



Etiology and Management of Hypoventilation Syndromes

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ABSTRACT

A number of diseases affecting central ventilation, breathing mechanics or both, characterize hypoventilation syndromes. The incidence of hypoventilation syndromes varies according to the underlying reason. The hypoventilation syndrome's clinical symptoms are generally vague and are in most cases due to the underlying clinical condition. More individuals develop hypercapnia and hypoxemia as hypoventilation continues to worsen. Therefore, clinical indications of hypoxemia such as cyanosis, and evidence of hypercapnia may also be present. Regardless of the etiology, successful hypoventilation therapy focuses on the underlying illness and noninvasive ventilation. Treatment for these diseases includes integrated main disorder treatment and, increasingly, non-invasive positive pressure breathing. In this paper, we overview current evidence regarding different etiologies and management of hypoventilation syndromes. Data was collected during the period of 6 months searching Pubmed, EPISCO, Web of science, Google scholar databases to include papers with relative topics.

Keywords: ventilation, hypoventilation, positive pressure ventilation, obesity, congenital.

1. INTRODUCTION

A number of diseases affecting central ventilation, breathing mechanics or both, characterize hypoventilation syndromes. Various processes can lead to hypoventilation associated with various medical diseases, including central ventilation control defects, mechanical breathing obstacles and gas exchange irregularities that contribute to increased ventilation of dead spaces [1].

The incidence of hypoventilation syndromes varies according to the underlying reason. The chronic obstructive lung disease affecting more than 15 million people in the United States is the most prevalent of these diseases. Most hypoventilation patients are elderly [2].

Obesity hypoventilation syndrome has significant cardiovascular and metabolic effects when unknown as clinically relevant disease. The mechanical difficulties of airflow blockage and an increase in dead space are the cause of asthma and COPD hypoventilation. Air weakness occurs in hypoventilation [3] in neuromuscular disease [3]. Decreases in thoracic volume and restricted chest expansion emphasize restrictive ventilation deficiencies in chest wall hypoventilation. Central alveolar hypoventilation is a genetically driven central respiratory control failure [4].

The presence of hypoxemia together with hypercapnia aggravates the clinical presentation observed with hypoventilation syndromes and patients with hypoventilated disease may develop severe hypoxemia. The acute or chronic hypoventilation can be caused by many factors [5].

The hypoventilation syndrome's clinical symptoms are generally nonspecific and are in most cases due to the underlying clinical condition. Developments differ depending on the severe nature of hypoventilation, the rates of hypercapnia development and the degree of correction for possible respiratory acidosis [6]. More individuals develop hypercapnia and hypoxemia as hypoventilation continues to worsen. Therefore, individuals may have hypoxemia clinically, such as cyanosis, and simultaneously exhibit symptoms of hypercapnia [7]. Anxiety may sometimes develop to delirium as additional symptoms of increasing hypoventilation. Effective hypoventilation is targeted at the underlying illness and the use of noninvasive ventilation, whatever the cause. Treatment for these diseases includes integrated main disorder treatment and, increasingly, non-invasive positive pressure ventilation [8,9].

2. OBESITY-HYPOVENTILATION SYNDROME

The presence of obesity (BMI 30 kg/m²) and daytime arterial hypercapnia (PaCO₂ 45 mmHg) in the absence of other causes of hypoventilation is classified as obesity hypoventilation syndrome (OHS) [10]. OHS prevalence is between 0.15 and 0.3 per cent in the adult population with a BMI of >40 kg/m². The population with obstructive sleep apnea has a higher prevalence obstructive sleep apnea (OSA). In individuals with OSA obesity, many studies estimate OHS prevalence between 10 and 20 percent [11]. The decreased quality of life and longer admission rate and duration in the critical care unit are linked to obesity hypoventilation. The death rate is considerably high among individuals with

additional diseases such as diabetes and asthma, with 23 per cent over 18 months and 46 per cent over 50 months. Early application of CPAP can lower the corresponding mortality by 10% [12].

It is not straightforward to interact with the respiratory system, as one impacts the other through several methods. Excessive accumulation of fat over the chest and abdomen has negative effects on mechanics of the lung respiratory system, resulting to physiological upheavals and disabilities in certain people following reduction of weight [13]. Obesity reduces compliance with the chest wall and respiratory muscle resistance with greater resistance to the airway and to the chest wall. In addition, expiratory reserve volume will be lost accompanied by decreased total lung capacity and functional residual capacity in instances of morbid obesity. Lower lung volumes with basal atelectasis predispose to localized hypoventilated areas, resulting in shunting and ventilation/perfusion mismatching. The final result is hypoxemia, especially in the supine position; impaired pulmonary function, which is determined on testing; and progressively worsening disability [14].

Sleep-disordered breathing is significantly connected with OHS (90 percent), OSA and hypoventilation most often associated with sleep (about 10 percent of the time. The increases in PaCO₂ are related to the halt in apnea and ongoing metabolic synthesis of CO₂ [15]. The PaCO₂ level may be normalized by Eucapnic individuals by compensatory increased alveolar breathing to improve CO₂ removal. The compensatory process is, however, impaired in OHS patients, producing CO₂ retention. The renal system reduces the clearance of the bicarbonate to compensate for the reduction in the hypercapnic pH in response to transient hypercapnia. Bicarbonate plasma rises, resulting in the progressive growth of bicarbonate. This integration ultimately blurs the ventilation reaction to carbon dioxide and hence promotes the development of nightly hypoventilation [16].

Only in minorities of individuals with severe OSA is wake hypercapnia found [15]. Meta-analysis of 15 studies revealed that hypercapnia patients had higher BMIs and reduced lung volumes consistent with lung physiology of restricted compounds and hypoxia of nocturnal pulse oximetry, compared with Eucapnic OSA patients [17].

3. CENTRAL ALVEOLAR HYPOVENTILATION

Central hypoventilation suggests that a central nervous system deficit is the fundamental cause of the problem rather than the respiratory system. Central hypoventilation is unknown and might be caused to a range of congenital or acquired disorders [18]. Central alveolar hypoventilation disorders indicate diseases caused by neurological abnormalities which are underlying and impact sensors as well as central controllers or signal integration. Such problems can result in inadequate ventilation, increased PaCO₂ (hyper carbonate) and a reduction in PaO₂ (hypoxemia). Congenital or adult, the condition may be impacted and newborn infants may be at risk. Central alveolar hypoventilation may be present during sleep alone or in more severe cases during sleep and wakefulness [19].

Congenital central hypoventilation syndrome (CCHS) is a rare, lifelong condition that causes primary alveolar hypoventilation. The starting age of CCHS is from neonatal birth (i.e. in the first thirty days of the life) to (less often) later inception (1 month to adulthood) [20]. It has the effect of apparent hypoventilation, with monotonous respiratory rates, and low respiration either in sleep alone or during sleep as well as during sleep; autonomous dysregulation of the nervous system including lower rates of heartbeat and sinus pauses; modified temperature regulation and altered pupil response to light [21].

CCHS hypoventilation pathogenesis is not fully known. Multiple investigations in children with CCHS examined the central and peripheral function of the chemoreceptor. CCHS patients demonstrated peripheral chemical receptor responsiveness similar to controls when hypertoxic or hypercarbic gas challenges are present and function in patients with CCHS who can ventilate appropriately on awakened conditions. The periphery of peripheral chemoreceptors is similar in nature to controls. But traditional response reactions to prolonged hypoxic or hypercapnic issues are anomalous [22].

Hypoventilation in individuals with CCHS varies; whereas most children are well ventilated during wakefulness, about 15 percent even when wakeful require air assistance. In general, a higher number of repetitions of polyalanine correspond with severe hypo ventilation with

genotypes 20/27 and 20/33 that commonly need a ventilating aid in sleep and awake [23].

A number of additional CCHS self-sufficient nervous system dysregulations, including Hirschsprung's illness, were related with around 20 percent of patients and neural crest tumours, generally in NPARM people. Other signs of autonomous dysfunction include thermal instability, pacemaker heart arrhythms, decreased pupil light responses, oesophageals, and aberrant feeling of discomfort or anxiety can also be observed [24].

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD) is a rare, complex and devastating disease whose etiology is poorly understood presenting in childhood with rapid weight gain, hypothalamic endocrine dysfunction, and severe hypoventilation [25]. Typically, rapid occurrence of obesity is the initial clinical indication in ROHHAD; commonly with a weight increase of 15 kg or more in just one year. Often in crises, children like respiratory insufficiency or cor pulmonary disease [26]. There are also typical delays in development, regression and behavioral issues. Around 40 percent of ROHHAD patients develop benign tumors of neural crest origin in addition to hypothalamic, respiratory and autonomic symptoms that characterize the disease [27].

With earlier detection and treatment, the forecast of ROHHAD has improved. There is significant morbidity in subdivisions of instances such as seizures, sadness, psychosis, hallucinations, and emotional lability due to a gradual neurologic or psychiatric deterioration. Certain patients can be affected with severe bradycardia due to autonomic nervous system dysfunction. Personal care is complicated and interdisciplinary, concentrates on endocrine, ventilating problems and includes ventilation assistance if hypoventilation is present [28].

Familial dysautonomia (FD) is a rare autosomal-recessive condition primarily affecting the Ashkenazi Jewish population. It affects sensory, sympathetic and parasympathetic neurons' growth and survival. Affected people experience GI, vomiting, repeated pneumonia, altered sensitivity to pain and warmth, and cardiovascular instability. Individuals with FD are prone to developing defects, renal illness and hypertrophy of the ventricular left as well as vomiting from sympathetic surges [29].

Hypoxia and hypercapnia were demonstrated to be abnormally ventilatory in patients with FD. A study of 22 FP individuals found a steady rise in breathing and paradoxical reduction in heart rate and blood pressure. Long-term apneas with deep desaturations were caused by hyperventilation. FD children had greater apnea and sleep disturbance than sleep controls [30].

Prader-Willi Syndrome (PWS) is a rare and complex genetic disease, with numerous implications on metabolic, endocrine, neurologic systems, with behavior and intellectual difficulties. An abnormal ventilation response was found in patients with PWS [31]. Although eucapnic is left at rest during arousal, people with PWS showed a paradoxical reaction to hyperoxia and no change in the ventilation of minutes in response to hypercapnia. The distinctive characteristics such as morbid obesity, tiny nasopharynx and the hypopharyngeal Hypotonia may be attributed to obstructive sleep apnea and obstructive hypoventilation [32].

Acquired Conditions Causing Central Hypoventilation include brain tumors, central nervous system infections, encephalitis, trauma, and sequelae from neurosurgical procedures. Depending upon the respiratory center damaged and the degree of damage [33], the level of resulting hypoventilation varies from moderate to severe. There are intermediate phases in some individuals, while artificial breathing is required in others, although most ventilatory malfunctions are worsening during sleep. In individuals who have a history of the central nervous system malignancies and respiratory diseases, hypoventilation should be evaluated [34].

4. NEUROMUSCULAR DISORDERS

Neuromuscular disease hypoventilation is due both to the respiratory weakening of muscles and to decreased chemoreceptor susceptibility, which are important in the ventilatory movement. Air failure, comprising dyspnea, tachypnea and tachycardia, is a sign of acute symptoms. A spectrum of neuromuscular diseases has acute or chronic respiratory failure; some are gradually and devastatingly treated others [35]. In chronic form, breath impairment affects the mechanical characteristics of the lungs and chest wall, lowers the capacity to remove secretions and eventually changes the role of the centers of the breath. Symptoms include orthopnea, fatigue, disturbed sleep, and hypersomnolence [36].

Myasthenia grave, amyotrophic lateral sclerosis, Guillain-syndrome Barré's and muscle dystrophy among neuromuscular disorders that can induce alveolar hypoventilation. Neuromuscular disease patients have a high-speed, poor breathing, and/or faulty function of the motor neuron [37].

In individuals with neuromuscular problems, the central respiratory drive is maintained. Hypoventilation is therefore related to weakening in the respiratory muscle. The most common nightly desaturation in the REM period of sleep is in patients with neuromuscular conditions. The level of nocturnal desaturation is linked to the degree of diaphragm failure. Nocturnal desaturation can precede daily hypoventilation and anomalies in gas exchange [38].

A decrease in ventilation and therefore deteriorating hypoventilation is linked to sleep. Sleep problems can be an early indication of future weakening of the muscles. They should be called upon to further examine them, but they may not be uniformly predictive when evaluating pulmonary function, arterial analysis and other tests are necessary [39]. Respiratory disorder timing is vary, but it is useful to evaluate neuromuscular patients via understanding of the clinical features, etiology and therapy for respiratory failure and hypoventilation. For those with progressive and terminal disease, additional factors such as end of life care, especially ventilation and cough, may be useful for the patient, caregivers, and treating medical personnel [40].

5. CHEST WALL DEFORMITIES

Chest wall deformities are a number of congenital conditions which are related with the development of alveolar hypoventilation, leading to respiratory failure and respiratory failure, covering a broad range of disorders such as kyphoscoliosis, fibrothorax [41].

There can be consideration of several pathogenic processes as functions of the sorts of thoracic diseases present. We examined the following as the reasons for these extra possible mechanisms: 1) inhomogeneity of the ventilation/perfusion (V/Q); 2) difficulty to cough; 3) malformation or respiratory centre malformations acquired; and 4) excessive blood volume and fluid retention, which worsens respiratory work and inhomogeneity of the V/Q [42].

The current assumption focuses on the disruption of the collagen metabolism, which leads in the sternal development of the cartilage and the sternocostal articulation deformity (sternum protrusion). The majority of Pectus deformation are separate illnesses, however research has connected the involvement of genetic mutation [43].

6. CHRONIC OBSTRUCTIVE PULMONARY DISEASE COPD

A prevalent and curable condition characterized by the gradual restriction of airflow and the elimination of tissues is Chronic Obstructive Pulmonary Disease (COPD). Structural lung alterations are most often linked to cigarette smoking because of chronic inflammation owing to extended exposure. Chronic inflammation causes airways to diminish and lung recoil to decrease. The illness commonly has cough, dyspnea, and sputum symptoms. Symptoms can range from asymptomatic to shortness of breath [44].

As the condition develops, exacerbations might increase and consequences can occur that are life-threatening. The last stage of COPD is marked by significant airway constraints, serious performance limitations and systemic consequences. Apneatic failure or lung infection is common in patients [45].

In individuals with severe COPD, hypoventilation is relatively uncommon. Alveolar hypoventilation in COPD normally does not take place until the forced expiratory volume is lower than 1L or 30% of the anticipated value in 1 second (FEV1). However, there is no hypoventilation in many individuals with significant airway obstructions. Other variables, such as poor ventilation control, hereditary susceptibility, and respiratory weakness, will thus probably contribute [46].

7. MANAGEMENT MODALITIES

The goal of treatment for all patients with hypoventilation syndromes is adequate ventilation and oxygenation during both sleep and wakefulness in a way that maintains a high quality of life [47].

- **Acute hypoventilation:** Noninvasive ventilation methods, such as positive-pressure ventilation, are treatments that might be useful (PPV). The most effective way of ensuring sufficient ventilation with

continuous ventilation is positive pressure ventilation via tracheostomy. Problems with this form of ventilation include the constant presence of skilled caregivers and the danger of mortality owing to decannulation, infection and speech delays Tracheostom [48].

Ventilatory assistance may be obligatory in patients for signs of nocturnal hypoventilation (such as day hypersomnolence, morning headaches, exhaustion, nightmares, and enuresis), dyspnea at rest, hypoventilation that causes pulmonary hypertension and cor pulmonale, nocturnal hypoxia (arterial oxygen saturation < 88%) in spite of supplementary oxygen, and patients with acute hypoventilation, diagnosed through symptoms and laboratory data, should be started on bilevel PPV urgently [49]. The benefits of this technique include the ability to remove the mask from the patient's face and utilize a portable, charger ventilator to deliver high pressures if necessary. If symptoms and test results cannot be improved within a short period of time (1-2h), consideration should be given for intubation and invasive mechanical breathing [50].

- **Chronic hypoventilation:** In patients with chronic respiratory impairment linked to COPD, nerve musculoskeletal illness and thoracic abnormalities, and idiopathic hypoventilation are commonly approved for non-invasive ventilation with nightly Bilevel PPV utilizing mask interfaces. Nocturnal bilevel PPV reduces nocturnal hypoventilation while improving carbon dioxide responsiveness [51].

In the postoperative phase after abdominal operations, non-invasive positive pressure ventilation (NPPV) can help improve breathing in obese individuals. The NPPV was superior in the night and daily treatment of blood gas anomalies, in a subset of patients with OHS (Obesity Hypoventilation Syndrome) [52], compared with nasal continuous positive airway pressure (NCPAP). Patients with neuromuscular disturbances with morning headaches, hyper-exposure throughout the day, sleep problems or cognitive impairment are advised to utilize nocturnal bilevel PPV.

The noninvasive bilevel PPV indicators of nightly hypoventilation syndromes have been created in the literature available [53]. Patients who received the treatment should have a disease

which is known to cause hypoventilation, symptoms and signs of hypoventilation, failure of first-line medications to respond to mild cases of hypoventilation, i.e. primary underlying disease treatment with bronchodilators, respiratory stimulants, weight loss, additional oxygen, or continuous positive air pressure (CPAP), and moderate to severe hypoventilation [54].

In addition to night bilevel PPV, around 50% of OHS patients require oxygen treatment. However, a decrease in minute ventilation, resulting in alveolar hypoventilation and the resultant increased volume of death-space-to-the-tidal volume may result in a deterioration of hypercapnicity in stable individuals with obesity related hypoventilation Breathing 100 percent oxygen. Thus oxygen treatment in individuals who are grossly obese should be provided cautiously [55].

Surgery such as tracheostomy reduces the blocking of airways when sleeping and hence enhances alveolar ventilation and PaCO₂. However, some patients may not return after tracheostomy to Eucapnic because they do not affect carbon dioxide generation and decreased muscular strength. hypoventilation surgery involves bariatric operations to encourage weight loss and the insertion of a phrenic nerve electrode for diaphragm pacing [56]. Based on their weight reduction process, the various operative alternatives accessible today may be divided into two groups. Vertical banded gastroplasty (VBG), adjustable gastric banding (AGB) and Roux-en-Y gastric bypass are all restrictive gastric procedures (RYGB). Malabsorption techniques include biliopancreatic diversion (BPD) and duodenal switch biliopancreatic diversion (BPD-DS). All the treatments successfully improved obesity-related comorbidities [57]. RYGB provides the greatest short- and long-term results for safety, effectiveness and durability and was demonstrated to be superior than AGB. The most frequent treatment is for AGB. RYGB is usually laparoscopically carried out. Long-term compliance and thorough nutritional follow-up are necessary in all processes [58].

In OHS; weight loss is an ideal treatment in obesity-hypoventilation syndrome. Weight loss improves the abnormal physiology and restores normal daytime gas exchange. In some individuals even a modest weight loss of 10 kg improves minute ventilation and normalizes daytime PaCO₂. In concomitant obstructive

sleep apnea, weight loss has been shown to decrease the number of sleep-disordered breathing events (apneas and hypopneas) and the severity of hypoxemia [59].

Also, several drugs may be used to treat hypoventilation syndromes. Most produce the desired effect by stimulating the central respiratory drive, by reversing the effects of other medications that can depress the central respiratory drive, or by inducing bronchial dilatation [60].

For example, bronchodilators such as beta-agonists (eg, albuterol), anticholinergic agents (eg, atropine), and methylxanthines (eg, theophylline) are helpful in treating patients with obstructive lung disease and severe bronchospasm. Additionally, theophylline may improve diaphragm muscle contractility and stimulate the respiratory center [60].

8. CONCLUSION

Current therapies for hypoventilation syndromes are supportive drugs for maintenance and support. The most successful and thoroughly studied treatment is supportive care and repair of anomalies underlying gas exchange by positive airway pressure therapy, potentially by supplementing with oxygen. Other therapies for hypoventilation were used.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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