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Diurnal hypercapnia in patients with neuromuscular disease

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SUMMARY

Subjects with progressive neuromuscular diseases undergo a typical sequence of respiratory compromise, leading from normal unassisted gas exchange to nocturnal hypoventilation with normal daytime gas exchange, and eventually to respiratory failure requiring continuous ventilatory support. Several different abnormalities in respiratory pump function have been described to explain the development of respiratory failure in subjects with neuromuscular weakness. Early in the progression of respiratory failure, the use of nocturnal assisted ventilation can reverse both night- and day-time hypercapnia. Eventually, however, diurnal hypercapnia will persist despite correction of nocturnal hypoventilation. The likely beneficial effects of mechanical ventilatory support include resting fatigue-prone respiratory muscles and resetting of the central chemoreceptors to $PaCO_2$. Recent experience shows that select patients who require daytime ventilation can be supported with non-invasive ventilation continuously to correct gas exchange abnormalities while avoiding detrimental aspects of tracheostomy placement.

INTRODUCTION

Patients with progressive neuromuscular disease (NMD) typically experience a sequence of events that lead to respiratory morbidity and eventually to respiratory failure or death.[1] Weakness of inspiratory, expiratory, and glottic muscles alone or in combination compromises airway clearance. As a result, patients become predisposed to recurrent episodes of aspiration, lower respiratory tract infections and atelectasis. With such recurrent or chronic episodes, lung compliance decreases. Simultaneously, chronic breathing at low lung volume causes a stiffening of the chest wall. Together, these events all increase the load against which the already weakened respiratory pump must work.

Weakness of the respiratory pump, with or without progressive weakness of pharyngeal muscles, eventually leads to hypoventilation during sleep, especially during rapid eye movement (REM) sleep (Fig. 1). The onset of sleep-disordered breathing is likely to occur in children with progressive neuromuscular weakness when the vital capacity falls below 60% of the predicted value.[2] Patients can develop either sleep-related hypopnoeas or frank obstructive apnoea. Episodes of hypoxemia and hypercapnia during sleep then can occur, but initially normocapnia continues to exist during wakefulness. As the severity of sleep-disordered breathing increases, however, carbon dioxide levels remain elevated both night and day. This diurnal hypercapnia may be preceded by other symptoms of nocturnal sleep-disordered breathing and sleep fragmentation, like worsening daytime fatigue and poor school performance.[3]

At this point, daytime hypercapnia and other symptoms of sleep-disordered breathing can often still be corrected with the institution of nocturnal ventilation.[4] With increasing weakness, however, ineffective ventilation during the day will ensue and daytime hypercapnia will occur even when nocturnal ventilation successfully corrects the sleep related hypoventilation. When left untreated, diurnal hypercapnia has a dire prognosis: patients with Duchenne muscular dystrophy (DMD) had a mean duration of survival of 9.7 months after the onset of diurnal hypercapnia in the absence of ventilatory support.[5]

INSTITUTION OF NON-INVASIVE VENTILATION (NIV)

The optimal time to have patients begin using NIV remains unknown: starting too early can lead to poor patient adherence, as no benefit is perceived, whereas waiting until the patient is clearly symptomatic exposes the patient to the dangers of progressive respiratory insufficiency and possible acute respiratory failure in the event of an intercurrent illness. Since the benefits of correcting sleep-related breathing problems are known,[3] the onset of such symptoms seems to be a reasonable time to introduce ventilatory support. To determine whether the finding of nocturnal hypoventilation with daytime normocapnia is a reasonable time to

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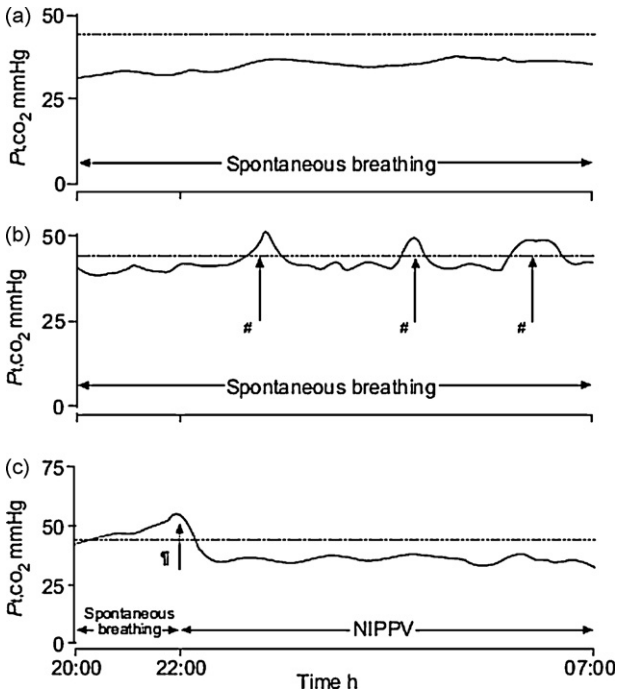

Figure 1. Schematic of transcutaneous CO_2 ($PtCO_2$) measurements from patients with NMD at various phases of respiratory compromise: a) a subject able to maintain normocapnia both awake and asleep without ventilatory assistance; b) a patient with episodic nocturnal hypoventilation ($PtCO_2$ >5.98 kPa) requiring ventilatory support (#) but daytime normocapnia; c) patient receiving nocturnal NIV to control sleep-related hypoventilation, but presence of end-diurnal hypercapnia ($PtCO_2$ >5.98 kPa). Adapted from ref. 24 with permission.

begin NIV, Ward and co-workers randomized patients with NMD or chest wall disease who had symptomatic nocturnal hypoventilation but normal daytime $PaCO_2$ into a control group that was followed without intervention and another group that was started on nocturnal NIV.[6] After 6 months of observation, 50% of the non-intervention group had been placed on NIV because of symptoms; 70% were using it by 12 months, and by 24 months all but 1 of the 10 patients in the control group was using NIV because of progression of symptoms. The authors concluded that patients with NMD and nocturnal hypoventilation are at risk to develop daytime respiratory failure within 12 – 24 months after the onset of their nocturnal symptoms. As such, they reasoned that the finding of nocturnal hypoventilation should precipitate discussion with patients and families about starting nocturnal ventilatory support, since symptoms of diurnal hypercapnia are likely to follow in short order.

CAUSES OF DIURNAL HYPERCAPNIA

The potential causes of diurnal hypercapnia (which reflect "respiratory pump failure") include an imbalance between the mechanical output of the respiratory pump and the imposed load, development of respiratory muscle fatigue, and an inadequate respiratory drive.[7] In the context of a progressive NMD, the imbalance between pump and load in part develops when the respiratory muscles become weak enough or fatigued to the point that they can no longer work effectively against their load (the lung parenchyma and chest wall itself). The development and progression of kyphoscoliosis will contribute to inefficiency of the respiratory pump to expand the chest, by creating a mechanical disadvantage around the costovertebral joints.

On the other side of this balance, load can increase. The chest wall becomes stiffer from prolonged periods without deep sigh breaths; this leads to the development of ankylosis around costovertebral joints and stiffening of ligaments and tendons. Additionally, muscle tissue is replaced by fibrous tissue after years of disuse. Obesity will also increase the mass of the chest wall, adding to overall load. Changes in the tissue properties of the lung parenchyma contribute to increased load as well. Recurrent infections, aspiration, or mucous plugging, as well as the development of microatelectasis from lack of sigh breaths lead to reduced lung compliance and possibly to increased resistance.

Alterations in respiratory control represent yet another potential mechanism for diurnal hypercapnia. Here, prolonged periods of nocturnal hypoventilation result in blunting of central drive so that the patient does not respond in an appropriate way to the challenge of elevated levels of CO_2. Importantly, these hypothetical mechanisms need not be mutually exclusive, and may actually be inter-connected.

In fact, many investigators believe that the respiratory centres modulate output to change the breathing pattern of subjects with progressive respiratory muscle weakness even in the face of hypercapnia, so as to avoid causing fatigue and possibly damage to the respiratory muscles.[8–11] While normocapnic subjects with NMD maintain a normal minute ventilation, Misuri et al found that they did so using smaller tidal volumes and shorter inspiratory and expiratory times compared with healthy controls.[8] Furthermore, in this group of subjects with NMD, there was a direct relationship between inspiratory time and tidal volume: the shorter the inspiratory time, the smaller the tidal volume. There was also a direct correlation between the respiratory frequency/tidal volume ratio (or Rapid Shallow Breathing index) and the $PaCO_2$. A similar pattern of breathing was found in a group of young men with DMD (Fig. 2).[9] Here, the rapid shallow breathing pattern distinguished those who required nocturnal NIV from those who maintained normocapnia unassisted day and night. In contrast, the rapid shallow breathing pattern was not a good discriminator for those who progressed to diurnal hypercapnia. This may be because those with weaker respiratory muscles experience additional changes in respiratory centre output to forestall respiratory muscle fatigue, or because of limitations in the mechanics of the weakened respiratory muscles. A third, sicker group in this study who developed hypercapnia by the end of each day despite using NIV to maintain nocturnal normocapnia demonstrated a greater reduction in tidal volume than either of the other two groups, but they

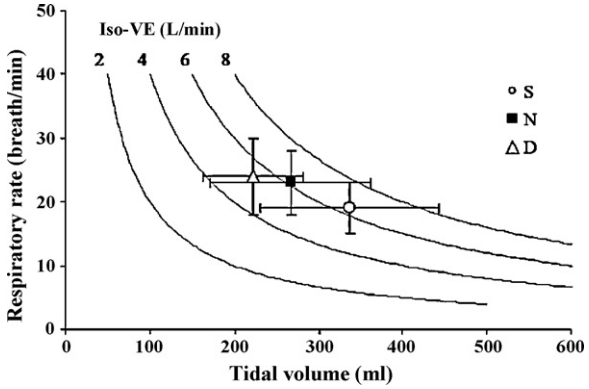

Figure 2. Changes in respiratory pattern seen at three stages of progressive respiratory compromise in subjects with DMD. Isobars represent combinations of respiratory rate and tidal volume that result in minute ventilation of 2, 4, 6, and 8 L/min. Open circles (S) represent those subjects able to maintain spontaneous unassisted ventilation; closed squares (N) are those who require nocturnal NIV but can still maintain normal unassisted daytime ventilation; open triangles (D) are subjects with diurnal respiratory failure. Note that N maintain normal minute ventilation, but do so by increasing respiratory rate and decreasing tidal volume. Subjects in the D group undergo similar changes in respiratory pattern, but no longer maintain the same minute ventilation. From ref. 9, with permission.