

Review Article

Respiratory and Sleep Disorders in Chronic Neuromuscular Disease, an Update and Therapeutic Approach

Abdul Ghani Sankri-Tarbichi*

Sleep Research Laboratory, John D. Dingell Veterans Affairs Medical Center, Wayne State University, USA

Corresponding author

Abdul Ghani Sankri-Tarbichi, Division of Pulmonary, Critical Care and Sleep Medicine, 3990 John R, 3-Hudson, Detroit, MI 48201 USA, Tel: (313) 745-6033; Fax: (313) 745-8725; Email: atarbich@med.wayne.edu

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Abstract

Respiratory and sleep disorders are common in patients with neuromuscular disease but under recognized especially during sleep or when patients are asymptomatic. In the last decades there has been great interest in understanding the mechanism of disease and developing a standard of care for these patients. This led to the development of new interventions but holistic and multidisciplinary approach is still lacking. Positive airway pressure and non-invasive ventilation are a common method of treating sleep and respiratory disorders but under-studied and utilized clinically. New techniques of therapy including pharmacological or non pharmacological therapies are needed especially in more advanced and complex conditions of neuromuscular disease.

INTRODUCTION

Several types of chronic neuromuscular diseases adversely affect respiration during wakefulness and more so during sleep. Most presentations are sub-acute and manifest clinically when the underlying disease gradually worsens. Respiratory disorders however are number one reason for mortality in patients with chronic neuromuscular disease [1,2], therefore early detection and treatment are very important to improve outcome and save lives. Patients with neurologic disease and early diaphragmatic or bulbar involvement are vulnerable to respiratory events during sleep, especially during the rapid eye movement (REM) sleep, even if they have no daytime symptoms. Common neuromuscular disorders that affect the respiratory system were recently classified anatomically [3] to the following five categories:

- Central nervous system
- Spinal cord
- Motor nerves
- Neuromuscular junction
- Respiratory muscles

This concise review will highlight specific patient centered care and therapeutic interventions to two common disorders: diseases of the brain and the spinal cord.

RESPIRATORY AND SLEEP DISORDERS IN PATIENTS WITH BRAIN DISEASE

Several neurological disorders affecting the brain can result in abnormal breathing, hypoventilation or respiratory failure. A classic type that results in hypoventilation is congenital central alveolar hypoventilation (CCAH) syndrome or “Ondine’s Curse”. This autosomal dominant disorder affects the autonomic respiratory centers in the brain stem and results in central apnea and hypoventilation primarily during sleep with reduced or absent central chemosensitivity [4]. It starts at early ages and can lead to death from progressive respiratory failure if not treated early [5]. CCAH has been linked to autonomic nervous system dysfunction since it was first described in 1970. A genetic basis of CCAH has been discovered in families with affected children, because of mother–child transmission, and because of reports of a polyalanine expansion mutation in PHOX2b. Therefore the identification of the PHOX2b mutation can lead to prenatal diagnosis for parents of CCAH and adults with CCAH in future pregnancies, and potentially allow therapeutic strategies for the treatment of CCAH. All patients with CCAH syndrome require life-long ventilatory support during sleep, although only one third of patients require continuous ventilatory support. Modalities of home mechanical-assisted ventilation include

positive pressure ventilation via tracheostomy, non-invasive positive pressure ventilation (bi-level ventilation), and negative pressure ventilation. Supplemental oxygen alone is inadequate treatment. Recent reports suggest that diaphragm pacers may offer a modality of ventilatory support to CCAH patients with maximal mobility instead of full-time ventilatory support through tracheostomy [6]. With early diagnosis and adequate ventilatory support, these children can have good outcomes and live productive lives [4].

Other disorders that affect the brain such as ischemic **stroke** can result in weak ventilatory motor output and control of breathing [7]. Ischemic stroke has been associated with high incidence of sleep disordered breathing (SDB) and obstructive apnea. Recent studies suggested a bidirectional relationship between stroke and SDB which can be modifiable risk factor [8]. Moreover recent study found that the majority of acute stroke patients had sleep apnea. Continuous positive airway pressure treatment particularly Auto-CPAP was well tolerated and appeared to improve neurological recovery from stroke [9]. In contrast to other patients with SDB, most stroke patients do not experience sleep apnea symptoms. Interestingly, important factor for adhering to CPAP therapy for these patients was found to be the desire to reduce the risk of subsequent cerebrovascular events [10]. Therefore, education and awareness among clinicians, patients and their families is critically important to achieve the desired outcome in this group of patients.

Traumatic brain injury (TBI) is a common disorder that affects sleep and respiration. In fact sleep disordered breathing affects 70% of sleepy TBI population, but under diagnosed and under treated [11]. Although about 50% reports sleepiness after chronic TBI, 70% have significant nocturnal hypoxia (oxygen saturation <90%) and 30 % had SDB defined by apnea hypopnea index of >10 event/hr [12]. The exact mechanism of sleep and breathing disorders after TBI is not yet known. It has been observed that TBI increases the susceptibility of the brain to hypoxia including prolonged apnea that occurs in ethanol-treated animals following brain injury [13]. This study suggests that alcohol intoxication suppresses ventilation following TBI and may contribute to worsening brain injury in intoxicated trauma survivors. Therefore it is important to identify highly susceptible individuals with TBI as early as possible to prevent hypoxia, correct breathing disorders during sleep, and avoid alcohol or other substances that suppress ventilation.

Multiple sclerosis (MS) is a recurrent demyelinating disorder that affects the central nervous system including the brain and spinal cord. MS is known to have higher incidence of sleep and breathing disorders than the general population [13]. Most MS patients have lung function abnormalities particularly those with moderate and severe multiple sclerosis and those with Bulbar dysfunction (controlled by cranial nerves VII, IX, X, and XII, which originate in the medulla or "bulb") [14-16]. Specifically, the ventilatory response to CO₂ in MS patients is significantly impaired while the inspiratory drive at rest is increased. Moreover the respiratory muscle weakness could contribute to the lower ventilatory response in these patients [14]. Howard et al found that 6 of 19 patients with multiple sclerosis and respiratory complications had abnormal respiratory control

[16]. Patients with multiple sclerosis can develop voluntary or autonomic respiration, diaphragmatic paralysis, paroxysmal hyperventilation, apneustic breathing (characterized by a pause after inspiration) and in advanced cases Cheyne-Stokes respiration and death if untreated [17].

There is a correlation between the severity of MS, upper muscle weakness and the degree of pulmonary dysfunction [18]. Both focused clinical with muscle forces assessment can provide good prediction of the presence of expiratory muscle weakness in MS patients. The clinical symptoms could be as simple as assessing for difficulty in clearing pulmonary secretions and weak cough in addition to observing patient exhalation and cough techniques [18]. Ventilation management can be provided either by non-invasive ventilation (NIV), through a mask, or invasive ventilation, via tracheotomy. NIV is preferable first choice since it improves survival and quality of life [19]. The most important indications for NIV are rapid decline in forced vital capacity to less than (50% predicted) and/ or awake arterial PCO₂ more than or equal to 45 mmHg. Similar to other neurological disorders who are either intolerant to NIV, have weak cough or evidence of Bulbar muscular dysfunction (include slurred speech, trouble swallowing liquids, aspiration manifesting, or frank choking spells), NIV is not recommended as it does not provide better outcome [20]. More recent studies showed that 8 weeks of expiratory muscle training resulted in improvement in MEP and peak expiratory flow (PEF). Likewise, ten-week inspiratory muscle training program was also shown to improve MIP and pulmonary function parameters [21]. Cough is impaired in patients with advanced multiple sclerosis hence recent study suggested that lung volume recruitment is associated with a slower rate of decline in lung function and peak cough flow [22]. Given it is a single study additional studies are needed to assess the role of lung volume recruitment in patients with multiple sclerosis.

In **Parkinson disease**, abnormalities of ventilatory control are more common in parkinsonism associated with autonomic dysfunction than in idiopathic parkinsonism, possibly because the susceptible areas in the brain are close to the areas involved in central respiratory control. Patterns of respiratory dysfunction in Parkinson disease include dysrhythmic breathing, central apneas, Cheyne- Stokes respiration, cluster breathing, apneustic breathing, and central hypoventilation. Additionally, central apnea and central hypoventilation syndrome (Ondine's curse) have been reported in Parkinsonism associated with autonomic dysfunction [23]. Likewise upper airway dysfunction and flow limitation have been reported frequently in Parkinson's and extrapyramidal disorders [24] which can lead to respiratory failure and dyspnea. Flow-volume loops with saw tooth oscillations and direct fiberoptic visualization of the upper airway indicate involuntary movements of the glottis and supraglottic structures causing intermittent obstruction [25]. On the other hand, While Levodopa therapy was reported to reverse upper airway obstruction acutely [26], augmentation to L-dopa therapy can lead to symptomatic respiratory disturbance and periods of central apneas which may be under-recognized in clinical practice [27]. Hence early recognition and targeted therapy particularly during sleep and preoperatively is highly recommended.

RESPIRATORY AND SLEEP DISORDERS IN PATIENTS WITH SPINAL CORD INJURY

Respiratory and sleep disorders are very common in spinal cord injury (SCI) patients. It usually depends primarily on the level and completeness of the cord injury. Following SCI, the mortality rate is higher than in the able-bodied, and the most common causes of death are due to respiratory disorders [28,29]. High cervical SCI (above the level of the phrenic motoneurons (C3, and C4) causes complete paralysis of both the inspiratory and expiratory muscles and require long-term ventilation mostly via tracheostomy or phrenic nerve stimulation [30]. Lower levels of SCI are associated with reduced lung volumes particularly forced vital capacity (FVC) in addition to possible changes in chest wall compliance and reduced respiratory muscle strength measured by maximal inspiratory and expiratory pressures (MIP and MEP respectively). Despite these impairments most patients do not complain of dyspnea or other respiratory symptoms but the prevalence of breathlessness is greater when the level of injury is higher [31] especially during exercise as tidal volume is smaller than lower SCI levels [32]. The respiratory function is also affected by the body position and sleep state. In contrary to able-bodied individuals and thoracic SCI, it was suggested that patients with tetraplegia have larger FVC and FEV1 in the supine compared with the seated upright positions, presumably because gravity dependent flattening of the diaphragm [33]. On the other hand another studies found conflicting findings related to body position during sleep in these patients, when the diaphragmatic excursion is more compromised by the supine position, resulting in intra-abdominal contents pushing the flaccid diaphragm [34]. Mansel et al observed a decrease in vital capacity in tetraplegic patients that is position-dependent. In addition in the supine position patients with cervical SCI are more prone to aspiration of stomach contents which may worsen their respiratory function. Further studies are needed to elucidate the best position for respiratory function in SCI.

Patient who have impaired diaphragm and pump muscles they will either be treated by home ventilation or by respiratory muscle/ phrenic nerve pacing which can restore the inspiratory function. However these patients may still need tracheostomy or positive airway pressure device to treat obstructive sleep apnea [30]. When the spinal cord injury spares the diaphragm patients do not require ventilation while awake. These patients however still at risk of decompensation including during sleep when they lose the wakefulness stimuli and need to be assessed and treated early. Respiratory muscle weakness; decrease vital capacity and poor cough can predispose these patients to fatigue of respiratory muscle and respiratory infections. Training the respiratory muscles may enhance and strengthen the respiratory muscles. One example is resistive respiratory muscle training by inhaling through a narrow orifice against progressively higher resistance to increased muscle strength over a period of 2-3 months at a target of 80% maximal inspiratory pressure [35]. Another technique to make cough more effective is direct stimulation of the spinal cord by epidural electrodes that produce strong contraction of the abdominal muscles.

There are very limited studies that used pharmacological therapy to improve respiratory muscle function. Theophylline

has been found beneficial in improving the diaphragm contractility in animal experiment after acute hemisection [36]. Clinical studies, however, showed that oral theophylline did not improve pulmonary function [37]. Another concern is the narrow therapeutic window and risk of toxicity.

Spinal cord injury (SCI) patient commonly complain about poor quality of sleep from multiple factors [38,39]. Recent epidemiological studies have found that sleep disordered breathing (SDB) is highly prevalent post SCI (ranging between 27% and 62%) [40-47]. In a study by Berlowitz et al, it was found that the prevalence of SDB in the Australian cohort of cervical SCI was 62% in the four weeks immediately post-injury and remained 60% after one year follow up [48]. The exact mechanisms of disease are not known yet but preliminary data suggests that cervical SCI are at more risk for central sleep apnea than thoracic patients or able-bodied control [49], which could be due to in part to sleep related hypoventilation which may be aggravated by sedating and pain medications [50]. Central and obstructive sleep apnea can overlap and may explain these findings. Sleep disordered breathing and sleep related hypoventilation can lead to long-term consequences if left untreated which have been proved in able-bodied individuals such as heart disease, stroke and neurocognitive dysfunction [8,51,52]. A multicenter randomized clinical trial is underway to assess the effectiveness of positive airway pressure (PAP) therapy in chronic SCI with obstructive SDB. The traditional PAP therapy has some limitations especially in cervical SCI with limited mobility to the upper extremities to adjust the mask and operate the device. Furthermore central SDB may not respond to conventional PAP therapy and will need alternative treatment. Oxygen therapy is a promising option to treat central SDB in able-bodied patient who fail PAP therapy [53]. Advanced mode of ventilation like adaptive servo-ventilation or intelligent volume assured pressure support are new modes that may play an important role in treating complex SDB but need further randomized studies to assess its effectiveness and feasibility.

CONFLICT OF INTEREST

The author has no conflict of interest conflicts of interest, and any off-label or investigational to disclose.

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