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307 Disorders of Ventilation

can delineate the extent of fibrosis. Tissue biopsy may be necessary to rule out malignancy. Treatment in chronic fibrosing mediastinitis is focused on relieving symptoms and preventing further complications. Therapy often includes a combination of surgical debulking or resection and endovascular interventions, including stenting, if veins or arteries are involved. Glucocorticoids have been used with variable success in cases of autoimmune-related and fibro-inflammatory causes of fibrosing mediastinitis. In cases of active fungal infection, antifungal therapies can be used, although they are generally ineffective. Emerging reports have shown success with the use of rituximab in mitigating symptoms and reducing metabolic activity in refractory disease. ■

■ **PNEUMOMEDIASTINUM** In this condition, gas is noted in the interstices of the mediastinum. The three main causes are (1) alveolar rupture with dissection of air into the mediastinum; (2) perforation or rupture of the esophagus, trachea, or main bronchi; and (3) dissection of air from the neck or the abdomen into the mediastinum. Typically, there is severe substernal chest pain with or without radiation into the neck and arms. The physical examination usually reveals subcutaneous emphysema in the suprasternal notch and Hamman's sign, which is a crunching or clicking noise synchronous with the beating heart and is best heard with a stethoscope applied to the anterior chest wall in the left lateral decubitus position. The diagnosis is confirmed with a chest radiograph. Usually no treatment is required, but the mediastinal air will be absorbed faster if the patient inspires high concentrations of oxygen. If mediastinal structures are compressed, the compression can be relieved with needle aspiration. Acknowledgment Richard W. Light contributed to this chapter in the 21st edition and some material from that chapter has been retained here. ■

■ **FURTHER READING** Ahua J et al: Approach to imaging of mediastinal masses. *Diagnostics (Basel)* 13:3171, 2023. Carter BW et al: ITMIG classification of mediastinal compartments and multidisciplinary approach to mediastinal masses. *Radiographics* 37:413, 2017. Duwe B et al: Tumors of the mediastinum. *Chest* 128:2893, 2005. Juanpere S et al: A diagnostic approach to the mediastinal masses. *Insights Imaging* 4:29, 2013. Manyeruke FD et al: Idiopathic fibrosing mediastinitis. *Afr J Thorac Crit Care Med* 27:10.7196/AJTCCM.2021.v27i2.064, 2021. Markman M: Diagnosis and management of superior vena cava syndrome. *Cleve Clin J Med* 66:59, 1999. Ponamgi SP et al: Catheter-based intervention for pulmonary vein stenosis due to fibrosing mediastinitis: The Mayo Clinic experience. *Int J Cardiol Heart Vasc* 8:103, 2015. Westerly BD et al: Targeting B lymphocytes in progressive fibrosing mediastinitis. *Am J Respir Crit Care Med* 190:1069, 2014. Khalid Ismail, George R. Washko

Disorders of Ventilation DEFINITION AND PHYSIOLOGY In health, the arterial level of carbon dioxide (Paco₂) is maintained between 37 and 43 mmHg at sea level. All acute and chronic disorders of ventilation result in abnormal measurements of the partial pressure of carbon dioxide in the arterial blood, Paco₂. Paco₂ will be above the normal physiologic range if production exceeds clearance by the lung. This chapter reviews chronic ventilatory disorders.

The continuous production of carbon dioxide (CO₂) by cellular metabolism necessitates its efficient elimination by the respiratory system. The relationship between CO₂ production and Paco₂ is described by the equation: $Paco_2 = (k) (V_{CO_2})/V.A$, where V. CO₂ represents the carbon dioxide production, k is a constant, and V.A is fresh gas alveolar ventilation (Chap. 296). Alveolar ventilation is not equivalent to minute ventilation (calculated as the product of respiratory rate and tidal breath volume) because not all parts of the ventilated respiratory system participate in gas exchange. The portion of each tidal breath that remains within the conducting airways is called the dead space fraction, represented as V_d/V_t. V.A is the minute ventilation minus that portion of minute ventilation apportioned to dead space and is calculated as minute ventilation × (1 - V_d/V_t). As such, all disturbances of Paco₂ must reflect altered CO₂ production, minute ventilation, or dead space fraction.

Disorders of Ventilation CHAPTER 307 Diseases that alter V. CO₂ are often acute (e.g., sepsis, burns, or pyrexia), and their contribution to ventilatory abnormalities and/or respiratory failure is reviewed elsewhere. Chronic ventilatory disorders typically involve inappropriate levels of minute ventilation or increased dead space fraction, both of which result in insufficient alveolar ventilation to maintain the Paco₂ in the normal physiologic range. This is called alveolar hypoventilation. Note that a person may exhibit abnormally rapid breathing and have an elevated minute ventilation but still suffer from alveolar hypoventilation (because of an increased fraction of dead space ventilation). An understanding of this apparent paradox and more general disorders of ventilation requires a review of the normal respiratory cycle. The spontaneous cycle of inspiration and expiration is automatically generated in the brainstem. Two groups of neurons located within the medulla are particularly important: the dorsal respiratory group (DRG) and the ventral respiratory column (VRC). These neurons have widespread projections including the descending projections into the contralateral spinal cord where they perform many functions. They initiate activity in the phrenic nerve/diaphragm, project to the upper airway muscle groups and spinal respiratory neurons, and innervate the intercostal and abdominal muscles that participate in normal respiration. The DRG acts as the initial integration site for many of the afferent nerves relaying information about Pao₂, Paco₂, pH, and blood pressure from the carotid and aortic chemoreceptors and baroreceptors to the central nervous system (CNS). In addition, the vagus nerve relays information from stretch receptors and juxtapulmonary-capillary receptors in the lung parenchyma and chest wall to the DRG. The respiratory rhythm is generated within the VRC as well as the more rostrally located parafacial respiratory group (pFRG), which is particularly important for the generation of active expiration. One particularly important area within the VRC is the so-called pre-Bötzinger complex. This area is responsible for the generation of various forms of inspiratory activity, and lesioning of the pre-Bötzinger complex leads to the complete cessation of breathing. The neural output of these medullary respiratory networks can be voluntarily suppressed or augmented by input from higher brain centers and the autonomic nervous system. During normal sleep, there is an attenuated response to hypercapnia and hypoxemia, resulting in mild nocturnal hypoventilation that corrects upon awakening. Once neural input has been delivered to the

respiratory pump muscles, normal gas exchange requires an adequate amount of respiratory muscle strength to overcome the elastic and resistive loads of the respiratory system (Fig. 307-1A) (also see Chap. 296). In health, the strength of the respiratory muscles readily accomplishes this important functional response, and normal respiration continues indefinitely. Reduction in respiratory drive or neuromuscular competence or substantial increase in respiratory load can diminish minute ventilation, resulting in hypercapnia (Fig. 307-1B). Alternatively, if normal respiratory muscle strength is coupled with excessive respiratory drive, then alveolar hyperventilation ensues and leads to hypocapnia (Fig. 307-1C). **HYPOVENTILATION ■ ■ CLINICAL FEATURES** Diseases that reduce minute ventilation or increase dead space fall into four major categories: parenchymal lung and chest wall disease, obesity

Excess respiratory muscle strength in health Chest wall elastic loads Adequate neural transmission to motor units Respiratory muscle strength Load Lung resistive loads Strength **PART 7 Disorders of the Respiratory System** Lung elastic loads Respiratory drive A Load > Strength Impaired neuromuscular transmission Amyotrophic lateral sclerosis Myasthenia gravis Phrenic nerve injury Spinal cord lesion Chest wall disease Kyphoscoliosis Obesity Abdominal distention (ascites) Sleep-disordered breathing Upper airway obstruction Intermittent hypoxemia Muscle weakness Myopathy Malnutrition Fatigue Load Strength Diminished drive Sleep-disordered breathing Narcotic/sedative use Brainstem stroke Hypothyroidism 1° Alveolar hypoventilation Lung disease Interstitial lung disease Airflow obstruction Atelectasis Pulmonary embolus B Increased drive with acceptable strength No chest wall disease Normal neural transmission Load Strength Increased drive Numerous initiating and sustaining factors (see text) No lung disease Normal respiratory muscle strength C **FIGURE 307-1** Examples of balance between respiratory system strength and load. A. Excess respiratory muscle strength in health. B. Load greater than strength. C. Increased drive with acceptable strength. hypoventilation syndrome, neuromuscular disease, and respiratory drive disorders (Fig. 307-1B). “Pump failure” refers to disorders affecting the respiratory drive, neuronal pathways, neuromuscular junction, and muscles. The clinical manifestations of hypoventilation syndromes are nonspecific (Table 307-1) and vary depending on the severity of hypoventilation, the rate at which hypercapnia develops, the degree of compensation for respiratory acidosis, and the underlying disorder. Patients with parenchymal lung or chest wall disease typically present with shortness of breath and diminished exercise tolerance. Episodes of increased dyspnea and sputum production are hallmarks of obstructive lung diseases such as chronic obstructive pulmonary disease (COPD),

TABLE 307-1 Signs and Symptoms of Hypoventilation Dyspnea during activities of daily living Orthopnea in diseases affecting diaphragm function Poor-quality sleep Daytime hypersomnolence Early morning headaches Anxiety Impaired cough in neuromuscular diseases whereas progressive dyspnea and cough are common in interstitial lung diseases. Excessive daytime somnolence, poor-quality sleep, and snoring are common among patients with sleep-disordered breathing and obesity hypoventilation syndrome. Sleep disturbance and orthopnea are also described in neuromuscular disorders. As neuromuscular weakness progresses, the respiratory muscles, including the diaphragm, are placed at a mechanical disadvantage in the recumbent position owing to the upward movement of the abdominal contents. New-onset orthopnea is one of the earliest symptoms and often heralds reduced respiratory muscle force generation. More commonly, however, extremity weakness or bulbar symptoms develop prior to respiratory muscle involvement in neuromuscular diseases such as amyotrophic lateral sclerosis (ALS) or muscular dystrophy. The

characteristic finding of “paradoxical breathing” on physical examination (the abdomen moving inward instead of outward with deep inspiration while supine) indicates significant diaphragmatic weakness or paralysis. Patients with respiratory drive disorders do not have symptoms distinguishable from other causes of chronic hypoventilation and are usually secondary in nature. A cause can usually be identified with a detailed medical history, including medications, or illicit drug use. The diagnosis of a primary respiratory drive disorder is otherwise that of exclusion. The clinical course of patients with chronic hypoventilation follows a characteristic sequence: an asymptomatic stage where daytime P_{aO_2} and P_{aCO_2} are normal, then nocturnal hypoventilation develops, initially during rapid eye movement (REM) sleep and later in non-REM sleep. As disease progresses, the vital capacity and corresponding volume of the tidal breaths decrease, leading to a further drop in alveolar ventilation. Eventually daytime hypercapnia develops. Symptoms can develop at any point along this time course and often depend on the pace of underlying disease progression. Regardless of cause, the hallmark of all alveolar hypoventilation syndromes is an increase in alveolar P_{CO_2} (P_{ACO_2}) and therefore in P_{aCO_2} . The resulting continuous respiratory acidosis eventually leads to a compensatory increase in plasma bicarbonate concentration. The increase in P_{aCO_2} displaces oxygen in the alveolus, leading to a decrease in P_{aO_2} , often resulting in hypoxemia. If chronic, hypoxemia can stimulate erythropoiesis and thereby induce secondary erythrocytosis. The combination of chronic hypoxemia and hypercapnia may also induce pulmonary vasoconstriction, leading eventually to pulmonary hypertension, right ventricular hypertrophy, and right heart failure. ■ ■

DIAGNOSIS The hallmark of the diagnosis of hypoventilation is a $P_{aCO_2} \geq 45$ mmHg, measured in arterial blood gas (ABG) analysis. A venous blood gas can be an alternative if ABG is not available, keeping in mind that venous P_{CO_2} is normally several points higher than P_{aCO_2} . Elevated serum bicarbonate (i.e., total serum CO_2 , which equals calculated bicarbonate plus dissolved CO_2) in the absence of volume depletion is suggestive of hypoventilation. However, it is important to point out that a serum bicarbonate level <27 mmol/L in the setting of normal renal function makes the diagnosis of hypoventilation very unlikely. By contrast, a serum bicarbonate level ≥ 27 mmol/L should trigger clinicians to measure P_{aCO_2} as a confirmatory diagnostic test. Therefore, serum bicarbonate can be used as a sensitive but not specific test to detect hypercapnia. An ABG demonstrating elevated P_{aCO_2} combined with normal pH confirms chronic alveolar hypoventilation.

Hypoventilation: Daytime Hypercapnia Step 1: Detailed history, physical examination, including detailed medication history

Lung disease

Chest wall disorders

Medication-related depressed respiratory drive

Lung disease:

- Obstructive
- Restrictive
- Neuromuscular
- Systemic
- Localized (diaphragm)

Obesity hypoventilation syndrome

- PSG to rule out OSA

FIGURE 307-2 A diagnostic algorithm to determine the etiology of hypoventilation. Note that more than one condition may be present. BMI, body mass index; CNS, central nervous system; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; OSA, obstructive sleep apnea; PSG, polysomnography. The subsequent evaluation to identify an etiology should initially focus on whether the patient has lung disease or chest wall abnormalities. Physical examination, imaging studies (chest x-ray and/or computed tomography [CT] scan), and pulmonary function tests are sufficient to identify most lung/chest wall disorders leading to hypercapnia (Fig. 307-2). If the ventilatory apparatus (lung, airways, chest wall) is not responsible for chronic hypercapnia, then the focus should shift to the respiratory pump (i.e., respiratory drive and neuromuscular disorders). In respiratory drive disorders, there is a blunted response in minute ventilation to elevated CO_2 and/or low O_2 . As mentioned earlier, secondary forms of the disease are far more common and can be excluded by

Careful review of medications, including sedating medications and chronic narcotic use, or metabolic derangements including significant hypothyroidism. Brain imaging (CT scan or magnetic resonance imaging) can sometimes identify structural abnormalities in the pons or medulla that can result in hypoventilation. Primary forms of the disease are difficult to diagnose and should be suspected when patients with hypercapnia are found to have normal respiratory muscle strength, normal pulmonary function, and normal alveolar-arterial P_{aO_2} difference. Hypoventilation is more marked during sleep in patients with respiratory drive defects, and polysomnography often reveals elevation in nocturnal CO_2 , in addition to central apnea and hypopneas. In neuromuscular disorders, 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 assess for respiratory muscle involvement in diseases with progressive muscle weakness. Decrease in vital capacity is first seen in the recumbent position, which makes testing for a 15–25% drop in FVC, from seated to supine position in the pulmonary function test laboratory, an invaluable screening tool for impending chronic respiratory failure in these patients. Polysomnography, although unnecessary for diagnosis in most cases, can confirm nocturnal hypercapnia and demonstrate pseudo-central apnea/hypopnea (due to decreased muscle tone, especially in REM sleep) and obstructive apneas, especially with bulbar involvement. If these evaluations are unrevealing, the clinician should screen for obesity hypoventilation syndrome (OHS). The diagnosis requires the following: body mass index (BMI) ≥ 30 kg/m² and chronic daytime alveolar hypoventilation, defined as $P_{aCO_2} \geq 45$ mmHg at sea level in

Step 2: Pulmonary function testing, chest imaging Step 3: Pulmonary function testing (seated/supine) MIP, MEP Disorders of Ventilation CHAPTER 307 Step 4: BMI ≥ 30 kg/m² in absence of alternative explanation Step 5: CNS imaging Primary hypoventilation syndromes Primary respiratory drive disorders CNS lesion • Stroke • Tumor the absence of other known causes of hypercapnia. In almost 90% of cases, obstructive sleep apnea (OSA) is present, with close to 70% exhibiting severe OSA. 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 it may be as high as 0.4% of the U.S. adult population (or 1 in 263 adults). Some, but not all, studies suggest that severe obesity (BMI >40 kg/m²) and severe OSA (apnea-hypopnea index [AHI] >30 events per h) are risk factors for the development of OHS. Several screening tools have been developed to identify patients at risk for OSA, including the Epworth Sleepiness Scale (ESS), which measures daytime sleepiness, but it is neither sensitive enough nor specific enough to screen for OSA. The Berlin Questionnaire has been validated in a primary care setting and identifies patients likely to have OSA. Another often used screening questionnaire is the STOPBang survey, which has been used in preoperative anesthesia clinics to identify patients at risk of having OSA. Ultimately, polysomnography is needed for the diagnosis of OSA in that patient population and to screen for nocturnal hypoventilation if suspected. These diagnostic recommendations are summarized in Fig. 307-2. TREATMENT Hypoventilation Nocturnal noninvasive positive-pressure ventilation (NIPPV) has been used successfully in the treatment of hypoventilation. It has been shown to improve daytime hypercapnia, prolong survival, and improve health-related quality of life when daytime hypercapnia is documented. There is accumulating evidence to guide timing of initiation of NIPPV and the choice of particular modes in specific disease processes, but more robust research is needed for more concrete recommendations. ■ ■ NEUROMUSCULAR DISEASE In patients with neuromuscular disease, the use of NIPPV has been best studied in the ALS patient population. ALS guidelines

recommend consideration of nocturnal NIPPV if symptoms of hypoventilation exist and one of the following criteria are present: $\text{Paco}_2 \geq 45$ mmHg; nocturnal oximetry demonstrates oxygen saturation $\leq 88\%$ for

5 consecutive min; maximal inspiratory pressure < 60 cmH₂O; or sniff nasal pressure < 40 cmH₂O and FVC $< 50\%$ predicted. 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. Once NIPPV is initiated, many of these patients will go from using it only during sleep to needing support while awake, as their disease progresses. The advent of new modern home ventilation devices, with advanced modes of ventilation, and a multitude of comfortable mask interfaces, including mouthpiece ventilation, have all revolutionized the way we manage these patients at home. In addition to improved survival and quality of life, we are able to delay the need for tracheostomy or long-term institutionalization significantly. Smaller portable ventilators, with longer battery life, allow patients to remain functional until late in their disease. Cough assist devices have helped patients cope with ineffective cough and reduced the risk of recurrent pneumonia, a common cause for acute deterioration in these patients.

PART 7 Disorders of the Respiratory System If NIPPV is initiated, the goal is to gradually correct hypoventilation and bring Paco_2 back to a level below 52 mmHg, or at least a 20% reduction from pretreatment levels. Excessive metabolic alkalosis should also be corrected, as serum 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, even at low concentrations, can worsen hypercapnia. In addition to NIPPV, if available, treatment 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. 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. ■ ■ **OBSIDITY HYPOVENTILATION SYNDROME** The pathogenesis of hypoventilation in patients with OHS is multifactorial and includes OSA, increased work of breathing, respiratory muscle impairment relative to the increased load because of excess adiposity, ventilation-perfusion mismatching, and depressed central ventilatory responsiveness to hypoxemia and hypercapnia. Treatment requires addressing all these variables. Defects in central respiratory drive often improve with treatment of sleep-disordered breathing and correction of hypoventilation with continuous positive airway pressure (CPAP) or NIPPV without any significant change in body weight, which suggests that decreased ventilatory responsiveness is a consequence rather than a primary cause of OHS. The treatment of OSA follows standard guidelines: weight reduction and positive airway pressure therapy during sleep with either CPAP or NIPPV. There is evidence that substantial weight loss (i.e., 20–25% of actual body weight) alone normalizes Paco_2 in patients with OHS. Unfortunately, achieving and sustaining this degree of weight loss without bariatric surgery are very challenging for most patients. CPAP improves daytime hypercapnia and hypoxemia in more than half of patients with OHS and concomitant severe OSA. Bilevel positive airway pressure

(BiPAP) without a backup rate (BiPAP spontaneous mode) should be reserved for patients who are not able to tolerate high levels of CPAP support or when obstructive respiratory events persist despite reaching the maximum CPAP pressure of 20 cmH₂O. NIPPV in the form of BiPAP with a backup rate (BiPAP ST or spontaneous timed) or volume-assured pressure support modes should be strongly considered if hypercapnia persists after several weeks of CPAP therapy with objectively proven adherence. There is now evidence from randomized controlled trials that both CPAP and NIPPV equally improve nocturnal and daytime symptoms, long-term PaCO₂ and bicarbonate levels, and cardiovascular as well as overall mortality in patients with

OHS and severe OSA (AHI >30 events per h). Otherwise, patients with OHS who have no evidence of significant OSA are typically started on BiPAP ST or volume-assured pressure support modes, as are patients presenting with acute decompensated OHS. ■ ■CHRONIC HYPERCAPNIC COPD Chronic hypercapnia in COPD is known to indicate a more advanced disease but has been shown to be associated with worse survival compared to patients with equal disease severity who were normocapnic. Use of NIPPV in patients with COPD has been well established in the acute setting, when patients present with acute-on-chronic hypercapnic respiratory failure. Home NIPPV, on the other hand, has been controversial. It has gained significant momentum over the past decade with the advent and success of high-intensity BiPAP. In patients with severe but stable chronic hypercapnic COPD (PaCO₂ >52 mmHg and a normal pH), the use of high-intensity BiPAP (inspiratory positive airway pressure 24–28 cmH₂O, with a backup rate), aimed to reduce PaCO₂ to <48 mmHg or a >20% drop from baseline, was associated with improved 1-year mortality in addition to improved physiologic and quality of life parameters, compared with standard of care (home oxygen). If patients are hospitalized with acute-on-chronic exacerbation, evidence suggests retesting for PaCO₂ elevation 2–4 weeks after discharge and only considering NIPPV in patients with persistent hypercapnia (PaCO₂ >52 mmHg) after their exacerbation has resolved. This approach has been shown to reduce hospital readmissions and 1-year mortality. ■ ■CENTRAL HYPOVENTILATION SYNDROME This syndrome can present later in life or in the neonatal period when it is often called Ondine's curse or congenital central hypoventilation syndrome (CCHS). Abnormalities in the gene encoding PHOX2b, a transcription factor with a role in neuronal development, have been implicated in the pathogenesis of CCHS. Regardless of the age of onset, these patients have absent respiratory response to hypoxia or hypercapnia, mildly elevated PaCO₂ while awake, and markedly elevated PaCO₂ during non-REM sleep. Interestingly, these patients are able to augment their ventilation and "normalize" PaCO₂ 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 (CO₂ production) leading to a reduction in PaCO₂. 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 PaCO₂ to ~20 mmHg. The ensuing onset of chest pain, breathlessness, paresthesia, or altered consciousness can be alarming. The resultant increase in minute volume to relieve these acute symptoms only serves to exacerbate symptoms that are often misattributed by the patient and health care workers to cardiopulmonary

disorders. An unrevealing evaluation for causes of these symptoms often results in patients being anxious and fearful of additional attacks. It is important to note that anxiety disorders and panic attacks are not synonymous with hyperventilation. Anxiety disorders can be both an initiating and sustaining factor in the pathogenesis of chronic hyperventilation, but these are not necessary for the development of chronic hypocapnia.

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