

Sleep-disordered Breathing

State of the Art Review

Chronic Alveolar Hypoventilation: A Review for the Clinician

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The term hypoventilation defines a condition in which alveolar ventilation (VA) is insufficient to meet the individual's metabolic demands, resulting in an inappropriately high arterial carbon dioxide tension (Paco₂). The normal range of Paco₂ at rest is generally accepted to be between 35 and 45 mm Hg. Alveolar hypoventilation may be an acute or chronic manifestation of a variety of pathologic processes. Although patients with acute alveolar hypoventilation generally present in a clinically obvious fashion, chronic alveolar hypoventilation may be characterized by an insidiously progressive course.

In the following review, the pathophysiology of chronic alveolar hypoventilation (a term used interchangeably with chronic ventilatory failure) will be examined and specific disorders discussed to illustrate important concepts. Emphasis will be placed on the contributory role of the physiologic changes that occur during sleep. Currently available diagnostic and management techniques will be examined, with particular emphasis placed on new therapeutic modalities that are proving to be valuable in the long-term management of patients with chronic alveolar hypoventilation.

PATHOPHYSIOLOGY

Under steady state conditions in normal individuals, Paco₂ is maintained within tightly controlled limits. The Paco₂ reflects the balance between CO₂ production

by the body (VCO₂) and its elimination through the alveolar ventilation, as expressed in the relationship:

$$Paco_2 = k(VCO_2/VA)$$

where Paco₂ is the arterial carbon dioxide tension (mm Hg), VCO₂ is the rate of metabolic production of carbon dioxide (milliliters per minute), and k is a constant.

Increased VCO₂ generally does not lead to chronic hypercapnia without concomitant decreases in VA due to coexistent ventilatory drive abnormalities, restrictive or obstructive thoracic abnormalities and/or abnormal transduction of the central nervous system (CNS) neural respiratory signal into mechanical activity. Thus decreased VA is the ultimate mechanism of increased Paco₂ in chronic alveolar hypoventilation. The VA is a reflection of the total volume of gas breathed over time (minute ventilation, VE) and the portion of each breath that ventilates lung units where gas exchange occurs. Ventilated portions of the respiratory system where oxygen and CO₂ are not exchanged are defined as dead space (VD). The fraction of each breath that fills the dead space and is therefore "wasted" is the dead space-to-tidal volume ratio (VD/VT). Either reduced VT or increased VD can increase VD/VT and contribute to alveolar hypoventilation. Clinically, these aberrations may cause chronic ventilatory failure if the breathing rate is not increased sufficiently to allow augmentation of VE to compensate for the reduction in VA.

It is useful to group disorders causing chronic alveolar hypoventilation on a clinical basis into those in which the patient "Can't Breathe" (i.e. because of neuromuscular weakness or excessive work of breathing) and those in which the patients "Won't Breathe" (i.e. due to inadequate drive from the ventilatory centers in the CNS) (Table 1). Many disorders include features

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TABLE 1. *Etiologies for chronic hypoventilation*

Won't breathe
Impaired ventilatory drive
Primary alveolar hypoventilation
Structural defects
CNS tumor
Bulbar poliomyelitis
Arnold–Chiari malformation
Cerebrovascular accident
Metabolic
Severe metabolic alkalosis
Medications (alone and/or in combination)
Narcotics, sedatives, ethanol
Can't breathe
Neuromuscular disorders
Neuropathic processes
Amyotrophic lateral sclerosis
Spinal cord injury
Diaphragmatic paralysis/weakness
Neuromuscular junction disorders
Myasthenia gravis
Eaton–Lambert syndrome
Myopathy
Muscular dystrophy
Myotonic dystrophy
Metabolic (e.g. acid maltase deficiency)
Congenital
Restrictive chest abnormalities
Kyphoscoliosis
Idiopathic, congenital
Secondary (post-polio, neuromuscular, connective tissue diseases)
Interstitial lung disease (late manifestation)
Post-tuberculosis (thoracoplasty)
Pulmonary resection
Mixed (may have both features)
Myxedema
Airway obstruction
Chronic obstructive pulmonary disease
Obesity–hypoventilation syndrome

of both groups, and consequently not all disease processes associated with chronic hypoventilation can be easily categorized. Some disorders may have well documented effects on both the ventilatory muscles and chemoresponsiveness (myxedema). In other disorders, where abnormal pulmonary or chest wall mechanics increase the work required to maintain a given level of ventilation, a compensatory increase in the ventilatory drive may not occur, and in fact decreased ventilatory responsiveness may exist. If reduced responsiveness does exist, this may be physiologically important as it may allow such individuals to decrease their work of breathing, albeit at the expense of developing alveolar hypoventilation.

CONSEQUENCES OF CHRONIC HYPOVENTILATION

The manifestations of hypercapnia are dependent upon the rapidity of its onset. The presentation of in-

TABLE 2. *Clinical consequences of chronic hypoventilation*

Central nervous system effects
Altered mentation
Hypersomnolence
Headache
Pulmonary artery hypertension
Cor pulmonale
Elevated serum bicarbonate
Impaired diaphragm function (possible)
Disability

dividuals with chronic hypoventilation can be non-specific and may be accentuated by coexistent hypoxemia. Hypercapnia, either directly or indirectly, affects the CNS, ventilatory system, heart and kidneys (Table 2). The CNS effects of chronic hypercapnia include hypersomnolence, altered mentation and headache. Whereas diaphragm contractility is impaired in the presence of acute hypercapnia (1,2), whether contractility in the chronic state is similarly influenced has not been studied. Pulmonary artery pressures may be elevated in patients with chronic hypercapnia, although to a large extent this is related to concomitant hypoxemia. Pulmonary artery hypertension may lead to cor pulmonale, reduced cardiac output, disability and death. Increased resorption of urinary bicarbonate by the kidneys serves to buffer the existing respiratory acidosis.

CONTROL OF VENTILATION AND CHANGES WITH SLEEP

Sleep is a particularly critical period for patients with chronic alveolar hypoventilation, as significant aberrations in ventilation may occur and potentially contribute to hypercapnia during wakefulness. During wakefulness, arterial blood gases are normally maintained within narrow limits by output from two control systems, the “automatic” and the “behavioral”. The automatic ventilatory control system is located in the brainstem, and its inherent rhythmogenicity is maintained by complex interactions within and between the dorsal and ventral respiratory groups of respiratory neurons. This automatic system receives input from central (medullary) chemoreceptors, which are primarily responsive to CO₂ tension (through changes in hydrogen ion concentration), and from peripheral chemoreceptors (carotid and aortic bodies), which are sensitive to both arterial oxygen tension (PaO₂) and, to a lesser degree, PaCO₂. Feedback to the central rhythm-generating centers, which is important for respiratory timing and coordination, is also provided to the automatic system from pulmonary receptors (stretch, juxtacapillary, irritant) via the vagus nerve as well as from chest wall receptors (joint, tendon, muscle) via

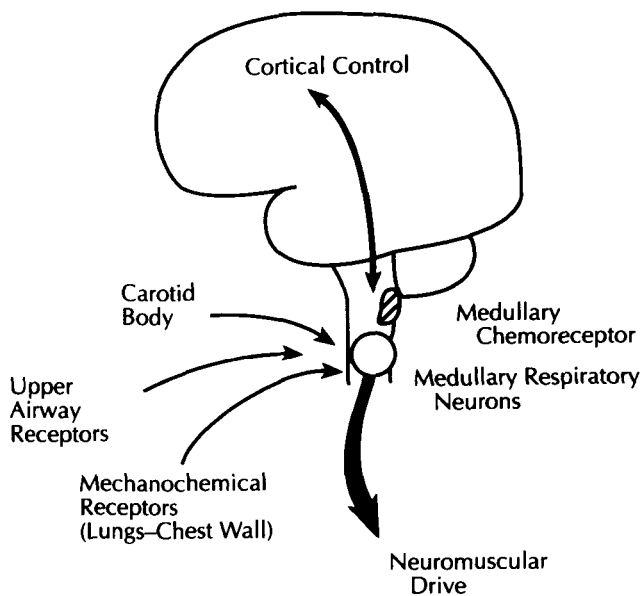


FIG. 1. The anatomic aspects of respiratory control are depicted in this view of the integrative features involved in homeostasis of gas exchange. Figure used with permission from (250).

spinal nerves (Fig. 1). The automatic system functions continuously and serves as the sole source of stimulus for breathing during nonrapid eye movement (NREM) sleep. During wakefulness, the behavioral system also modulates breathing through input to the brainstem from higher cortical locations (3,4). The behavioral system may permit overriding of the constraints imposed by the automatic system to permit activities such as speaking and singing.

In normal individuals, \dot{V}_E falls during NREM sleep and changes variably during rapid eye movement (REM) sleep (5), resulting in a mild increase in P_{aCO_2} (average 5 mm Hg across all sleep stages) and a decrease in P_{aO_2} (6). The reduction in \dot{V}_E and increase in P_{aCO_2} may in part be due to altered chemosensitivity, as both hypoxic and hypercapnic ventilatory responsiveness decline during sleep, with decreases being most prominent during stage REM (7,8). Reduced \dot{V}_E and increased P_{aCO_2} during sleep are also contributed to by an incomplete ventilatory response to elevated upper airway resistance created by reduced dilator muscle tone (9,10). In addition to being associated with the most profound alterations in chemoresponsiveness, stage REM sleep is also noteworthy for hypotonia of the intercostal and accessory ventilatory muscles as well as the cranial and limb muscles. This may be particularly important in individuals with lung and chest wall disorders, as their breathing even during wakefulness may require significant contributions from the intercostal and accessory muscles. Thus while the physiologic changes accompanying REM sleep may have little significance in normal individuals, patients

with lung and chest wall disorders may be at particular risk for hypoventilation because of the nondiaphragmatic ventilatory muscles on which they may be dependent.

“CAN’T BREATHE”: DISORDERS OF THE CHEST WALL, VENTILATORY MUSCLES AND PULMONARY PARENCHYMA

Kyphoscoliosis

Kyphoscoliosis (KS) may be congenital, idiopathic or a secondary manifestation of numerous disease processes (poliomyelitis, neuromuscular diseases, rickets, vertebral abnormalities, heritable connective tissue disorders). Mortality of patients with idiopathic KS is more than twice that expected, with more than half of the deaths due to cardiopulmonary causes (11). Development of idiopathic KS at an early age and severe spinal curvature (Cobb angle $> 120^\circ$) are both predictive of subsequent disabling dyspnea, cardiac failure and death (12–14). Early mortality also occurs in congenital KS and in KS secondary to poliomyelitis, rickets and tuberculosis (15,16).

Chronic ventilatory failure in KS may occur as a result of altered chest wall mechanics, diaphragm dysfunction and/or increased CO_2 production. Kyphoscoliosis causes chest wall restriction (14,17), to which affected individuals respond by breathing with a reduced \dot{V}_T , with consequent elevation of \dot{V}_D/\dot{V}_T . The abnormally increased \dot{V}_D/\dot{V}_T is further worsened by coexistent ventilation-perfusion mismatching (18). If a compensatory increase in breathing rate does not occur, alveolar hypoventilation develops (14). The abnormal thoracic configuration in KS may place the diaphragm at a mechanical disadvantage, with subnormal ability to generate maximal transdiaphragmatic pressures (19). Finally, the reduced chest wall compliance (stiffer chest wall) in KS patients mandates increased energy expenditure (work) to maintain a given level of ventilation, which results in increased CO_2 production (17). The specific role of defective central respiratory drive in chronic ventilatory failure due to KS remains unclear.

Ventilatory changes accompanying sleep may also have a significant impact on KS patients. Both accentuation of underlying oxyhemoglobin desaturation and elevation of end-tidal CO_2 level (P_{ETCO_2}) are generally consistent observations during REM sleep (20–22). In the presence of underlying diaphragmatic dysfunction, KS patients may be particularly dependent on their intercostal and accessory muscles of breathing, and the

expected reduction in activity of these muscles during REM sleep can have a devastating effect on the ability to maintain adequate ventilation. Additionally, KS patients may be prone to central, mixed and obstructive apneas and hypopneas during REM sleep (20–22). Limited evidence suggests that these nocturnal events play a significant role in the development of daytime cardiopulmonary dysfunction (22), but the precise nature of the nocturnal ventilatory changes cannot be predicted from the awake status, and thus polysomnography (PSG) may be required.

Chronic obstructive pulmonary disease

Increased severity of chronic obstructive pulmonary disease (COPD), as measured by gas exchange and ventilatory function, is predictive of decreased long-term survival (23,24). In eucapnic COPD patients, \dot{V}_E is above normal levels (25), providing compensation for the increased \dot{V}_D/\dot{V}_T created by parenchymal lung disease. As airflow limitation worsens, however, further increases in \dot{V}_E cannot be maintained and hypercapnia develops (26). The rapid, shallow breathing pattern adopted by COPD patients further increases \dot{V}_D/\dot{V}_T and contributes to alveolar hypoventilation (27–31).

Historically, patients with COPD have been categorized as being either “blue bloaters” (patients who have chronic bronchitis) or “pink puffers” (patients who have emphysema), although most patients present with clinical and pathologic manifestations of both subgroups. “Blue bloaters” are typically obese, hypoxemic during wakefulness and prone to develop chronic hypercapnia. On the other hand, “pink puffers” are of normal or subnormal body weight, usually have radiographic evidence of lung hyperinflation, maintain a normal or low Paco_2 and generally do not develop cor pulmonale until the disease is far advanced. The increased propensity for hypercapnia in chronic bronchitis patients may be partly due to their relatively fixed lower airway narrowing, in contrast to the more compliant and collapsible airways in emphysema patients with similar degrees of airflow limitation (32). Concurrent obesity and/or obstructive sleep apnea (OSA) in the chronic bronchitis patients may also contribute to the development of chronic alveolar hypoventilation.

Investigators have examined ventilatory muscle function in COPD patients to gain further insight into the mechanisms of hypoventilation. Increased lower airway resistance in COPD increases the energy cost and work of breathing (33–37). Flattening of the diaphragm’s normal dome-shaped configuration places the muscle at a mechanical disadvantage and decreases its pressure generating efficiency (37–39). Impairment may

be accentuated by a decreased blood supply to the muscle (40). Thus the combination of increased work load and contractile limitation of the diaphragm predispose to the development of muscle failure and alveolar hypoventilation. Support for ventilatory muscle dysfunction in COPD, unexplained by the mechanical disadvantage imposed by pulmonary hyperinflation, is found in the association of reduced maximal inspiratory pressure (MIP) with elevated Paco_2 (41). Additionally, although stable COPD patients can be made to augment their ventilation for brief periods of time (42,43), assessment of their resting diaphragmatic tension-time index reveals that they have little ventilatory reserve (44) and display evidence of inspiratory muscle fatigue (45). The diaphragm tension-time index takes into account the diaphragm contraction time as well as the magnitude of the pressure generated relative to the muscle’s maximum pressure generating capacity (40).

Altered ventilatory drive has also been considered to be a potential pathogenic factor in the development of chronic ventilatory failure in COPD. However, it is not feasible to directly measure the output of the CNS respiratory center(s) in humans, and evaluation of ventilatory chemoresponsiveness (augmented ventilation in the presence of hypoxemia or hypercapnia) may inaccurately reflect the drive to breathe in the setting of lower airways obstruction. There are conflicting data regarding CO_2 responsiveness in COPD patients. Although there is some evidence indicating that hypercapnic COPD patients have diminished ventilatory responses to CO_2 (46,47), central chemoresponsiveness to CO_2 , as assessed by diaphragmatic and intercostal electromyogram (EMG), has been shown to be increased in hypercapnic COPD patients (48). Additionally, although some data suggest that hypoxic drive is decreased in hypoxemic COPD patients (49), most of the study subjects were also hypercapnic, potentially leading to significant bias. If abnormal chemoresponsiveness is present, it may in part be attributable to familial factors, as healthy offspring of hypercapnic COPD patients have been variably shown to have decreased chemoresponsiveness (50).

Central respiratory drive may also be diminished on an acquired basis, and it is with this notion that the concept of “central fatigue” has been developed (51–53). The development of central fatigue in COPD patients has been postulated to serve as a protective mechanism in individuals whose ventilatory muscle work is dangerously close to a fatiguing level, placing them at risk of catastrophic respiratory failure. This could also apply to patients with restrictive or neuromuscular diseases. If central fatigue allows ventilation to decrease, the work of breathing could be decreased and theoretically the patient distanced from

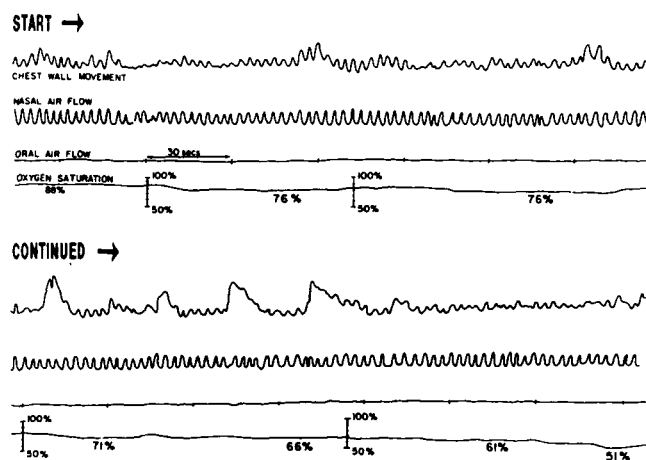


FIG. 2. Prolonged desaturation during REM sleep in a patient with COPD. Note that nasal airflow is constant. Figure used with permission from (251).

the level of ventilation that may be associated with the development of acute ventilatory muscle failure. Central fatigue has not been convincingly demonstrated in COPD patients.

As in patients with KS, sleep may be a pathophysiologically significant period in COPD patients, as it is associated with exacerbation of hypoxemia, particularly during stage REM (54) (Fig. 2). The awake oxyhemoglobin saturation may provide a clinical clue to predict the degree of nocturnal desaturation (55,56). Nocturnal desaturation may be explained by hypoventilation (57,58), ventilation-perfusion mismatching (56-58) and reduced oxygen stores (57). Additionally, the degree of oxyhemoglobin desaturation during sleep is related to awake chemoresponsiveness in COPD patients (59,60), although it is difficult to discern the degree to which these processes are interactive (61). Episodic nocturnal oxyhemoglobin desaturation in COPD patients may contribute, by virtue of its cardiac effects, to morbidity, and its onset usually reflects worsening of both the underlying pulmonary disease and daytime arterial blood gas values (62). Finally, co-occurrence of COPD and obstructive sleep apnea/hypopnea syndrome (the "overlap syndrome") is increasingly recognized (54,63-65), and affected individuals are at increased risk for development of cardiopulmonary dysfunction (66) and chronic ventilatory failure (67).

In summary, chronic alveolar hypoventilation in COPD is related to a variety of pathophysiologic processes including increased work of breathing due to airways disease, mechanical disadvantage and/or fatigue of the ventilatory muscles, decreased ability to augment ventilation in response to chemostimuli and potentially the adverse impact of sleep related exacerbation of blood gas abnormalities. These factors meet

in a final common pathway and increase V_D/V_T to precipitate and sustain hypercapnia.

Diseases of the neuromuscular system

Alveolar hypoventilation may occur if the ventilatory "pump" is sufficiently impaired despite normal CNS control mechanisms, pulmonary parenchyma and airways. Thus abnormalities involving the spinal cord, nerve roots, nerves (i.e. phrenic), neuromuscular junction and muscles may predispose to chronic ventilatory failure. These disease processes may be confined to muscles of the ventilatory system or be part of a systemic illness. Most persons with isolated, bilateral diaphragmatic paralysis remain eucapnic during wakefulness, demonstrating that with otherwise normal pulmonary parenchyma and thoracic mechanics, adequate alveolar ventilation can be maintained by the intercostal and accessory muscles of ventilation. A rapid, shallow breathing pattern is usually adopted. Not unexpectedly, nocturnal hypoventilation and oxyhemoglobin desaturation do occur, particularly during REM sleep (68-72). However, although complaints of dyspnea on exertion, orthopnea and poor sleep are not uncommon, chronic ventilatory failure usually does not occur in patients with isolated diaphragmatic disease in the absence of other disorders (73).

The pulmonary effects of diffuse neuromuscular disorders (NMD) vary widely. Although ventilatory muscle dysfunction generally parallels the overall musculoskeletal manifestations, the correlation is not always strong (74). While patients commonly present with symptoms related to diffuse muscle weakness, manifestations of chronic ventilatory failure may occasionally be noted on initial evaluation (75-79). Individuals with increasing disability related to NMD may adopt a sedentary lifestyle and have few pulmonary complaints despite significant declines in objective parameters of pulmonary function.

In patients with generalized NMD, particularly those with severe diaphragmatic dysfunction, sleep may be characterized by marked alveolar hypoventilation (70,71,80). Hypoventilation in NMD patients is most noteworthy during REM sleep, and this is largely attributable to placement of the full burden of ventilation on the dysfunctional diaphragm. Although the magnitude of these nocturnal events may not always be apparent to the clinician from aberrations in the awake arterial blood gases, the clinical importance is underscored by the results of one study of 20 NMD patients (14 with awake hypercapnia). There were direct relationships between the awake $Paco_2$ and both the nadir of Sao_2 during REM sleep and the fall in FVC in the supine (as compared to the erect) position (80). The

latter parameters are indicators of the degree of the diaphragm weakness.

"WON'T BREATHE": DISORDERS OF DECREASED VENTILATORY DRIVE

If the CNS ventilatory control center(s) provide(s) an inadequate prompt to breathe, alveolar hypoventilation may occur despite normal lung parenchyma and airways, normal ventilatory musculature and intact neural pathways to the ventilatory muscles. Although this type of hypoventilation is generally termed "central" in its etiology, it may be subdivided into "Primary Alveolar Hypoventilation" if it occurs in the absence of identifiable CNS disease and "Central Alveolar Hypoventilation" if it is associated with a defined etiology.

Primary alveolar hypoventilation (PAH) is a rare cause of chronic ventilatory failure. Initial reports emphasized its prevalence in males who are in their third or fourth decades (81) and a presentation characterized by congestive heart failure, hypercapnia-related mental status changes, sleep disturbances and daytime fatigue (82–85). When recognized in infancy, this disorder has been termed Ondine's Curse. Notably, affected individuals usually do not complain of dyspnea at rest or during exercise (82,83,85). Ventilatory responsiveness to hypercapnia and hypoxemia is negligible, an observation that is not explained by abnormalities of pulmonary mechanics (83,84,86). In fact, the ability of these patients to voluntarily hyperventilate and return their blood gases to near normal values attests to the integrity of the ventilatory "pump" (85,86). Similar results can be obtained using electrophrenic stimulation (82,83,87). Half of these patients also exhibit a decrease in ventilation during exposure to hyperoxia (83), suggesting persistent modulation of breathing by peripheral chemoreceptors.

PAH patients experience marked exacerbation of hypoventilation during sleep, thus emphasizing the importance of input from the behavioral control system in contributing to their ventilation during wakefulness (81,83,84,88). The nocturnal hypoventilation of PAH patients may be manifested by central apnea. One recent study of central sleep apnea patients revealed a subgroup of individuals with chronic ventilatory failure associated with reduced ventilatory chemosensitivity, some of whom met the criteria for PAH (89).

Central alveolar hypoventilation (CAH) may be associated with CNS lesions in or near the brainstem. This disorder has been observed in patients with vascular accidents (90,91), brainstem tumors, high spinal cord lesions (92,93), encephalitis (94–97), bulbar poliomyelitis (98,99), the Arnold–Chiari malformation (100), Shy–Drager syndrome (101) and possibly syph-

ilis (102). As is the case of patients with PAH, individuals with CAH have alveolar hypoventilation that is unexplained by pulmonary parenchymal disease or ventilatory muscle dysfunction. Patients are often able to voluntarily hyperventilate to a near normal P_{aCO_2} ; hence they "won't breathe" as opposed to "can't breathe". Patients with CAH, like those with PAH, often exhibit markedly abnormal breathing patterns during sleep, especially central apneas (97,103,104). Apart from symptoms that are specifically related to the underlying disorder precipitating CAH, the clinical presentation is similar to that of PAH.

MIXED DISORDERS

Obesity–hypoventilation syndrome

The obesity–hypoventilation syndrome (OHS) is characterized by obesity and chronic hypercapnia, often with coexistent OSA. Although only a small portion of patients (10%) with OSA develop OHS, those that do are usually morbidly obese (105). The development of OHS is probably multifactorial in nature. The exact contribution of the sleep-disordered breathing is unclear. Impaired central drive, ventilatory muscle dysfunction, abnormal load responsiveness and obstructive lung disease (106–108) are likely pathophysiologic elements of OHS, but their precise contributions remain to be elucidated and thus strict categorization of OHS into a "can't breathe" or "won't breathe" subgroup is not yet possible. As it is likely that more than one of these elements, which are described below, is involved in the pathogenesis of OHS, we have elected to include it in the group of "mixed" disorders.

Some but not all data support the theory that abnormal ventilatory regulation contributes to awake hypercapnia in OHS patients. Reduced hypercapnic ventilatory responsiveness has been reported in these patients (109–112), although potential blunting of the response by compensatory elevations of blood bicarbonate may confound interpretation of these data (113). Some OHS patients do retain the ability to voluntarily hyperventilate to a normal value of P_{aCO_2} (114), implying that chest wall and lung mechanics are not sufficiently impaired to prevent achievement of a normal P_{aCO_2} and thus leaving open the possibility of a pathophysiologic role for abnormal ventilatory drive. Additionally, coexistent OSA in OHS patients may play a role in decreasing ventilatory drive, because it has been shown that ventilatory responsiveness to CO_2 is decreased in obese OSA patients relative to obese non-OSA individuals (110). On the other hand, in a study comparing the CNS ventilatory drive (mouth occlusion pressure, $P_{0.10}$) and diaphragmatic EMG responses to progressive hypercapnia between groups of normal

TABLE 3. *Modalities for evaluation of chronic alveolar hypoventilation*

Arterial blood gas analysis—the confirmatory test
Physical examination—with emphasis on thoracic and neurologic examinations
Thyroid function studies
Serum electrolytes, calcium, magnesium, phosphorus, hematocrit
Chest radiograph
Pulmonary function studies
Spirometry
Maximal inspiratory and expiratory pressures
Maximal voluntary ventilation
Diaphragmatic studies
Fluoroscopy
Transdiaphragmatic pressure measurement—with or without twitch stimulation
Chemoresponsiveness evaluation
Progressive hyperoxic hypercapnia
Progressive eucapnic hypoxia
Central nervous system evaluation
Computed tomography
Magnetic resonance imaging
Lumbar puncture
Polysomnography

subjects, obese subjects, obese eucapnic OSA patients and patients with OHS, Lopata and coworkers were unable to distinguish the eucapnic OSA patients from the OHS patients (115). Furthermore, OHS patients may return to eucapnia following therapy (continuous positive airway pressure or tracheostomy) without a change in their hypercapnic responsiveness (112), suggesting that some abnormality other than or in addition to altered ventilatory drive must be present.

Conceptually, patients with OHS are susceptible to ventilatory muscle fatigue because of obesity-related alteration of thoracic mechanics, decreased ventilatory efficiency, underlying lung disease and, if there is co-existent OSA, repetitive nocturnal airway occlusions. OHS patients do have markedly reduced chest wall compliance (116,117), which leads to increased energy costs of breathing (118). In addition, ventilatory muscle performance is impaired in obesity because of abnormal ventilatory system mechanics and metabolic inefficiency of the ventilatory muscles (116, 119–121). Conceivably these factors contribute to the declines in MIP and maximal voluntary ventilation (MVV) observed in OHS patients (117). When OSA or upper airway resistance syndrome (122) coexists with OHS, it confers a predisposition to ventilatory muscle fatigue because of repetitive inspiratory efforts against an occluded upper airway. The significance of ventilatory muscle dysfunction in the pathogenesis of OHS is reinforced by the observation that weight loss is associated with increased MVV and forced vital capacity (FVC) as well as reduced P_{aCO_2} despite little change in ventilatory system compliance (117). Along these lines, significant improvement in hypercapnic ventilatory responsiveness may occur within 24 hours of initiating

positive airway pressure in OHS patients (123), and the rapidity of this response may be consistent with relief of ventilatory muscle fatigue.

OHS patients are clearly subjected to abnormal ventilatory loads including those imposed by chest wall mass, increased elastance of the ventilatory system and possibly increased upper airway resistance (124,125). Load compensation, the action taken to defend alveolar ventilation in the presence of a mechanical stress on the system, may be abnormal in individuals with OHS, but its presence in this disorder and its role in the development of hypercapnia has yet to be defined.

EVALUATION OF PATIENTS WITH CHRONIC ALVEOLAR HYPOVENTILATION

There is no uniform clinical presentation that identifies patients with alveolar hypoventilation with a high degree of sensitivity and specificity. Clinical clues regarding the presence of hypercapnia may be provided by such signs and symptoms as morning headache, sleep disruption, daytime fatigue, mental status changes and the development of dependent edema, orthopnea or other manifestations of pulmonary vascular hypertension and cor pulmonale that are not readily explained by other diagnostic entities. As noted previously, dyspnea is not uniformly present. Clinicians must maintain a high index of suspicion in order to perform the definitive test for alveolar hypoventilation, arterial blood gas analysis. The subsequent evaluation may include a number of examinations which are detailed below and outlined in Table 3.

Alveolar hypoventilation should not be considered a disease, but rather a manifestation of a disease process that in turn should be the object of diagnostic efforts. The physical examination may help guide the evaluation and close attention should be paid to chest wall configuration, signs of pulmonary parenchymal disease, and the functional integrity of the ventilatory muscles. Neurologic examination may also provide insight into the etiology of the hypoventilation. A chest radiograph may be useful in defining the contributions of underlying lung disease, thoracic cage abnormalities or diaphragmatic dysfunction to the development of hypoventilation or in documenting the presence of pulmonary hypertension.

Spirometric evaluation and measurement of lung volumes, MVV, MIP and maximal expiratory pressures (MEP) yield information regarding lung and ventilatory muscle function. If performed with maximal effort, measurement of the MIP and MEP may provide an early indication of ventilatory muscle weakness in patients with NMD (74,126–130). In contrast, the FVC is reduced only after there has been significant im-

pairment of muscle function. In patients with known disorders, these tests may also be of use in monitoring the progression of disease (131). Although these measurements may not definitively predict development of ventilatory failure in individual patients, awake hypercapnia appears to be particularly likely in NMD patients when the FVC falls below 55% of predicted values (129,132). The MIP and MEP also have prognostic utility in NMD, with hypercapnia particularly likely when ventilatory muscle strength falls below 30% of predicted (132). The MVV is theoretically an estimate of an individual's maximum sustainable ventilation (133), and abnormalities may indicate impending ventilatory failure. As with the MIP and MEP, it is critical that the patient be motivated and maximal effort made in order for the MVV to provide an accurate reflection of ventilatory muscle function.

A significant reduction in FVC when changing from the erect to supine position in patients with NMD and/or diaphragm dysfunction and an MIP less than 60 cm H₂O in amyotrophic lateral sclerosis patients reflect a degree of diaphragm weakness which predisposes to nocturnal oxyhemoglobin desaturation (80,134). Relative sparing of expiratory muscle strength is often noted in patients with polyneuropathy or distal muscle diseases (74), as opposed to the more profound expiratory weakness associated with amyotrophic lateral sclerosis, Duchenne's muscular dystrophy, myotonic dystrophy and myasthenia gravis (135–138).

Individuals in whom there is concern about isolated diaphragmatic weakness or paralysis require specific evaluation. Fluoroscopic imaging of diaphragm motion has been used for this purpose, but in patients with bilateral diaphragmatic paralysis, pseudo-normal diaphragm movement may lead to test misinterpretation by the inexperienced clinician and thus diminish its value (139). Direct measurement of transdiaphragmatic pressure (P_{DI}) using esophageal and gastric balloons is the most precise quantitative technique for assessing diaphragmatic function. Measurements may be obtained during maximal inspiratory efforts, sniffing maneuvers, and inspiration to maximum volume. Measurement of P_{DI} during sniffing maneuvers in individuals with normal lung mechanics appears to be particularly useful because of ease of performance and reproducibility of results (140–143).

Although generally not widely performed outside of research facilities (144–146), there may be considerable utility in measuring P_{DI} during electrical twitch stimulation of the phrenic nerves. Performance of maximal inspiratory maneuvers during airway occlusion with and without supramaximal phrenic twitch stimulation may prove to be clinically useful in diagnosing "central" respiratory fatigue (51,147,148), although further studies are needed to determine if this

somewhat invasive test offers distinct advantages over the more widely available conventional tests.

In patients with chronic hypoventilation that is unexplained by airway obstruction, a restrictive process or NMD, abnormal central control of respiration should be considered. Demonstration of the ability to voluntarily "hyperventilate" down to a normal P_aCO₂ may provide indirect evidence of a central defect ("won't breathe") (82,85,86). Tests of hypoxic and hypercapnic chemoresponsiveness can be performed in specialized laboratories and may provide diagnostic insight. A search for CNS disease (Table 1) when an acquired central defect in chemoresponsiveness is suspected may include brainstem magnetic resonance imaging, cranial computed tomography and lumbar puncture.

In the absence of other obvious etiologies of alveolar hypoventilation, an assessment of thyroid function should be conducted to exclude hypothyroidism. Screening for serum calcium, potassium (hypokalemic periodic paralysis), magnesium and phosphorus abnormalities or acid maltase deficiency may reveal the etiology of chronic muscular weakness in selected patients. Measuring the hematocrit may provide information regarding the chronicity and physiologic impact of hypoventilation or the presence of isolated nocturnal hypoventilation and desaturation.

The decision to perform nocturnal PSG in an individual with chronic hypoventilation must be made in response to the clinical suspicion of nocturnal alveolar hypoventilation/desaturation or concurrent OSA in conjunction with a reasonable expectation that the study will provide clinically useful information. An increasingly large body of knowledge supporting the therapeutic utility of nocturnal noninvasive positive pressure ventilation (NIPPV), particularly in patients with restrictive and central causes for hypoventilation, heightens the value of efforts to identify nocturnal hypoventilation and its etiology. Assessing the magnitude of hypoventilation and oxyhemoglobin desaturation during sleep may also yield insight regarding the likelihood of developing cardiopulmonary dysfunction in patients who are left untreated.

Some investigators have advocated monitoring oxyhemoglobin saturation alone as a screening tool to detect or exclude patients with sleep-disordered breathing (149). However, the usefulness of oximetry in quantifying hypoventilation may be significantly limited by the sigmoidal shape of the oxyhemoglobin dissociation curve, on which minimal degrees of desaturation may be recorded despite substantial reductions in P_aO₂ associated with hypoventilation. The diagnostic utility of oximetry may further be limited in patients receiving supplemental oxygen during sleep. Thus direct assessment of nocturnal P_aCO₂ is a desir-

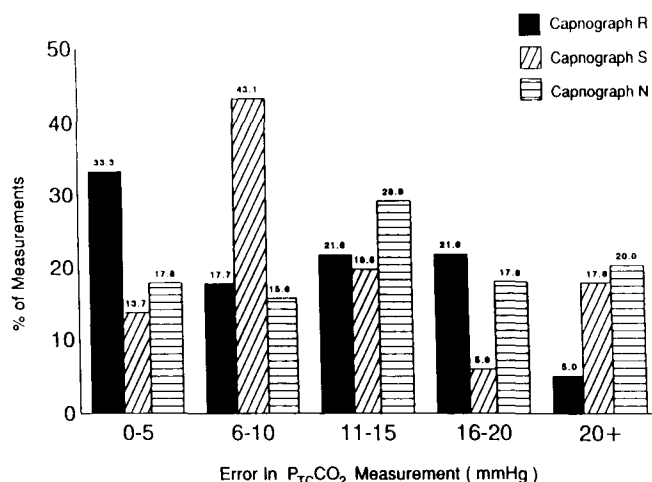


FIG. 3. Distribution of the $tcPCO_2$ error for three different capnographs across all measurements made in the study population. Figure used with permission from (156).

able, but invasive, measurement to determine the degree of nocturnal hypoventilation. Two noninvasive monitoring methods that have been considered to reflect $Paco_2$ include measurement of end-tidal carbon dioxide tension (P_{ETCO_2}) and transcutaneous carbon dioxide ($tcPCO_2$). The P_{ETCO_2} provides a reasonable estimate of $Paco_2$ during mechanical ventilation in endotracheally intubated patients in the absence of parenchymal lung disease (150,151). This parameter loses some measure of its accuracy, however, in the presence of increased dead space (152–155). It is therefore not surprising that P_{ETCO_2} is a poor reflection of $Paco_2$ in nonintubated individuals suspected of having nocturnal hypoventilation or sleep-disordered breathing while they are sleeping on room air, supplemental oxygen or noninvasive positive pressure ventilatory support with constant flow systems such as bi-level positive airway pressure (156).

Transcutaneous Pco_2 monitoring has been considered as an alternative to invasive blood gas monitoring. Because of relatively slow response times, however, these monitors are unacceptable when it is necessary to identify rapid changes in Pco_2 . In early studies involving hemodynamically stable ICU patients and patients undergoing anesthesia, data from these monitors have a strong correlation between $Paco_2$ and $tcPCO_2$ when correction factors for the heating of the skin probe are applied (157–166). However, despite strong correlations over a relatively large number of data points, there is often a variable degree of scatter in the relationship between $Paco_2$ and $tcPCO_2$, limiting the utility of individual $tcPCO_2$ measurements in predicting $Paco_2$ (158,161,165). In evaluating the accuracy of three $tcPCO_2$ monitors in sleeping patients suspected of having sleep-disordered breathing or nocturnal hypoventilation,

we observed that the magnitudes of errors between $tcPCO_2$ and $Paco_2$ limited the clinical usefulness of the monitors (Fig. 3) (156). The coefficients of determination were such that the $tcPCO_2$ predicted only 20–64% of the variability in $Paco_2$ (156). In summary, although $tcPCO_2$ and P_{ETCO_2} monitoring may provide information about trending of $Paco_2$ in select groups of patients, neither modality has been shown to provide sufficiently accurate or consistent results to warrant confidence for determining the degree of nocturnal hypoventilation.

THERAPY

Management efforts in caring for patients with chronic hypoventilation should be directed toward preventing or minimizing hypercapnia and hypoxemia and their physiologic consequences. To the extent possible, application of the often used medical axiom “treat the underlying disease” is appropriate, although there are relatively few individuals with chronic hypoventilation in whom disease-specific therapy of the primary medical problem is feasible or which will return ventilation to normal. For this reason, treatment of patients with chronic hypoventilation has focused on the prevention or amelioration of hypercapnia, treatment of secondary complications such as pulmonary hypertension and congestive heart failure, and improvement of the functional status of affected individuals. Nocturnal administration of supplemental oxygen to patients with chronic ventilatory failure is intuitively pleasing, as it has the potential to ameliorate the declines in cardiovascular function related to hypoxemia/hypoventilation during sleep. However, supplemental oxygen may prolong apneas and consequently worsen respiratory acidosis in OSA patients with or without concomitant COPD (167–169). Its application, therefore, may require PSG monitoring and should not preclude consideration of other therapeutic modalities outlined below.

Pharmacologic therapy

Medroxyprogesterone (MPA) is a ventilatory stimulant (170) which has been reported to be useful in the therapy of patients with chronic hypoventilation. In two small uncontrolled studies in OHS patients, MPA therapy was associated with improvement of both hypercapnia and hypoxemia, with deterioration of blood gases noted upon discontinuation of therapy (171,172). Use of MPA is associated with side effects (173), and presently there is little clinical evidence to support its long-term use in OHS. Similar usage of MPA in hypercapnic COPD patients results in reductions of $Paco_2$

during wakefulness (174–176) and NREM sleep (177); however no long-term benefits from use of MPA have been demonstrated, and its use cannot be advocated at the present time.

Acetazolamide (ACT) increases ventilatory drive by increasing urinary bicarbonate excretion, thus creating a metabolic acidosis. Compared to MPA, ACT appears to be a weaker stimulant in COPD patients (174), and it has little role in the treatment of chronic ventilatory failure.

Diaphragmatic pacing

The development of radiofrequency electrophrenic stimulation has allowed diaphragmatic pacing to be performed using an implantable receiver that is powered and controlled by an external transmitter (178). The receiver stimulates the phrenic nerve(s) via an attached electrode(s). For successful diaphragmatic pacing, both intact phrenic nerve conduction and diaphragmatic function must be demonstrated (179). Unilateral diaphragmatic pacing may provide satisfactory ventilation in patients with abnormal ventilatory drive (83,178,180), and by performing this more limited procedure, the risks of bilateral phrenic trauma and infection may be minimized. Significantly improved blood gases have been documented in these individuals, particularly during sleep, and selected patients may do well with exclusively nocturnal pacing (83,178,181). Under both of these conditions, the phrenic–diaphragm pathway remains intact. Diaphragmatic pacing is not an appropriate therapy for hypoventilation related to diseases with increased work of breathing (COPD, KS) or neuromuscular weakness.

Diaphragmatic pacing is not without complications. Stimulation during sleep may precipitate upper airway obstruction during inspiration due to lack of coordination between the diaphragm and upper airway dilator muscles (182). This has resulted in the need for tracheostomy in many patients (103). Pacing-induced diaphragmatic fatigue was recognized in some patients shortly after initiation of long-term pacing and may be associated with permanent damage to the nerve or diaphragm (178,180,183). Deconditioning of the diaphragm appears to play a major role in its occurrence. The use of pacing schedules that slowly increase stimulation periods (87,183–186), multipolar phrenic electrodes that stimulate different motor units of the diaphragm (185), and low frequency stimulation (183,187,188) have helped alleviate this problem. In alveolar hypoventilation due to abnormal central drive, pacing of the diaphragm should thus be considered as a therapeutic alternative in individuals able to protect their airway.

Ventilatory assistance

In the past decade, significant advances have been made in the modalities which are available for augmentation of ventilation in patients with chronic respiratory failure. Prior to this period, the only methods available for this purpose involved body ventilators or positive pressure ventilation through a tracheostomy. More recently, acquiring the ability to provide positive pressure ventilation in a noninvasive fashion has provided an important new way to treat these patients. For successful application, each of these methods requires careful patient selection and monitoring of therapy. As will be discussed, the benefits of using assisted ventilation are not equally applicable for all disease processes associated with chronic ventilatory failure.

Ventilatory assistance with body ventilators

The use of body ventilators to augment ventilation involves the cyclical application of negative and/or positive pressure around the trunk (in whole or in part) in order to indirectly inflate or deflate the lungs. Initial attempts with this technique began in the 19th century (189), and widespread usage occurred during this century's polio epidemics. The most widely applied body ventilators have used negative pressure ventilation (NPV). The reader is referred to a recent review for a description of rocking beds and pneumobelts (190). The NPV devices vary in size from the "iron lung", which entirely envelops patients below the neck, to the cuirass, which is a rigid shell that fits over only the chest and upper abdomen. The efficiency of NPV is dependent upon the surface area of the trunk to which pressure is applied as well as the compliance of the lung and chest wall (190). Thus while devices such as the cuirass are relatively small and quite portable, their relative convenience is at the expense of being less efficient than the large and more cumbersome iron lung. As is the case with diaphragm pacing, a common complication of NPV is upper airway obstruction during sleep (191), which is created by lack of physiologic linkage between the development of negative intra-airway pressure and increased upper airway dilator muscle activity. Recognition of this complication is particularly important, because NPV is often applied initially during sleep in individuals with chronic ventilatory failure. Continued symptoms related to nocturnal hypoventilation in patients on NPV warrant a PSG to look for this complication, not empiric increases in the level of therapy. Should upper airway obstruction occur during NPV, possible solutions include tracheostomy, concomitant CPAP, or switching to an alternative therapeutic modality.

Use of nocturnal NPV on a chronic basis to treat

hypercapnic ventilatory failure has succeeded in improving ventilatory symptoms and reducing Paco_2 in patients with a variety of restrictive thoracic diseases and neuromuscular diseases (192–196). Long-term survival with this therapy has been reported in the latter group of patients (197,198). Improvement has also been noted in patients with respiratory failure due to abnormal central respiratory drive (199). In patients with COPD, short term application of NPV can improve ventilatory muscle function and decrease Paco_2 (200,201). However, the use of long-term NPV with daily to weekly frequency in hypercapnic COPD patients has had mixed results. Some studies reveal improved ventilatory muscle function and Paco_2 after therapy (202–204), and others reveal that COPD patients do not clearly benefit from this therapy and/or are unable to tolerate it (205,206). One investigation showed no additional benefit to severe COPD patients when NPV was added to a pulmonary rehabilitation program (207).

Ventilatory assistance via tracheostomy

Application of chronic positive pressure ventilation (PPV) via a tracheostomy may take place as a planned intervention or as a result of failure to wean an individual from mechanical ventilation initiated as an acute lifesaving therapy. Although creation of a tracheostomy during the latter may improve patient comfort and still allow for lower airway access and pulmonary toilet, its chronic use may be undesirable because of disfigurement, difficulty with speaking, tracheal stenosis or tracheomalacia (208). Thus its usefulness in the management of chronic ventilatory failure is changing as noninvasive methods of ventilation become more widely used. Its use is still appropriate in patients who are unable to maintain a stable protected airway or fail other methods of ventilatory assistance. Use of nocturnal PPV via tracheostomy in hypercapnic patients with restrictive chest wall disorders has been associated with rapid improvement of both respiratory symptoms and awake Paco_2 , and it has decreased the need for hospitalization during long-term followup (209–211). The noted improvement in daytime gas exchange with the use of nocturnal PPV has important implications with regards to the ability of patients to perform activities of daily living in an unencumbered fashion, and this will be noted with other methods of ventilatory assistance as well. Use of PPV via tracheostomy can also be considered for treatment of chronic respiratory failure due to etiologies other than restrictive chest wall impairment, such as neuromuscular disease or central drive abnormalities. In hypercapnic COPD patients, limited evidence suggests that daytime use of PPV via tracheostomy may be helpful in improving

respiratory muscle function and Paco_2 (202). In general there has been less enthusiasm for initiating this therapy on an elective basis in COPD patients than in patients with restrictive disorders, because long-term survival has been considered to be poor in COPD. However, a recent retrospective, uncontrolled study of home PPV via tracheostomy in 259 COPD patients, most of whom had this therapy initiated after failure to wean from mechanical ventilation after acute respiratory failure, revealed a 44% five-year survival rate (252). The decision for instituting this therapy in any individual must be based upon the nature of the underlying disease process, long term prognosis, applicability and tolerance of other modalities, and the patient's wishes (212).

Noninvasive positive pressure ventilatory assistance

Development of NIPPV has provided an important therapeutic alternative to use of PPV via tracheostomy or NPV. The current standard of care for patients with chronic ventilatory failure is now primarily NIPPV, with masks and nasal prongs replacing tracheostomy tubes as the interface between the patient and the positive pressure device.

Using NIPPV is intuitively attractive because it avoids the need for tracheostomy and promotes upper airway patency. Initial attempts to administer NIPPV to awake COPD patients involved intermittent application through a mouthpiece and were without demonstrable benefit (213,214). More recently, however, patients with ventilatory failure related to previous poliomyelitis have been found to enjoy an excellent response to both awake and asleep applications of NIPPV through a mouthpiece, with resultant improved gas exchange (215). The use of a mouthpiece requires competent buccopharyngeal muscles however, and air leaks and aspiration of gastric and mouth contents are potential problems. Given the limitations of this interface, there has been considerable enthusiasm for application of NIPPV by the nasal route, using interfaces similar to those used to administer CPAP therapy to sleep apnea patients. Use of nasal NIPPV still mandates intact bulbar function for protection of the upper airway. Individuals with diffuse muscular weakness who cannot ventilate on their own in the event of a dislodged interface are not considered suitable candidates for long-term NIPPV. Complications related to the nasal route of NIPPV are similar to those which may be encountered with CPAP therapy for sleep apnea, and include nasal drying, nasal congestion or rhinorrhea, discomfort from a suboptimal mask fit, skin irritation, air leakage in to the eyes and epistaxis (216). When complications related to nasal masks do

occur they are generally easily treated (217). If there is a mask leak of sufficient magnitude to preclude adequate ventilatory assistance, an alternative interface such as an oral-nasal mask may be used (218,219).

Because worsening hypoventilation is recognized to occur during sleep in patients with awake hypoventilation, efforts have focused on administering NIPPV during sleep. Initially, small series and case reports attested to successful nocturnal NIPPV with volume-cycled ventilators in patients with NMD, OHS, restrictive disorders and central ventilatory defects (217,220–231,253). As with other modalities of nocturnal ventilatory assistance, many patients had significantly improved awake arterial blood gases with use of nasal NIPPV. Subsequently, larger studies over longer follow-up periods (years) have confirmed the findings of the initial reports (216,232,233).

NIPPV may be provided by pressure or volume-limited machines. Bi-level positive airway pressure devices which provide a form of pressure support therapy are an alternative to NIPPV with portable, volume-cycled ventilators (234). With a bi-level positive airway pressure device, inspiratory and expiratory positive airway pressures can be independently adjusted to augment alveolar ventilation and, if needed, to maintain upper airway patency during sleep. Currently available bi-level positive airway pressure devices are relatively leak tolerant and cycle properly in the presence of leaks that are inherent with mask or nasal prong ventilation (i.e. at the mask-skin interface or through the mouth). Early small studies of noninvasively applied nocturnal bi-level positive airway pressure therapy in patients with chronic ventilatory failure due to NMD, OHS, restrictive disorders and central ventilatory defects have been promising, with improved arterial blood gases and subjective symptom improvements being reported (234–237). Prescribing NIPPV to carefully selected patients with hypoventilation due to neuromuscular or chest wall disorders is appropriate to alleviate symptoms and may also prolong life (233,238).

There is no consistent evidence that NIPPV provides effective therapy for COPD patients with chronic hypoventilation. COPD patients are often intolerant of the mask or prong interface, thus precluding application of therapy (239,240). In addition, although there are reports of improved gas exchange and Paco_2 after chronic NIPPV therapy in COPD patients, these studies are small and generally uncontrolled (220,240,241). Long-term study of NIPPV in COPD patients has been plagued by high dropout rates (216). Until such a time when more compelling evidence is available to support its use, advocating widespread application of NIPPV in COPD patients is not appropriate.

Ventilatory assistance: mechanism of action and titration of therapy

The mechanism(s) by which application of nocturnal ventilatory assistance result(s) in improved ventilatory symptoms and Paco_2 in patients with hypoventilation due to NMD, OHS, restrictive disorders and central ventilatory defects is unclear. The mechanism may vary among the patient groups but, in general, may include improved ventilatory muscle function due to relief of chronic fatigue, improved ventilatory muscle function due to relief of chronic hypercapnia and hypoxemia, and normalization of chronically blunted central ventilatory drive. With regard to ventilatory muscle function, use of these therapies may acutely reduce diaphragmatic EMG activity (204,206,242–247), perhaps reflecting muscle rest, with resultant improvements in ventilatory muscle strength and/or endurance (192,200–204,225,228,248). It is not possible, however, to exclude changes in central ventilatory drive occurring in conjunction with this therapy.

Because of the uncertainty regarding the mechanism for improved gas exchange in these patients after institution of nocturnal NIPPV, there is uncertainty regarding the best method for establishing the optimal level of ventilatory assistance. If muscle rest is the therapeutic goal, nocturnal therapy should be adjusted with the aid of diaphragm and sternocleidomastoid EMG monitoring (249). However, use of surface electrodes to monitor the diaphragm EMG is technically difficult in these patients, who often have distortion of the chest wall. Using an esophageal electrode to monitor diaphragm function and needle electrodes to assess accessory muscle activity is invasive and not widely used in the clinical setting. If reversal of blunted central ventilatory drive is desired, then therapy could be specifically directed towards preventing hypercapnia during sleep. To accomplish this during titration of nocturnal NIPPV, Paco_2 , or an accurate reflection of Paco_2 , must be assessed. Such monitoring of this variable will not only assure that treatment goals are met, but also that potentially dangerous hypocapnia and respiratory alkalosis are not inadvertently precipitated. In the absence of systematic data to provide guidance, the objective of titration in our laboratory is to establish a level of ventilatory assistance that reduces the Paco_2 to no more than 10 mm Hg below the awake (hypercapnic) value or at least prevents sleep-related increases in Paco_2 .

SUMMARY

Chronic alveolar hypoventilation may present in an insidious fashion with nonspecific manifestations. The clinician should be aware of the potential for devel-

oping this condition in patients with certain thoracic and systemic diseases. Once chronic alveolar hypoventilation is confirmed with arterial blood gas analysis, a systematic evaluation can often point to the underlying etiology. As sleep in affected individuals is often associated with marked worsening of gas exchange and may also contribute to worsening daytime cardiopulmonary dysfunction, polysomnography is often indicated to determine the severity of nocturnal aberrations and to look for coexistent obstructive sleep apnea. Therapy of chronic alveolar hypoventilation often focuses on elimination of the nocturnal deterioration in gas exchange, and recent applications of noninvasive positive pressure ventilation during sleep have proven useful in the management of individuals with obesity-hypoventilation syndrome, restrictive thoracic disorders, neuromuscular diseases and central causes for hypoventilation. It is unclear whether wide-spread application of nocturnal ventilatory support to patients with chronic ventilatory failure due to chronic obstructive pulmonary disease is of long-term benefit.

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