NIV in neuromuscular disease

Non-invasive mechanical ventilation: when to start for what benefit?

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When is the optimal time to perform polysomnography in patients with neuromuscular disease?

Non-invasive ventilation (NIV) is recognised as an efficient therapeutic option in patients with chronic respiratory insufficiency due to neuromuscular disorders. However, the long standing clinical experience with NIV contrasts with the absence of validated criteria for initiating this treatment and the paucity of data on its long term physiological and psychometric effects.

Several consensus conferences agree on the value of daytime hypercapnia and an acute exacerbation as criteria for starting NIV because they are characteristic signs of established ventilatory failure.[1–3] However, these two classical criteria are preceded by a variable period of nocturnal hypoventilation during which treatable symptoms—such as frequent arousals, severe orthopnoea, daytime fatigue, and alterations in cognitive function—may cause deterioration in the quality of the patient's daily life.

The first problem is to decide when to perform polysomnography in a patient with only a few symptoms.[4] Polysomnography should be undertaken without delay when the patient develops symptoms related to sleep disordered breathing, but patients with neuromuscular disorders tend to underestimate symptoms such as fatigue before using mechanical ventilation. Sleep disordered breathing is difficult to establish in children because of reliance on parents and other caregivers who have a different perception of the child's disease. Lung function parameters are poor indicators of nocturnal hypoventilation and data are only available for patients with neuromuscular disorders. Indeed, forced expiratory volume in 1 second (FEV_1) has been shown to be inversely correlated with daytime arterial carbon dioxide tension ($Paco_2$) and base excess in patients with Duchenne muscular dystrophy.[5] But the recommendation to perform polysomnography when the $Paco_2$ is $\geq$6 kPa (45 mm Hg) may already be too late. Moreover, none of the physiological parameters (FEV_1, $Paco_2$, or base excess) has been shown to be both sufficiently sensitive and specific to detect sleep disordered breathing.[5 6]

In the study reported by Ward and coworkers in this issue of *Thorax*,[7] patients were recruited for polysomnography when vital capacity fell below 50% predicted or when symptoms suggestive of nocturnal hypoventilation were present. These screening criteria may be too large. Indeed, even if the authors chose a cut-off value for peak transcutaneous carbon dioxide tension ($Tcco_2$) of >6.5 kPa as a definition of nocturnal hypoventilation in the absence of daytime hypercapnia, they admitted that, in practice, nearly all patients had a $Tcco_2$ value of >6.5 kPa for more than 30% of the total study period. Sleep disordered breathing is characterised not only by episodes of hypercapnia but also by desaturations.[8] Nocturnal desaturation is common in patients with respiratory muscle weakness, especially during rapid eye movement (REM) sleep but, here again, no reliable correlation has been established between any lung function parameter and the importance of nocturnal desaturation.[8] Respiratory muscle testing was also performed but the correlation of these data with nocturnal hypoventilation was not available. Thus, neither lung function nor respiratory muscle parameters nor symptoms seem to be sufficiently pertinent for the scheduling of polysomnography in patients with neuromuscular disease. The optimal timing of polysomnography is also unknown in patients with alveolar hypoventilation resulting from other causes such as chronic obstructive pulmonary disease and cystic fibrosis. Although it has been shown that these patients progressively develop rapid shallow breathing as their FEV_1 falls below 50% of the predicted value,[9] no correlation has been established between any index of respiratory function or respiratory muscle performance and the severity of sleep disordered breathing.

The second difficulty concerns the use of $Tcco_2$ for the diagnosis of hypercapnia. $Tcco_2$ generally overestimates $Paco_2$. This is attributed to the heating effect of the electrode. Nevertheless, strong correlations have been observed between $Tcco_2$ and $Paco_2$ values and between changes in $Tcco_2$ and in $Paco_2$.[10]

The third difficulty concerns the other indications for nocturnal NIV. As previously discussed, the indication is usually based on a cut-off $Paco_2$ value which is transgressed during a defined percentage of the sleep time or the study period. But other respiratory events during sleep—for example, those recently recommended for the diagnosis of sleep related breathing disorders[11] such as sleep fragmentation—may also need to be taken into account. Moreover, it may be possible that the optimal definition of nocturnal hypoventilation differs according to the underlying disease and also in children compared with adults. A definition based exclusively on the Pco_2 value may be too restrictive and insufficiently relevant from a clinical perspective.

If NIV is proposed earlier in the course of ventilatory failure, it should be accompanied by a significant improvement in measurable symptoms attributable to nocturnal hypoventilation, disruption of sleep architecture, and poor quality of sleep. NIV is able to improve nocturnal gas exchange in patients with neuromuscular disease, cystic fibrosis,[12 13] and obstructive sleep apnoea, both in adults and children.[14] But, in all these studies, patients had overt daytime hypoventilation. NIV initiated according to the ''classical criteria'' was associated with an improvement in survival in patients with Duchenne muscular dystrophy,[15 16] but the only study that has evaluated the ''preventive'' use of NIV in patients with Duchenne muscular dystrophy showed negative results with a significantly greater mortality rate in the NIV group.[17] In this study the main inclusion criteria were a vital capacity of 20–50% of the predicted value and a $Paco_2$ value below 6 kPa. The patients did not undergo polysomnography before and after the initiation of NIV and no information was given on the symptoms attributable to sleep disordered breathing. Patients with a variable level of nocturnal hypoventilation could therefore have been included without a control to determine the efficacy of NIV and an objective measure of compliance with its use. This argues for a more precise evaluation of subjective measures (such as symptoms) and objective measures of sleep disordered breathing before initiation of NIV.

In addition to an improvement in nocturnal hypoventilation and survival, it would be highly desirable if the use of

''early'' NIV was also associated with a significant decrease in acute exacerbations and, in patients with neuromuscular disease and cystic fibrosis, with a slowing in the decrease in lung function and respiratory muscle performance. A delay in acute exacerbations has not been observed in neuromuscular patients and would be very difficult to prove in patients with cystic fibrosis. NIV seems to be associated with a slower rate of decline in pulmonary function in patients with Duchenne muscular dystrophy compared with control subjects,[15 18] and in children with various neuromuscular disorders.[19] However, in cystic fibrosis, such data are not yet available. In children, particularly those with neuromuscular disorders, it would be interesting to examine whether ''early'' NIV is associated with better lung growth. Indeed, mechanical forces generated by the contractile activity of the diaphragm and the intercostal muscles have been shown to play an important part in normal lung growth and development in animal models by their effect on cell proliferation.[20 21]

Two other major aspects of NIV have been poorly studied. Sleep disordered breathing causes impaired cognitive function and is associated with a poor quality of life. These adverse effects may affect the patient's daily life and the school performances of a child before the occurrence of daytime hypercapnia. Studies of the effect of ''early'' initiation of NIV should evaluate these outcomes according to the underlying disease and the age of the patient.

In conclusion, having established that NIV can reverse alveolar hypoventilation in patients with neuromuscular and lung disease, the time has come to evaluate, for each disease, the optimal timing for polysomnography—the most pertinent indicator for proposing NIV—and to evaluate its benefits with regard to the course of the disease, stabilisation of lung function and respiratory muscle performance, improvement in cognitive functioning, possible preservation of lung growth in young children and, most importantly, the quality of life of the patient and his/her family.

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