the worldwide obesity epidemic persists. Although no population-based prevalence studies of OHS have been performed, some estimates suggest there may be as many as 500,000 individuals with OHS in the United States.

Some, but not all, studies suggest that severe obesity (BMI >40 kg/m²) and severe OSA (AHI >30 events per hour) are risk factors for the development of OHS. The pathogenesis of hypoventilation in these patients is the result of multiple physiologic variables and conditions including OSA, increased work of breathing, respiratory muscle impairment, ventilation-perfusion mismatching, and depressed central ventilatory responsiveness to hypoxemia and hypercapnia. These defects in central respiratory drive often improve with treatment, which suggests that decreased ventilatory responsiveness is a consequence rather than a primary cause of OHS. The treatment of OHS is similar to that for OSA: weight reduction and nocturnal NIPPV. There is evidence that weight loss alone lowers Pa_{CO_2} in patients with OHS. However, treatment with NIPPV should never be delayed while the patient attempts to lose weight. Continuous positive airway pressure (CPAP) improves daytime hypercapnia and hypoxemia in more than half of patients with OHS and concomitant OSA. Bilevel positive airway pressure should be reserved for patients not able to tolerate high levels of CPAP support or patients who remain hypoxemic despite resolution of obstructive respiratory events. NIPPV with bilevel positive airway pressure should be strongly considered if hypercapnia persists after several weeks of CPAP therapy with objectively proven adherence. Patients with OHS and no evidence of OSA are typically started on bilevel positive airway pressure, as are patients presenting with acute decompensated OHS. Finally, comorbid conditions that impair ventilation, such as chronic obstructive pulmonary disease, should be aggressively treated in conjunction with coexisting OHS.

CENTRAL HYPOVENTILATION SYNDROME

This syndrome can present later in life or in the neonatal period where it is often called Ondine's curse or congenital central hypoventilation syndrome. Abnormalities in the gene encoding PHOX2b, a transcription factor with a role in neuronal development, have been implicated in the pathogenesis of congenital central hypoventilation syndrome. Regardless of the age of onset, these patients have absent respiratory response to hypoxia or hypercapnia, mildly elevated Pa_{CO_2} while awake, and markedly elevated Pa_{CO_2} during non-REM sleep. Interestingly these patients are able to augment their ventilation and "normalize" Pa_{CO_2} during exercise and during REM sleep. These patients typically require NIPPV or mechanical ventilation as therapy and should be considered for phrenic nerve or diaphragmatic pacing at centers with experience performing these procedures.

HYPERVENTILATION

CLINICAL FEATURES

Hyperventilation is defined as ventilation in excess of metabolic requirements (C_{O_2} production) leading to a reduction in Pa_{CO_2}. The physiology of patients with chronic hyperventilation is poorly understood, and there is no typical clinical presentation. Symptoms can include dyspnea, paresthesias, tetany, headache, dizziness, visual disturbances, and atypical chest pain. Because symptoms can be so diverse, patients with chronic hyperventilation present to a variety of health care providers, including internists, neurologists, psychologists, psychiatrists, and pulmonologists.

It is helpful to think of hyperventilation as having initiating and sustaining factors. Some investigators believe that an initial event leads to increased alveolar ventilation and a drop in Pa_{CO_2}