Sleep Breath
DOI 10.1007/s11325-017-1538-x

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

# Sleep-disordered breathing in patients with neuromuscular disease

**Mohamad Ammar Albdewi**[1,2,3] · **Giuseppe Liistro**[4,5] · **Riëm El Tahry**[6,7,8]

Received: 12 April 2017 / Revised: 9 June 2017 / Accepted: 4 July 2017


**Abstract** Sleep-disordered breathing (SDB) is relatively common in general population as well as in patients with neuromuscular disease. SDB comprises a wide spectrum of disorders varying from simple snoring to complete closure of the upper airway as seen in obstructive sleep apnoea (OSA). It includes also other disorders like prolonged hypoxemia, hypoventilation, and central sleep apnoea (CSA). Neuromuscular diseases (NMD) form a group of disorders that can cause significant reduction in the quality and span of life. The involvement of respiratory system in the context of these disorders is the most serious complication, and it is considered as the leading cause of death in those patients. NMD can affect ventilation, cough, swallowing, and phonation. The involvement of respiratory muscles makes NMD patients vulnerable to sleep-disordered breathing with a significant prevalence of SDB among such patients.

**Keywords** Neuromuscular diseases · Hypoventilation · Noninvasive ventilation · Sleep-disordered breathing

## Introduction

Neuromuscular disease (NMD) is a group of disorders that can affect any part of the nerve and muscle. These disorders are subdivided into subgroups depending on the site and the etiology of involvement. Motor neuron disease (NMD), such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), results from the involvement of motor neurons in the brain, spinal cord, and periphery. NMD also includes peripheral neuropathies such as Charcot-Marie-Tooth disease (CMT) which affects both motor and sensory nerves. Muscles can be directly involved in NMD resulting in muscular dystrophy (MD) such as Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD). The involvement of muscles can also be in the form of myasthenia gravis (MG) in which neuromuscular transmission is affected. The predominant feature of all these disorders is the progressive deterioration of muscle strength. NMD can affect all muscles but the most

✉ Mohamad Ammar Albdewi
mohamad.albdewi@student.uclouvain.be; ammarbd@gmail.com

Giuseppe Liistro
giuseppe.liistro@uclouvain.be

Riëm El Tahry
riem.eltahry@uclouvain.be

[1] Damascus University, Damascus, Syria

[2] Université Catholique de Louvain, Brussels, Belgium

[3] Service de Pneumologie, Cliniques Universitaires Saint-Luc, Av. Hippocrate 10, 1200 Brussels, Belgium

[4] Institut de Recherche Expérimentale et Clinique (IREC), Pôle de Pneumologie, ORL & Dermatologie, Université Catholique de Louvain, Brussels, Belgium

[5] Service de Pneumologie, Epreuves Fonctionnelles Respiratoires, Centre de Médecine du Sommeil, Cliniques Universitaires Saint-Luc, Av. Hippocrate 10, 1200 Brussels, Belgium

[6] Department of Neurology-Center for Refractory Epilepsy, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Av. Hippocrate 10, 1200 Brussels, Belgium

[7] Department of Pneumology- Sleep Laboratory, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Av. Hippocrate 10, 1200 Brussels, Belgium

[8] Cleveland Clinic Epilepsy Center, Cleveland, OH 44195, USA

Published online: 12 July 2017

serious involvement is that of the respiratory muscles which can lead to respiratory failure. Despite the introduction of new techniques to manage respiratory involvement in NMD, it is still considered the leading cause of death in this group of patients [1] . Moreover, NMD patients are especially vulnerable to sleep-disordered breathing (SDB) due to several factors. Although there could be some differences depending on the type of NMD, common features can be seen in all patients such as nocturnal hypoxemia mainly during REM sleep. The prognosis in NMD depends on respiratory muscle strength [2]. However, some respiratory indices, such as low nocturnal $O_2$ saturation, were found to be associated with poor prognosis [3].

## Ventilation in normal subjects

The diaphragm is the main muscle involved in ventilation as it provides almost 70% of inspiratory tidal volume (Vt) in normal subjects [4]. External intercostal muscles and accessory muscles play a role during deep inspiration and in case of increased respiratory load such as during exercise or even at rest in patients with obstructive or restrictive lung disease [4]. Internal intercostal muscles and abdominal muscles support exhalation and aid the cough. The patency of upper airway is assured by bulbar muscles [4].

As illustrated in Fig. 1, the maintenance of spontaneous ventilation is guaranteed by the balance between the work of respiratory muscles and the respiratory load [5]. The latter is determined by the mechanics of the lungs, thorax, and the airway. In normal conditions, respiratory muscle strength exceeds the respiratory load so that normal ventilation is preserved during rest, exercise, and sleep. Figure 1 illustrates the balance between the work of respiratory muscles and the respiratory load.

Finally, $PaCO_2$ is determined by $CO_2$ production divided by Alveolar ventilation [(which in turn equals minute ventilation (tidal volume × respiratory rate) − dead space ventilation)]. Hypercapnia can result when alveolar ventilation cannot meet the metabolic needs. This can be seen with a decrease in minute ventilation, an increase in dead space ventilation or rarely an increase in $CO_2$ production.

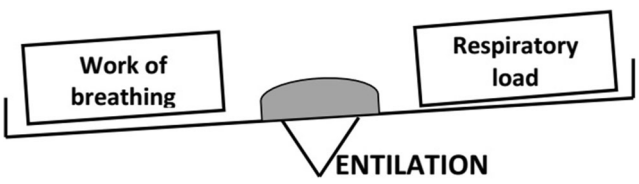


**Fig. 1** Maintenance of spontaneous ventilation guaranteed by the balance between the work of respiratory muscles and the respiratory load

## Respiratory muscle involvement in NMD

Respiratory muscles are almost always involved in NMD [6]. In conjunction with respiratory muscle weakness, the respiratory load in NMD patients is also increased so that the previous balance is disturbed. The increase in the respiratory load results mainly from the following factors:

1. Patients with NMD may be unable to take deep breaths; thus, lung expansion is significantly limited leading to chronic microatelctasis and decreased lung compliance [7].
2. Muscle atrophy, extra-articular contractures and intra-articular adhesions can cause irreversible degeneration of the joint cartilage of the rib cage leading to increased chest wall stiffness [8].
3. The contractility of respiratory muscles can be impaired due to spinal deformities seen in NMD patients such as thoracic scoliosis [9].

Moreover, respiratory muscle weakness can increase the susceptibility of the diaphragm to superimposed fatigue. A pressure-time-index has been specifically developed for the diaphragm. This index can be calculated as follows:

$$Pressure\text{–}time\ index = \left(T_i \middle/ T_{tot}\right) \times \left(P_{di} \middle/ P_{dimax}\right)$$

$T_i$ inspiratory time
$T_{tot}$ total respiratory cycle time
$P_{di}$ mean transdiaphragmatic pressure
$P_{dimax}$ maximal diaphragmatic pressure)

Ballemare and co-workers [10] found that when this index exceeded 0.15, the diaphragm was more likely to fatigue and to be unable to maintain contraction. This index also correlates well with measurements of oxygen consumption of the diaphragm [11].

A pre-existing diaphragmatic weakness (decreased $P_{dimax}$) increases this index, thus favoring the development of diaphragmatic fatigue. In order to avoid this, patients tend to have a breathing pattern that minimizes inspiratory time and transdiaphragmatic pressure (a rapid shallow breathing). This pattern decreases the vital capacity (VC) and increases the carbon dioxide arterial partial pressure ($PaCO_2$) [12].

In conclusion, with increased respiratory muscles weakness and decreased lung and chest wall compliance, the ability of patients to have an effective sigh or to breathe deeply is diminished. This can lead to microatelectasis and in consequence can create a physiologic right to left shunt. As a result, patients can be caught in a vicious cycle that leads to increased respiratory load. Figure 2 illustrates the vicious cycle leading to increased respiratory load.

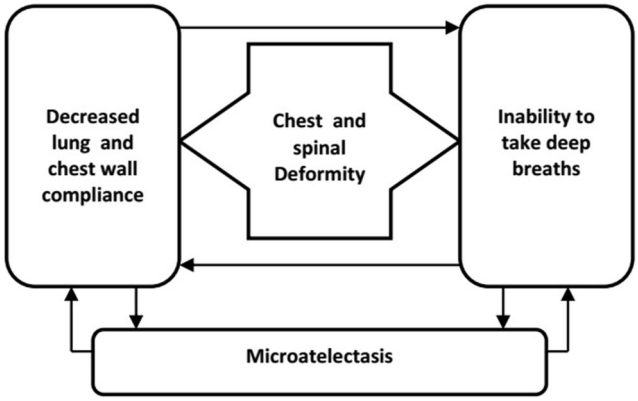


**Fig. 2** Vicious cycle leading to increased respiratory load

With advancing respiratory muscles weakness, airflow decreases and alveolar hypoventilation occurs with ongoing gradual decline in VC [4] and disturbed gas exchange escorted by ventilation-perfusion mismatch [13]. The decrease in VC can be undetected until the pressures produced be respiratory muscles are decreased by up to 50% of predicted value [14]. With further progression of diaphragmatic involvement and the continuing decline in VC, patients become more susceptible to sleep-disordered breathing. Alveolar hypoventilation appears at first during REM sleep [15].With sustained nocturnal hypoventilation, the control of breathing will be disturbed and diurnal hypoventilation develops progressively [16].

The respiratory involvement in NMD results in a restrictive defect in which VC declines before the reduction in total lung capacity (TLC) [17]. This early decrease in VC results from increased residual volume due to the weakness of expiratory muscles [17]. VC is further reduced in the supine position. A fall of VC in the supine position of more than 25% with respect to the sitting position indicates a significant diaphragmatic weakness and probable nocturnal hypoxemia [18].

## Clinical manifestations of respiratory muscle involvement in NMD

Some respiratory symptoms such as dyspnoea, may only appear late in the course of these disorders especially in patients with reduced mobility [13]. Respiratory muscle involvement can reduce cough quality, predisposing patients to respiratory tract infections and respiratory failure [6]. Upper airway region with its complex musculature system achieves sophisticated functions such as phonation, swallowing, and respiration [19]. The involvement of this region can affect all these functions. Diaphragmatic weakness can result in orthopnoea and dyspnoea when a subject is immersed in water. Dyspnoea when upright can also result from intercostal muscle weakness. When patients develop hypoventilation or SDB, they might complain of restlessness, unrefreshing sleep, vivid dreams, poor concentration, daytime sleepiness, and mood disorders. Hypercapnia can result in headache, drowsiness, confusion, and poor appetite. Table 1 illustrates the signs, symptoms, and results of pulmonary function tests used to assess NMD patients.

## Physiological changes of breathing during sleep

In normal subjects, sleep can affect respiratory system in different aspects. First, the tidal volume (Vt) and the respiratory rate decrease [20]. In addition, the chemosensitivity of the breathing control center is diminished [21], with a notable decrease in hypoxic and hypercapnic ventilatory responses especially during REM sleep [22]. The pharyngeal dilator activity is also reduced [23]. These changes are accompanied by the loss of suprapontine neural input to the medullary respiratory pattern generator leading to reduced rhythmic and tonic activation of hypoglossal and phrenic motor neurons (loss of wakefulness respiratory drive) [24]. All these factors contribute to increase $PaCO_2$ by 2–4 mmHg during sleep [20]. During REM sleep, muscle atonia causes a reduction in rib cage contribution to Vt from 44% in wakefulness to 19% [25]. The diaphragm which is innervated by the phrenic nerve is only slightly affected by REM atonia, whereas the most suppression is seen in inspiratory laryngeal, expiratory pharyngeal, and inspiratory and expiratory intercostal muscle activities [26].

## Sleep assessment in patient with NMD

The prevalence of SDB in NMD is importantly significant. It varies according to the type of NMD disorder and according to the age of patients. Most of the information about SDB in NMD children comes from studies describing DMD patients. The largest study on SDB in children with DMD was that of Suresh and co-workers [27]. They studied 32 DMD children aging from 1 to 15 years. Symptoms related to sleep were reported by 64% of children. OSA was found in 31% of patients while hypoventilation was found in 32%. In another study, Pincherle and co-workers studied 40 patients with myotonic dystrophy type 1, aged from 18 to 70 years [28]. OSA was present in 55% of patients. As the majority of neuromuscular disorders have the tendency to progress over time, the prevalence of SDB might grow larger in more advanced disorders. In general, polysomnography (PSG) is the gold standard for the assessment of SDB. As PSG is expensive and not readily available in all hospitals, other methods to detect SDB were investigated. The simplest way investigated to assess SDB is overnight oximetry monitoring. Oxygen desaturation can result from OSA, hypoventilation or other cardiovascular or respiratory diseases. With OSA, oximetry traces can show the typical saw-tooth pattern of repeated oxygen desaturation. In hypoventilation, oximetry traces will show periods of sustained $O_2$ desaturation. However, these patterns are not always present so that

**Table 1** Signs, symptoms, and results of respiratory function tests used to assess NMD adult patients

| Box (A): symptoms and signs of potential respiratory impairment | | Box (B): results of the respiratory function tests | |
|---|---|---|---|
| Symptoms | Signs | VC or FVC | SNIP or MIP |
| Breathlessness | Increased respiratory rate | VC or FVC <50% of predicted value | SNIP or MIP <40 cm $H_2O$ |
| Orthopnea | Shallow breathing | | |
| Recurrent chest infections | Weak cough | | |
| Disturbed sleep | Weak sniff | | |
| Non-refreshing sleep | Abdominal paradox (inward movement of the abdomen during inspiration) | VC or FVC < 80% of predicted value plus any symptom or sign of respiratory impairment particularly orthopnea (see box A). | SNIP or MIP <65 cm $H_2O$ for men or 55 cm $H_2O$ for women or signs or symptoms of respiratory of respiratory impairment particularly orthopnea (see box A) |
| Nightmares | | | |
| Daytime sleepiness | | | |
| Poor concentration and/or memory | Use of accessory muscles | | |
| Confusion | | | |
| Hallucinations | | | |
| Morning headache | Reduced chest expansion on maximal inspiration | | A rate of decrease of SNIP or MIP of more than 10 cm $H_2O$ per 3 months on repeated regular tests |
| Fatigue | | | |
| Poor appetite | | | |

hypoventilation and OSA cannot be accurately distinguished from each other with oximetry alone [29]. In addition, in patients with additional lung obstructive disease, hypercapnia may appear before oxygen desaturation is detected. Finally it should be mentioned that oximetry cannot always detect REM-dependent desaturation. For example, in ALS patients with diaphragmatic involvement, REM sleep can be diminished or even absent [30]. Nevertheless, the British Thoracic Society guidelines for respiratory management of children with muscular weakness considered that oximetry alone is an acceptable technique of screening for hypoventilation in asymptomatic children with NMD when $CO_2$ monitoring is not available [29].. Oxycapnography, which involves the use of portable devices that can perform transcutaneous carbon dioxide measurement, can be used to monitor oxygen and carbon dioxide during sleep. Periods of sustained desaturation coupled with sustained hypercapnia during REM sleep can suggest the presence of hypoventilation.

Some respiratory indices were also investigated as predictors of SDB. In one study [31], Ragette and co-workers investigated the patterns and predictors of sleep-disordered breathing in primary myopathies. They concluded that SDB was unlikely in patients with a VC >60% of predicted. However, a VC value <60% of predicted was associated with SBD onset with a sensitivity and specificity of 91 and 89%, respectively. Patients with VC < 40% of predicted should undergo a capnometry for further evaluation as this value correlated with continuous hypercapnic hypoventilation with a sensitivity and specificity of 94 and 79%, respectively. Authors also found that a VC < 25% was accompanied by diurnal respiratory failure with a sensitivity and specificity of 92 and 93%, respectively. Maximal inspiratory pressure (MIP), which is a measure of inspiratory muscle strength, was also investigated in the same study. An MIP value of less than 4.5 kPa (46 cm $H_2O$) correlates with SDB onset with a sensitivity and specificity of 82 and 89%, respectively. MIP of less than 4 kPa (41 cm $H_2O$) was accompanied by continuous hypoventilation with a sensitivity and specificity of 95 and 65%, respectively. Diurnal respiratory failure correlated with MIP value of less than 3.5 kPa (36 cm $H_2O$) with a sensitivity and specificity of 92 and 55%, respectively. Another study found that in most patients with NMDs hypercapnia did not develop until the maximal inspiratory pressure at the mouth declined below 30% of normal values [14].

## The level of sleep monitoring in NMD patients

According to the American Thoracic consensus statement [32], PSG with continuous $CO_2$ monitoring is the ideal test to evaluate sleep in patients with Duchenne muscular dystrophy if available (no other published consensus statements about other NMD). When PSG is not available, overnight pulse oximetry with continuous $CO_2$ monitoring can give a good idea about nocturnal gas exchange but it cannot detect SDB that is not accompanied

by increased $CO_2$ or desaturation. A simple morning capillary blood gas on arousal can refer to $CO_2$ retention but it is not as sensitive as continuous capnography.

Figure 3 (coupled with Table 1) illustrates the general assessment of adult patients with NMD according to the National Institute for Health and Care Excellence (NICE) published in February 2016 [33], while Fig. 4 illustrates the general assessment of children patients with NMD according to the British Thoracic Society guidelines for respiratory management of children with muscular weakness [29].

## Treatment of respiratory involvement in NMD

NIV is considered now the cornerstone in the management of respiratory involvement in NMD. Survival improvement with the use of NIV was established in most types of these disorders [22]. For example, patients with DMD, previously known to have a median age of death of 18–20 years, might live now till their 30s or 40s when NIV is introduced [34].In one study [35], Mellies and co-workers found that NIV has a positive longtime effect on nocturnal and diurnal gas exchange and sleep in NMD patients. They also found that in non-DMD patients, lung function stayed fairly stable or even improved slightly. Additionally, a relevant decline in vital capacity was always accompanied by a progression of scoliosis in those patients. The European Federation of Neurological Societies (EFNS) guidelines on the clinical management of amyotrophic lateral sclerosis-revised report of an EFNS task force [36] stated that NIV can prolong survival for months (level A) and may improve the patient's quality of life (level C). Another advantage of NIV is that dysphagia might improve significantly with the introduction of NIV using a mouthpiece [37]. These favorable effects resulted in a

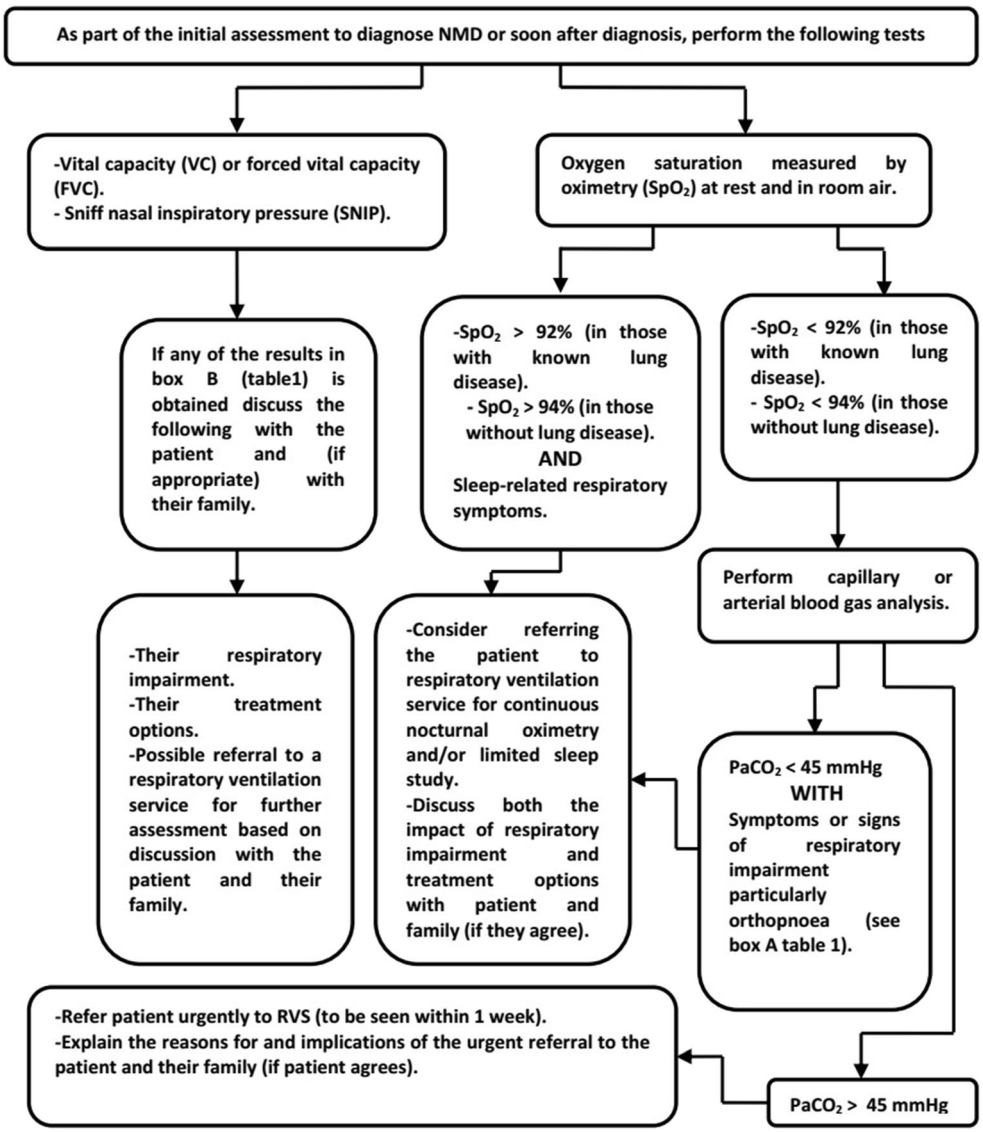


**Fig. 3** General assessment of adult patients with NMD according to the National Institute for Health and Care Excellence (NICE) published in February 2016

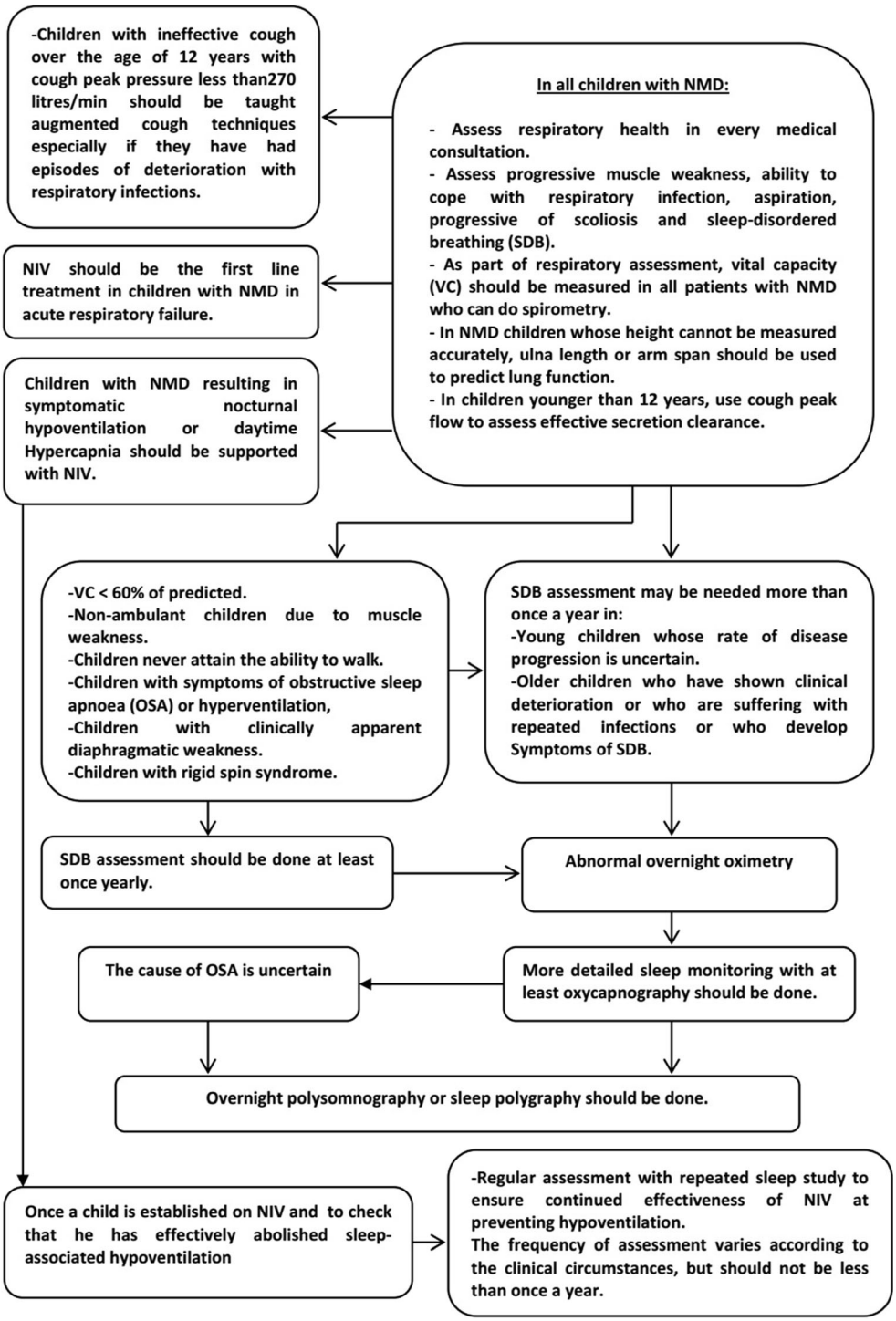


**Fig. 4** General assessment of children patients with NMD according to the British Thoracic Society guidelines for respiratory management of children with muscular weakness

tendency to early initiate NIV before the development of diurnal hypercapnia. In one randomized controlled trial [38], Ward and co-workers found that NMD patients with nocturnal hypoventilation are likely to deteriorate within 2 years, and that they may benefit from the introduction of nocturnal NIV before the development of diurnal hypercapnia. In another study [39], Villanova and co-workers found that the introduction of NIV in the presence of nocturnal hypercapnia alone delayed the development of diurnal hypercapnia till 4–5 years after NIV. In patients with ALS, the benefits of NIV were more prominent in those with normal or moderately decreased bulbar function; however, the available evidence is for offering NIV to all patients with ALS including those with poor bulbar function [40]. In the same way, the presence of cardiomyopathy in a patient with DMD should not delay the use of NIV. In fact, the improvement of survival of DMD patients

during the last three decades has been directly linked to NIV in addition to the optimal cardiac and supportive management [41]. Finally, it should be noted that NIV settings should be established in the sleep laboratory so that nocturnal apneas and hypopneas could be eliminated.

## Sleep-disordered breathing events in patients with NMD

The type of SDB may sometimes reflect the distribution of respiratory muscle dysfunction which can vary depending on the type of NMD. When the upper airway or the intercostal muscles are involved while the diaphragm is intact, obstructive events will predominate. On the contrary, the involvement of the diaphragm with the associated suppression of the intercostal and other accessory muscles during REM sleep will result in nocturnal hypoventilation [42]. The disturbed ventilatory control will also contribute to the development of hypoventilation, first during sleep and eventually during wakefulness. Taking all these abnormalities into account, one can expect to see central and obstructive events in addition to hypoventilation in NMD even within the same disease process.

**Diaphragmatic or pseudocentral SDB** These events represent hypopneas that are neither obstructive nor central as the inspiratory EMG activity is present but only reduced [15]. The lack of more specific terminology led to the use of the terms (pseudocentral) or (diaphragmatic) to refer to these events [43]. Actually, hypoventilation/hypopnea might be the most common SDB in patients with NMD [22]. These events are characterized by a saw-tooth pattern of oxygen desaturation dips during phasic REM sleep. They result from reduced contribution of the rib cage in tidal volume due to impaired intercostal muscle activity leading to an increase in the load on the already weak diaphragm [44, 45]. They are considered as an early warning sign of respiratory muscle weakness in NMD [44].

**Nocturnal hypoventilation** Hypoventilation is the hallmark of sleep-disordered breathing in NMD. As explained previously, the ability to maintain adequate ventilation depends on three main factors: respiratory muscle strength, the load applied on these muscles, and the adequacy of the central drive to breathe. As all these factors might be disturbed in NMD, such patients are at increased risk of developing hypoventilation. With diaphragmatic involvement progression and REM-associated reduced activity of intercostal and accessory respiratory muscles hypoventilation appears first during REM sleep [15]. With further progression of the disease, persistent nocturnal hypoventilation can be seen in REM and NREM sleep once VC falls to below 40% [31]. In patients with preserved diaphragmatic function, such as those with type 2 spinal muscular atrophy, mild hypoxemia with minimally increased or even normal $PaCO_2$ might be seen overnight [46]. Even with normal level of ventilatory drive, some patients cannot maintain normal $PaCO_2$ as the normal ventilatory drive is inadequate to face chronic inspiratory muscle weakness [46].

The prevalence of hypoventilation in NMD varies according to the different definitions found in the literature [47]. According to the 2012 American Academy of Sleep Medicine (AASM) guidelines [48], hypoventilation during sleep is present if either of the following occurs:

- An increase in the $PaCO_2$ (or surrogate) to >55 mmHg for >10 min.
- An increase >10 mmHg in $PaCO_2$ (or surrogate) during sleep (in comparison to an awake supine value) to a value of more than 50 mmHg for >10 min.

These guidelines recommend the use of end-tidal $PCO_2$ ($P_{ET}CO_2$) or transcutaneous $PCO_2$ ($P_{TC}CO_2$) as surrogates to $PaCO_2$.

In a recent study [47], authors compared the prevalence of hypoventilation among patients with NMD according to different definitions of hypoventilation found in the literature. They found that it was 4% when hypoventilation was defined as a $P_{TC}CO_2 > 55$ mmHg. When defined as an increase in $P_{TC}CO_2 > 10$ mmHg (in comparison to an awake supine value) to a value of more than 50 mmHg for >10 min, the prevalence was 9%. Other definitions were also used such as peak $P_{TC}CO_2 \geq 49$ mmHg (with a prevalence of 28%) and mean $P_{TC}CO_2 > 50$ mmHg (with a prevalence of 2%). The prognostic value of nocturnal hypoventilation was also studied recently by Ogna and co-workers [49]. They found that nocturnal hypercapnia with daytime normocapnia seems to predict the need for home mechanical ventilation (HMV) over the following few years. Nocturnal peak $P_{TC}CO_2 \geq 49$ mmHg was the best predictor for the initiation of HMV (with a hazard ratio of 2.1[95%CI]).

**Obstructive sleep apnea-hypopnea syndrome** The risk factors for OSA in NMD patients are generally similar to those in general population. However, some pathophysiologic features found in NMD patients, such as bulbar dysfunction and pharyngeal muscle weakness, can predispose to OSA. Macroglossia, a known risk factor for obstructive sleep apnea in general population, may also play a role in the pathogenesis of OSA in NMD patients. Macroglossia can be seen in certain NMD such as muscular dystrophies [50].

**Periodic breathing and Cheyne-Stokes breathing (CSB)** This pattern of central breathing disorders is a specific form of periodic breathing with waxing and waning amplitude of

flow or tidal volume. It is characterized by a crescendo-decrescendo pattern of respiration between central apneas or central hypopneas [48]. It can be seen in NMD due to cardiomyopathy accompanying muscle dystrophies [51] or due to disturbed breathing control as a result of diaphragmatic weakness [28].

Finally and as previously mentioned, there could be some differences in the pattern of SDB depending on the type of NMD. For example, in upper motor neuron lesion such as cerebral palsy, upper airway muscles are mostly affected making OSA the most common SDB seen in such patients. [52]. In brainstem lesions as in Arnold-Chiari malformation, the most affected muscles are the abdominals and those of the upper airway. Such patients are particularly vulnerable to central apnea [52, 53].

## Noninvasive ventilation associated sleep-disordered breathing events

NIV has shown positive effects on the span and quality of life of NMD patients and has shown to improve SDB in such patients. However, NIV can also be accompanied by some SDB events.

These events are not limited to NMD patient, but the fact that NMD is a common indication of noninvasive ventilation makes this issue of special importance.

**Air leaks** Air leaks can lead to some asynchronies such as autotriggering and prolonged insufflation [54]. They are usually associated with hypercapnia and can reduce sleep quality [55].

**Asynchrony** Patient-machine asynchronies can increase arousals and desaturations, impair sleep architecture, and reduce adherence to the NIV [56, 57].

**Prolonged insufflations** Prolonged insufflation refers to a prolonged breath delivery by the machine which exceeds the subject's desired inspiratory time [54]. Usually, it is not associated with desaturations or arousals [54]. It is more common in NREM sleep [54].

**Ineffective effort** It might be the most common asynchrony in NMD patients who use NIV [58]. It describes an effort to breathe without subsequent breath delivery from the machine. On polysomnography, a respiratory effort is seen without being accompanied by a pressure delivery by the machine [59]. It is mainly seen in NREM sleep [54] and can usually lead to reduced REM sleep [58], increased arousals [60], and reduced tolerance of NIV [58]. In patients with NMD, ineffective effort of breathing is usually associated with higher levels of pressure support and higher respiratory rate, both of which can cause dynamic hyperinflation [58]. Lowering pressure support might correct this disorder [60].

## Conclusion

Sleep-disordered breathing seems to be common in patients with neuromuscular diseases. These disorders can affect patients with or without noninvasive ventilation. NIV is considered now a cornerstone in the management of NMD. It should be considered in patients with nocturnal hypoventilation even with normal daytime $PaCO_2$. The early introduction of NIV was found to have positive effects on such patients. However, NIV can be accompanied by sleep disorders that have a negative effect on patients' quality of life. In general, NIV settings are set empirically during wakefulness so it is highly recommended that a sleep study be performed to test the validity of these settings during sleep. Sleep assessment is very essential in the workup of NMD patients and PSG, despite being sophisticated and time consuming, remains the gold standard for the assessment and diagnosis of SDB in both NMD patients and general population when available. The lack of ability to perform a complete overnight sleep study with PSG should not delay the assessment of sleep in NMD patients as other techniques, even less sensitive, can be used.

**Compliance with ethical standards**

**Funding** No funding was received for this research.

**Conflict of interest** All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

**Ethical approval** Not applicable

**Informed consent** Not applicable

## References

1. Benditt JO, Boitano LJ (2013) Pulmonary issues in patients with chronic neuromuscular disease. Am J Respir Crit Care Med 187: 1046–1055. doi:10.1164/rccm.201210-1804CI
2. Lyall RA, Donaldson N, Polkey MI et al (2001) Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. Brain 124:2000–2013
3. Pinto A, de Carvalho M, Evangelista T et al (2003) Nocturnal pulse oximetry: a new approach to establish the appropriate time for non-invasive ventilation in ALS patients. Amyotroph Lateral Scler

Other Motor Neuron Disord 4:31–35. doi:10.1080/14660820310006706
4. Mangera Z, Panesar G, Makker H (2012) Practical approach to management of respiratory complications in neurological disorders. Int J Gen Med 5:255–263. doi:10.2147/IJGM.S26333
5. Perrin C, Unterborn JN, Ambrosio CD', Hill NS (2004) Pulmonary complications of chronic neuromuscular diseases and their management. Muscle Nerve 29:5–27. doi:10.1002/mus.10487
6. Fauroux B, Khirani S (2014) Neuromuscular disease and respiratory physiology in children: putting lung function into perspective. Respirology 19:782–791. doi:10.1111/resp.12330
7. Gozal D (2000) Pulmonary manifestations of neuromuscular disease with special reference to Duchenne muscular dystrophy and spinal muscular atrophy. Pediatr Pulmonol 29:141–150
8. Papastamelos C, Panitch HB, Allen JL (1996) Chest wall compliance in infants and children with neuromuscular disease. Am J Respir Crit Care Med 154:1045–1048. doi:10.1164/ajrccm.154.4.8887605
9. Bergofsky EH (1979) Respiratory failure in disorders of the thoracic cage. Am Rev Respir Dis 119:643–669
10. Bellemare F, Grassino A (1982) Effect of pressure and timing of contraction on human diaphragm fatigue. J Appl Physiol 53:1190–1195
11. Field S, Sanci S, Grassino A (1984) Respiratory muscle oxygen consumption estimated by the diaphragm pressure-time index. J Appl Physiol 57:44–51
12. Misuri G, Lanini B, Gigliotti F, et al (2007) Mechanism of CO2 retention in patients with neuromuscular disease mechanism of CO2 retention in patients with neuromuscular disease*. 447–453. doi: 10.1378/chest.117.2.447
13. Ambrosino N, Carpene N, Gherardi M (2009) Chronic respiratory care for neuromuscular diseases in adults. Eur Respir J 34:444–451. doi:10.1183/09031936.00182208
14. Braun NM, Arora NS, Rochester DF (1983) Respiratory muscle and pulmonary function in polymyositis and other proximal myopathies. Thorax 38:616–623
15. White JE, Drinnan MJ, Smithson AJ et al (1995) Respiratory muscle activity and oxygenation during sleep in patients with muscle weakness. Eur Respir J 8:807–814
16. Fauroux B, Aubertin G, Clement A et al (2009) Which tests may predict the need for noninvasive ventilation in children with neuromuscular disease? Respir Med 103:574–581. doi:10.1016/j.rmed.2008.10.023
17. De Troyer A, Borenstein S, Cordier R (1980) Analysis of lung volume restriction in patients with respiratory muscle weakness. Thorax 35:603–610. doi:10.1136/thx.35.8.603
18. Fromageot C, Lofaso F, Annane D et al (2001) Supine fall in lung volumes in the assessment of diaphragmatic weakness in neuromuscular disorders. Arch Phys Med Rehabil 82:123–128. doi:10.1053/apmr.2001.18053
19. Ludlow CL (2004) Recent advances in laryngeal sensorimotor control for voice, speech and swallowing. Curr Opin Otolaryngol Head Neck Surg 12:160–165
20. Douglas NJ, White DP, Pickett CK et al (1982) Respiration during sleep in normal man. Thorax 37:840–844
21. Douglas NJ, White DP, Weil JV et al (1982) Hypercapnic ventilatory response in sleeping adults. Am Rev Respir Dis 126:758–762. doi:10.1164/arrd.1982.126.5.758
22. Aboussouan LS, Mireles-Cabodevila E (2017) Sleep-disordered breathing in neuromuscular disease: diagnostic and therapeutic challenges. Chest. doi:10.1016/j.chest.2017.03.023
23. Wiegand L, Zwillich CW, White DP (1989) Collapsibility of the human upper airway during normal sleep. J Appl Physiol 66:1800–1808
24. Orem J, Osorio I, Brooks E, Dick T (1985) Activity of respiratory neurons during NREM sleep. J Neurophysiol 54:1144–1156
25. Tabachnik E, Muller NL, Bryan AC, Levison H (1981) Changes in ventilation and chest wall mechanics during sleep in normal adolescents. J Appl Physiol 51:557–564
26. Kubin L, Davies RO, Pack AI (1998) Control of upper airway Motoneurons during REM sleep. News Physiol Sci 13:91–97
27. Suresh S, Wales P, Dakin C et al (2005) Sleep-related breathing disorder in Duchenne muscular dystrophy: disease spectrum in the paediatric population. J Paediatr Child Health 41:500–503. doi:10.1111/j.1440-1754.2005.00691.x
28. Pincherle A, Patruno V, Raimondi P et al (2012) Sleep breathing disorders in 40 Italian patients with myotonic dystrophy type 1. Neuromuscul Disord 22:219–224. doi:10.1016/j.nmd.2011.08.010
29. Hull J, Aniapravan R, Cham E et al (2012) British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. BTS Guidel 67:654–694. doi:10.1136/thoraxjnl-2012-202043
30. Arnulf I, Similowski T, Salachas F, Garma L, Mehiri S, Attali V, et al. (2000) Sleep disorders and diaphragmatic function in patients with amyotrophic lateral sclerosis. Am J Respir Crit Care Med 161: 849–856. doi:10.1164/ajrccm.161.3.9805008
31. Ragette R, Mellies U, Schwake C et al (2002) Patterns and predictors of sleep disordered breathing in primary myopathies. Thorax 57:724–728. doi:10.1136/thorax.57.8.724
32. Finder JD, Birnkrant D, Carl J et al (2004) Respiratory care of the patient with duchenne muscular dystrophy: ATS consensus statement. Am J Respir Crit Care Med 170:456–465. doi:10.1164/rccm.200307-885ST
33. (UK). NCGC (2016) Motor neurone disease: assessment and management. London Natl Inst Heal Care Excell (UK)
34. Ishikawa Y, Miura T, Ishikawa Y et al (2017) Duchenne muscular dystrophy: survival by cardio-respiratory interventions. Neuromuscul Disord 21:47–51. doi:10.1016/j.nmd.2010.09.006
35. Mellies U, Ragette R, Dohna Schwake C et al (2003) Long-term noninvasive ventilation in children and adolescents with neuromuscular disorders. Eur Respir J 22:631–636. doi:10.1183/09031936.03.00044303
36. Andersen PM, Abrahams S, Borasio GD et al (2012) EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)–revised report of an EFNS task force. Eur J Neurol 19: 360–375. doi:10.1111/j.1468-1331.2011.03501.x
37. McKim DA, Griller N, LeBlanc C et al (2013) Twenty-four hour noninvasive ventilation in Duchenne muscular dystrophy: a safe alternative to tracheostomy. Can Respir J 20:5–9
38. Ward S (2005) Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. Thorax 60: 1019–1024. doi:10.1136/thx.2004.037424
39. Villanova M, Brancalion B, Mehta AD (2014) Duchenne muscular dystrophy: life prolongation by noninvasive ventilatory support. Am J Phys Med Rehabil 93:595–599. doi:10.1097/PHM.0000000000000074
40. Radunovic A, Annane D, Mk R, Mustfa N (2013) Mechanical ventilation for amyotrophic lateral sclerosis / motor neuron disease ( review ). Cochrane Database Syst Rev. doi:10.1002/14651858.CD004427.pub3.www.cochranelibrary.com
41. Ishikawa Y, Miura T, Ishikawa Y et al (2011) Duchenne muscular dystrophy: survival by cardio-respiratory interventions. Neuromuscul Disord 21:47–51. doi:10.1016/j.nmd.2010.09.006
42. Piper A (2002) Sleep abnormalities associated with neuromuscular disease: pathophysiology and evaluation. Semin Respir Crit Care Med 23:211–219. doi:10.1055/s-2002-33029
43. Quera-Salva MA, Guilleminault C, Chevret S et al (1992) Breathing disorders during sleep in myasthenia gravis. Ann Neurol 31:86–92. doi:10.1002/ana.410310116
44. Weinberg J, Klefbeck B, Borg J, Svanborg E (2003) Polysomnography in chronic neuromuscular disease. Respiration 70:349–354 Doi: 72896

45. Gould GA, Gugger M, Molloy J et al (1988) Breathing pattern and eye movement density during REM sleep in humans. Am Rev Respir Dis 138:874–877. doi:10.1164/ajrccm/138.4.874
46. Simonds AK (2013) Chronic hypoventilation and its management. Eur Respir Rev 22:325–332. doi:10.1183/09059180.00003113
47. Ogna A, Quera Salva MA, Prigent H et al (2016) Nocturnal hypoventilation in neuromuscular disease: prevalence according to different definitions issued from the literature. Sleep Breath 20: 575–581. doi:10.1007/s11325-015-1247-2
48. Berry RB, Budhiraja R, Gottlieb DJ et al (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. J Clin Sleep Med 8:597–619. doi:10.5664/jcsm.2172
49. Ogna A, Prigent H, Quera Salva M-A et al (2016) Prognostic value of nocturnal hypoventilation in unventilated neuromuscular disease patients. Eur Respir J 48
50. Renard D, Humbertclaude V, Labauge P (2010) Macroglossia in adult Duchenne muscular dystrophy. Acta Neurol Belg 110:288
51. Lemay J, Series F, Senechal M et al (2012) Unusual respiratory manifestations in two young adults with Duchenne muscular dystrophy. Can Respir J 19:37–40
52. Arens R, Muzumdar H (2010) Sleep, sleep disordered breathing, and nocturnal hypoventilation in children with neuromuscular diseases. Paediatr Respir Rev 11:24. doi:10.1016/j.prrv.2009.10.003
53. Dauvilliers Y, Stal V, Abril B, et al (2007) Chiari malformation and sleep related breathing disorders. 1344–1348. doi: 10.1136/jnnp.2006.108779
54. Crescimanno G, Canino M, Marrone O (2012) Asynchronies and sleep disruption in neuromuscular patients under home noninvasive ventilation. Respir Med 106:1478–1485. doi:10.1016/j.rmed.2012.05.013
55. Gonzalez J, Sharshar T, Hart N et al (2003) Air leaks during mechanical ventilation as a cause of persistent hypercapnia in neuromuscular disorders. Intensive Care Med 29:596–602. doi:10.1007/s00134-003-1659-5
56. Crescimanno G, Greco F, Marrone O (2017) Monitoring noninvasive ventilation in neuromuscular patients: feasibility of unattended home polysomnography and reliability of sleep diaries. Sleep Med 15:336–341. doi:10.1016/j.sleep.2013.09.029
57. Fanfulla F, Taurino AE, Lupo NDA et al (2007) Effect of sleep on patient/ventilator asynchrony in patients undergoing chronic noninvasive mechanical ventilation. Respir Med 101:1702–1707. doi:10.1016/j.rmed.2007.02.026
58. Carlucci A, Pisani L, Ceriana P et al (2013) Patient-ventilator asynchronies: may the respiratory mechanics play a role? Crit Care 17: R54. doi:10.1186/cc12580
59. Pepin J-L, Borel J-C, Contal O et al (2017) Scoring abnormal respiratory events on polysomnography during noninvasive ventilation. Sleep Med Clin 9:327–339. doi:10.1016/j.jsmc.2014.05.002
60. Fanfulla F, Delmastro M, Berardinelli A et al (2005) Effects of different ventilator settings on sleep and inspiratory effort in patients with neuromuscular disease. Am J Respir Crit Care Med 172:619–624. doi:10.1164/rccm.200406-694OC