Hypoventilation Syndromes

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KEYWORDS

• Hypoventilation • Hypoxia • Hypoxemia • Hypercapnia
• Chest wall disease • Neuromuscular disease
• Control of breathing

DEFINITION

Hypoventilation is conventionally said to exist when arterial pCO_2 ($PaCO_2$) exceeds the upper limit of normal. Data for the normal range of this parameter began to appear in the literature in about 1942, with most sources estimating a mean value of about 38 mm Hg and the upper 95% confidence limit to be about 45 mm Hg.[1] Consequently, a value of $PaCO_2$ greater than 45 mm Hg (presumably only applicable at or near sea level) is commonly used to define the presence of hypoventilation. Basic pulmonary physiology teaches us that arterial pCO_2 is proportional to CO_2 production divided by alveolar ventilation, and that alveolar ventilation is the product of tidal volume (V_t), respiratory rate (RR), and the dead space to tidal volume ratio (V_d/V_t).

MECHANISMS OF HYPOVENTILATION

Theoretically, elevated levels of $PaCO_2$ can result from either overproduction of carbon dioxide or reduced alveolar ventilation. In the real world, overproduction is rarely a factor except in situations whereby alveolar ventilation is already marginal.[2,3] For the purposes of this review, hypoventilation can therefore be attributed to reduced alveolar ventilation; in turn, this may be the result of reduced minute ventilation (decreased tidal volume and or respiratory rate) or increased V_d/V_t, or some combination of these factors. Yet another way of looking at hypoventilation pathophysiology holds that reduced alveolar ventilation can be attributed to either: (1) decreased ventilatory drive (''won't breathe''), or (2) worsening respiratory mechanics and/or severely deranged gas exchange. (''can't breathe'').

Ventilatory Drive

In this age of polypharmacy, the administration of respiratory depressant medications (opiates; benzodiazepines or other sedative medications that depress ventilatory drive) may be the most common etiologic agent for reduced central ventilatory drive.[4] However, a variety of central nervous system (CNS) pathologies (usually involving the brainstem or diencephalic regions) can impair control of breathing and lead to hypoventilation; both congenital and acquired etiologies have been described.[5,6] In addition, impaired control of breathing may occur in some disorders that have a major component of abnormal respiratory mechanics, for example, obesity hypoventilation (Pickwickian) syndrome (OHS). It has been posited that depressed ventilatory drive in these conditions is an adaptive CNS response to the

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hypoventilation initially attributable to abnormal respiratory mechanics: increased $PaCO_2$ leads to elevated levels of cerebrospinal fluid bicarbonate, which then blunts the usually vigorous ventilatory response to elevated $PaCO_2$.[7] However, other possibilities include compensatory metabolic alkalosis from renal bicarbonate retention[8] or other factors as yet unknown.[9] Among these other possible factors is intriguing evidence concerning leptin's role as a ventilatory stimulant, and acquired resistance to this effect of leptin in some patients with OHS as a possible factor in mediating hypoventilation.[10] Finally, a small number of patients exhibit diurnal hypoventilation even after all other conditions (no apparent CNS lesion, primary lung disease, skeletal malformations, significant obesity, or neuromuscular disorder) have been excluded. Some of these patients exhibit other CNS abnormalities, particularly related to hypothalamic function, and it seems probable that many have anatomic or functional defects of central ventilatory control that have not yet been well characterized.[11,12]

Respiratory Mechanics

Altered respiratory mechanics can induce hypoventilation through several mechanisms. Hypoventilation in obstructive airways disease is readily explained; it is intuitively obvious that airflow limitation will necessarily constrain maximal minute ventilation and thus maximal alveolar ventilation, and this has been repeatedly demonstrated in such patients.[13] Only a fraction of maximal voluntary ventilation is sustainable over the long term (usually about 50%), and if airflow obstruction is profound enough to reduce this maximum sustainable ventilation below the threshold for maintaining eucapnia, hypoventilation will occur by definition. Restrictive ventilatory impairment from nonneuromuscular chest wall disease or interstitial lung disease usually does not impair maximum sustainable minute ventilation until late in the course of the disorder because compensation for reduced tidal volumes due to the restrictive disorder can usually be attained by increasing respiratory rate. However, shallow tidal volumes necessarily result in higher values of V_d/V_t, and at some point in the progression of disease the combination of elevated dead space fraction and reduced maximum sustainable minute ventilation will produce alveolar hypoventilation and hypercapnia.[14,15] A combination of these factors leads to hypoventilation in neuromuscular disorders affecting the ventilatory muscles. As in obstructive disorders, maximum sustainable ventilation is generally reduced in tandem with indices of vital capacity and airflow,[16,17] but in addition a rapid shallow breathing pattern is assumed, leading to higher V_d/V_t as seen in other restrictive chest wall diseases and interstitial lung disease.[18]

Gas Exchange

In addition to the effect of rapid shallow breathing on dead space ventilation, disorders that obliterate pulmonary vasculature will result in lung units that are ventilated but not well perfused, thus increasing V_d/V_t by increasing physiologic dead space. These disorders include pulmonary vascular diseases such as primary pulmonary hypertension, pulmonary hypertension caused by collagen-vascular disorders, and pulmonary hypertension from chronic pulmonary thromboembolic disease; and interstitial lung diseases such as usual interstitial pneumonia, sarcoidosis, or adult respiratory distress syndrome (ARDS). However, alveolar hypoventilation from this mechanism usually does not occur until very late in the course of disease because alveolar ventilation can usually be maintained by increasing minute ventilation (by using higher respiratory rates) as noted earlier. However, hypercapnia from this mechanism may be seen in end-stage ARDS patients receiving invasive positive pressure ventilation despite maintenance of normal or even elevated minute ventilation.[19]

HYPOVENTILATION DUE TO NEUROMUSCULAR AND CHEST WALL DISORDERS

Obesity Hypoventilation Syndrome

Burwell and colleagues[20] first used the term Pickwickian syndrome in 1956 to describe patients with obesity, awake hypercapnia and hypoxemia, sleepiness, polycythemia, and *cor pulmonale*. The eponym was based on the character "Joe" in Charles Dickens' *The Posthumous Papers of the Pickwick Club* who was described as "a natural curiosity," "…always asleep. Goes on errands fast asleep, and snores as he waits at table."[21] The disorder was later rechristened with the less literary, but probably more accurate, name of obesity hypoventilation syndrome (OHS) because it is more likely that Joe had obstructive sleep apnea syndrome rather than necessarily suffering from OHS. A diagnosis of OHS commonly requires awake alveolar hypoventilation ($PaCO_2$ >45 mm Hg) in an obese patient (body mass index [BMI; body weight divided by height squared] >30 kg/m^2; other investigators have used >35 kg/m^2) with no other identifiable cause of hypoventilation.[22]