Sleep-disordered Breathing in Neuromuscular Disease

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Abstract

Sleep-disordered breathing in neuromuscular diseases is due to an exaggerated reduction in lung volumes during supine sleep, a compromised physiologic adaptation to sleep, and specific features of the diseases that may promote upper airway collapse or heart failure. The normal decrease in the rib cage contribution to the tidal volume during phasic REM sleep becomes a critical vulnerability, resulting in saw-tooth oxygen desaturation possibly representing the earliest manifestation of respiratory muscle weakness. Hypoventilation can occur in REM sleep and progress into non-REM sleep, with continuous desaturation and hypercarbia. Specific characteristics of neuromuscular disorders, such as pharyngeal neuropathy or weakness, macroglossia, bulbar manifestations, or low lung volumes, predispose patients to the development of obstructive events. Central sleep-disordered breathing can occur with associated cardiomyopathy (e.g., dystrophies) or from instability in the control of breathing due to diaphragm weakness. Mitigating factors such as recruitment of accessory respiratory muscles, reduction in REM sleep, and loss of normal REM atonia in some individuals may partially protect against sleep-disordered breathing. Noninvasive ventilation, a standard-of-care management option for sleep-disordered breathing, can itself trigger specific sleep-disordered breathing events including air leaks, patient-ventilator asynchrony, central sleep apnea, and glottic closure. These events increase arousals, reduce adherence, and impair sleep architecture. Polysomnography plays an important role in addressing pitfalls in the diagnosis of sleep-disordered breathing in neuromuscular diseases, identifying sleep-disordered breathing triggered by noninvasive ventilation, and optimizing noninvasive ventilation settings.

Keywords: neuromuscular diseases; sleep-disordered breathing; noninvasive ventilation; polysomnography; hypoventilation

Neuromuscular disorders are a diverse group of acquired or inherited conditions involving the nerves, muscles, or their connections. These disorders may share common features of reduced diaphragmatic strength, neuromuscular weakness of upper airway dilators, or cardiomyopathy that contribute to the development of sleep-disordered breathing. In turn, sleep-disordered breathing is a strong contributor to the morbidity of neuromuscular diseases, as demonstrated by the survival and quality-of-life benefits of nocturnal noninvasive ventilation (1, 2). This review covers sleep-disordered breathing events associated with neuromuscular diseases (Table 1), those associated with noninvasive positive pressure ventilation therapy (Table 2), and the role of polysomnography for the differentiation of various sleep-disordered breathing events and in the positive airway pressure titration process.

Pathophysiology

Pattern of Lung Restriction in the Supine Position and during Sleep in Neuromuscular Disease

Although total lung capacity (TLC) is the recommended volume to detect restrictive lung disorders (3), the vital capacity may be reduced well ahead of the TLC in restrictive pulmonary impairment from neuromuscular disease (Figure 1) (4, 5). The early decline in vital capacity reflects the increase in residual volume (RV) with decreasing expiratory muscle strength, as the TLC remains initially preserved with declining respiratory muscle strength (4–6). The vital capacity is further reduced in the supine position with diaphragm weakness, resulting in early symptoms of orthopnea and sleep disruption. The supine drop in vital capacity occurs predominantly from a fall in the supine TLC, such that a 25% or greater fall in vital capacity between the sitting and supine position is 90% sensitive and 79% specific for diaphragm weakness, whereas bilateral diaphragm paralysis may be associated with a 40 to 50% drop in vital capacity (7, 8). Occasionally, platypnea, orthodeoxia, and an increase in the supine vital capacity are seen in C4 to C7 tetraplegia, perhaps reflecting gravity-dependent flattening and impaired...
mechanical properties of the diaphragm (9). Some studies have shown a normal to slightly increased FRC in neuromuscular diseases (5, 10), and others have shown a decreased FRC in proportion to the inspiratory muscle strength (4). The FRC is reduced by the supine position (11) and further reduced during sleep (12, 13). The tidal volume is also reduced by about 10% during sleep (14, 15). With a relatively preserved or reduced FRC, and an elevated RV, subjects with neuromuscular diseases have a reduction of the expiratory reserve volume (ERV) (Figure 1).

Low lung volumes, and in particular the ERV, may be a risk factor for the development of obstructive sleep apnea perhaps by reducing traction and stability of the upper airway (16, 17). Furthermore, the respiratory disturbance index correlates with lung volumes such as the TLC (18) or vital capacity (19, 20). The drop in oxygen saturation with superimposed sleep-disordered breathing is more profound and more accelerated at lower lung volumes.

Table 1. Characteristics, Polysomnographic Features, and Resolution Options for Disease-related Sleep-disordered Events

<table>
<thead>
<tr>
<th>Sleep Disorder</th>
<th>Causes</th>
<th>Polysomnographic Features</th>
<th>Resolution Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocentral events</td>
<td>Diaphragm weakness, REM-related atonia</td>
<td>Reduced chest relative to abdomen signal. Positional variability: best sleep on the weaker side. Occurs in phasic REM.</td>
<td>Back-up rate, increase IPAP–EPAP gradient (pressure support)</td>
</tr>
<tr>
<td>Hypoventilation</td>
<td>Low lung volumes, decreased ventilatory response to hypercarbia from weakness and/or hypercapnia</td>
<td>$P_{\text{aCO}<em>2} &gt; 55 \text{ mm Hg for } &gt;10 \text{ min, or } a &gt;10-\text{ mm Hg increase in } P</em>{\text{aCO}_2}$ to $&gt;50 \text{ mm Hg for } 10 \text{ min.}$ Hypoxemia but no saw-tooth. Worse in REM.</td>
<td>Increase IPAP–EPAP gradient (pressure support)</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>Neurologic; pharyngeal hypotonia or neuropathy, bulbar symptoms Anatomic/structural: macroglossia, low volumes</td>
<td>Chest/abdomen signals in phase opposition, snoring, flow limitation, arousals terminate events. Saw-tooth desaturations. Worse in the supine position or in REM.</td>
<td>Increase the EPAP for obstructive apneas Increase IPAP for obstructive hypopneas</td>
</tr>
</tbody>
</table>

Definition of abbreviations: EPAP = expiratory positive airway pressure; IPAP = inspiratory positive airway pressure.

Table 2. Characteristics, Polysomnographic Features, and Resolution Options for Device-related Sleep-disordered Events

<table>
<thead>
<tr>
<th>Sleep Disorder</th>
<th>Causes</th>
<th>Polysomnographic Features</th>
<th>Resolution Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air leak</td>
<td>Mask fit, airway pressure</td>
<td>Fall in pressure signal, amputated expiratory flow, increased inspiratory time, decreased thoracic and abdominal signals. Efforts seen on flow, thoracic, and abdominal signals that are not associated with pressure delivery from the device. Usually in NREM sleep.</td>
<td>Change mask, consider chin strap.</td>
</tr>
<tr>
<td>Ineffective breathing</td>
<td>Muscle weakness, dynamic hyperinflation</td>
<td>High-pressure support. Efforts seen on flow, thoracic, and abdominal signals that are not associated with pressure delivery from the device. Usually in NREM sleep.</td>
<td>Reduce pressure support, increase trigger sensitivity, increase EPAP.</td>
</tr>
<tr>
<td>Autotriggering</td>
<td>Air leaks, water condensation, cardiac oscillations</td>
<td>At least three successive pressure delivery events in excess of the patient’s respiratory rate. Usually in NREM: more common in N1 and N2. Usually in NREM: slightly more common in N3.</td>
<td>Adjust mask, lower trigger sensitivity, drain circuit.</td>
</tr>
<tr>
<td>Prolonged insufflation Central apnea</td>
<td>Air leaks, volume guarantee devices Ventilation to a $\text{CO}_2$ below a hypocapnic apneic threshold</td>
<td>Absent flow and effort. Associated with a decrease in $\text{CO}_2$ if measured. Usually absent in REM.</td>
<td>Correct leaks, shorten inspiratory time.</td>
</tr>
<tr>
<td>Central apnea</td>
<td>Excess ventilatory support hyperventilation</td>
<td>Reduced or absent thorax and abdomen excursion with machine-delivered breaths. Worse in N2, associated with hyperventilation and lower $\text{CO}_2$.</td>
<td>Reduce pressure support.</td>
</tr>
</tbody>
</table>

Definition of abbreviations: EPAP = expiratory positive airway pressure; N1 = stage N1 sleep; N2 = stage N2 sleep; N3 = stage N3 sleep; NREM = non-REM sleep.
The nadir and mean nocturnal oxygen saturations are inversely correlated with the decline in vital capacity between sitting and supine positions (22), and the low ERV can compound the severity of desaturation that can occur with sleep-disordered breathing (23).

**Physiologic Changes in Breathing during Sleep**

The arterial PaCO\(_2\) normally increases by 2 to 4 mm Hg during sleep due to a reduction in tidal volume (14, 15), reduced respiratory rate (24), reduced chemosensitivity of the central controller of breathing (25), loss of the basal wakefulness drive to breathe (26), and a decrease in activity of pharyngeal dilators (27).

The normal loss of muscle tone during REM sleep decreases the rib cage contribution to the tidal volume to 19% relative to 40% in wakefulness and quiet sleep (24, 28). This REM atonia is due to \(\gamma\)-aminobutyric acid and glycnergic-mediated inhibition as well as reduced excitation (disfacilitation) of motor neurons (29, 30). There is a differential in the susceptibility of different respiratory motor neurons to REM atonia, with the least depression of respiratory muscle output found in the phrenic nerve and the most suppression in inspiratory laryngeal, expiratory pharyngeal, and inspiratory and expiratory intercostal nerve activities (31). Therefore, the chest wall excursion in REM sleep is dependent predominantly on the preserved diaphragm function. The impact of REM atonia on breathing pattern is most evident during phasic REM sleep (i.e., associated with eye movement), with findings of marked reduction in intercostal muscle activity and decreased tidal volumes in phasic REM sleep relative to all other sleep stages, including tonic REM sleep (15, 22).

An intact diaphragm and accessory respiratory muscles generally compensate for these existing sleep vulnerabilities. For instance, the increased workload in non-REM (NREM) sleep is matched by an increase in intercostal activity, which maintains the rib cage contribution to the tidal volume (24, 28). Similarly, an increase in diaphragm EMG activity compensates for the decrease in intercostal activity in REM sleep (24). As a result, minute ventilation is well maintained except in phasic REM sleep, during which tidal volume and minute ventilation are decreased (15). These physiologic changes during sleep become critical vulnerabilities in the context of neuromuscular and respiratory muscle weakness.

**Sleep-disordered Breathing Events Associated with Neuromuscular Diseases**

**Pseudocentral or Diaphragmatic Sleep-disordered Breathing**

Perhaps the most common sleep-disordered breathing in neuromuscular disease is hypopneas/hypoventilation with a saw-tooth pattern of desaturation dips occurring during phasic REM sleep, representing a “canary in the coal mine” early warning of respiratory muscle involvement (20, 22).
For instance, in a study of subjects with diverse causes of muscle weakness and a mean sitting vital capacity of 57%, REM desaturations were noted in all those in whom REM sleep was achieved (22). The inspiratory EMG activity is present but reduced during those events, arguing against a central or obstructive etiology (20). For lack of a more specific terminology, the substitute terms "pseudocentral" or "diaphragmatic" sleep-disordered breathing have been proposed (18, 32). Those events are due to suppressed intercostal muscle activity and reduced contribution of the rib cage to the tidal volume and shift in the burden of breathing to the already weak diaphragm (15, 20). They can be recognized by the timing of events to phasic REM sleep and the greater reduction in chest wall relative to abdominal excursions (Figure 3).

**Nocturnal Hypoventilation**

As the neuromuscular disease progresses, hypoventilation develops initially in REM sleep with decreased intercostal EMG activity (22), then in NREM sleep (33). Hypoventilation is due to the combined effects of a drop in lung volumes in the supine position during sleep and a decrease in the ventilatory response to hypercarbia, either from neuromuscular weakness despite an intact central drive (34) or from a decrease in chemosensitivity with chronic hypercapnia (35).

Nocturnal hypoventilation during sleep is defined for adults as an increase in the arterial PaCO2 to a value greater than or equal to 55 mm Hg for greater than or equal to 10 minutes, or a greater than or equal to 10-mm Hg increase in the arterial PaCO2 relative to the awake supine value, to a value exceeding 50 mm Hg for 10 minutes or more (36). For children, hypoventilation is scored when more than 25% of the sleep time is spent with an arterial PaCO2 greater than 50 mm Hg (36). These criteria may be difficult to find in the absence of daytime hypercapnia. However, using a more liberal definition, nocturnal hypoventilation with an arterial PaCO2 greater than or equal to 50 mm Hg for greater than or equal to 5% of monitoring in adults or greater than or equal to 2% of monitoring time in children is seen in more than 40% of subjects with neuromuscular disease not using noninvasive ventilation and with no daytime hypercapnia (37, 38). An average increase in PaCO2 of 20 mm Hg during sleep may be seen in neuromuscular diseases (39). On oximetry, the pattern of hypoxemia tends to be sustained in NREM sleep or associated with prominent variability (saw-tooth pattern) in REM sleep (22) (Figure 2). The latter pattern corresponds to phasic REM, as already discussed. However, desaturations are not specific and may reflect sleep-disordered breathing, low lung volumes, or atelectasis instead of hypoventilation, and a normal saturation level may occur despite nocturnal hypoventilation, especially with supplemental oxygen (40, 41). Therefore, capnography with transcutaneous or end-tidal CO2 monitoring is necessary to assess for hypoventilation and to monitor the adequacy of noninvasive ventilation settings (40).

**Obstructive Sleep Apnea–Hypopnea Syndrome**

Risk factors of obstructive sleep apnea in neuromuscular diseases are generally similar to those of the general population (including...
obesity, male sex, or adenotonsillar enlargement in children), and desaturation events are predominantly due to hypoventilation from reduced inspiratory muscle activity in association with phasic REM sleep rather than obstructive events (22, 42). Nevertheless, pathophysiologic features of some neuromuscular diseases may predispose to obstructive events, including factors that impair the compensatory neuromuscular response (such as pharyngeal hypotonia or neuropathy, or bulbar dysfunction) and to a lesser extent anatomic and structural changes (such as macroGLOSSIA and reduced lung volumes).

**Upper airway muscle hypotonia.** Sleep-disordered breathing can be seen in 79% of adults with diverse myopathies (19). Events consist predominantly of REM-related pseudocentral or diaphragmatic hypopneas but also obstructive apneas. The latter occur in 20% of subjects with dystrophies and 17% of those with acid maltase deficiency, perhaps suggesting a particular susceptibility of these specific myopathies to the development of obstructive events (19).

The pattern of sleep-disordered breathing in Duchenne muscular dystrophy (DMD) is bimodal, with obstructive sleep apnea in the first decade of life overlapping then transitioning to hypoventilation in subsequent decades (43, 44). In one study, 31% had obstructive sleep apnea (median age, 8 yr), whereas 32% had hypoventilation (median age, 13 yr) (44). Similarly, in a study of older subjects with DMD (aged 13–23 yr), 57% had apneas associated with desaturation, of which the majority (60%) were obstructive in nature but progressing with advancing age to central/pseudocentral events (43). The obstructive nature of the events was ascertained by the persistence of effort and by the presence of thoracoabdominal paradox (43).

Subjects with acid maltase deficiency have a similar bimodal sleep-disordered breathing pattern, with an early susceptibility to the development of obstructive sleep apnea combined with or followed by hypoventilation (33, 45). In infantile-onset acid maltase deficiency (ages to 0.5–17.5 mo), 41% had obstructive sleep apnea and 38% had hypoventilation (45). In contrast, in late-onset acid maltase deficiency (average age, 39 yr), 11% had obstructive sleep apnea, whereas 44% had REM-sleep hypopneas or hypoventilation associated with diaphragm weakness (33).

Sleep apnea has also been reported in 55% of subjects with myotonic dystrophy (46). However, with objective classification of events through esophageal pressure monitoring, obstructive events represented less than 15% of the total sleep-disordered breathing, with the majority of the events being pseudocentral/diaphragmatic (47).

A 32 to 56% prevalence of obstructive sleep apnea has been reported in myasthenia gravis (48, 49). Although those events were considered to be obstructive in nature and unrelated to diaphragm weakness, an earlier study that used esophageal pressure monitoring to determine the nature of the events emphasized that the sleep-disordered breathing events in myasthenia gravis were predominantly REM related rather than obstructive (18). Medical or surgical treatment of myasthenia can normalize severe sleep-disordered breathing (48, 50).

**Pharyngeal neuropathy.** An apnea–hypopnea index greater than 5 events/h was found in 38% of subjects with hereditary motor sensory neuropathy type 1 (also known as Charcot-Marie-Tooth) compared with 5% of control subjects, with apneic events being predominantly obstructive in nature (51). A possible insight into the pathophysiology was provided in a study of 14 family members with hereditary motor sensory neuropathy, showing that 11 of the 14 (79%) had evidence of mainly obstructive sleep apnea, with a strong correlation between the severity of the apnea–hypopnea index and the median nerve compound muscle action potential, indirectly suggesting that pharyngeal neuropathy is the reason for the obstructive events (52). As evidence that diaphragm impairment was not a confounder of the sleep-disordered events, the authors indicate that there was no clinical or physiologic evidence of diaphragmatic dysfunction, and events were not restricted to REM sleep (52).

**Bulbar dysfunction.** Bulbar dysfunction may be found in amyotrophic lateral sclerosis (ALS), spinal-bulbar muscular atrophy, myasthenia gravis, postpolio syndrome, and the Guillain-Barré syndrome and may predispose to the development of obstructive sleep events, although the evidence is rather weak. For instance, obstructive events were noted to be rare in ALS, but more than 10 obstructive events per hour were noted in 9% of those with bulbar symptoms compared with 2% of those without bulbar symptoms (53). Similarly, in ALS without respiratory or sleep-related complaints, hypopneas and central or obstructive apneas were found in 27% of subjects with the bulbar form of ALS (54). Conversely, in another study, 44% of subjects with ALS with bulbar involvement had hypopneas predominantly during REM sleep but essentially no obstructive sleep apnea (55). Additionally, although sleep apnea was noted to be more frequent in postpoliomyelitis with, relative to those without, bulbar impairment, the increase was predominantly due to central events (56). In another study of postpoliomyelitis, sleep-disordered breathing was no more frequent in subjects with, relative to those without, bulbar involvement (57). Bulbar symptoms may adversely affect adherence to positive airway pressure therapy (1).

**Anatomic causes of increased upper airway collapsibility.** In subjects with spinal cord injury with sleep-disordered breathing objectively classified by supraglottic pressure measurements, 33% of those with cervical cord injury and 25% of those with thoracic cord injury had obstructive sleep apnea due to an increase in passive upper airway collapsibility (58, 59). The neuromuscular compensatory response to upper airway obstruction was similar to that of control subjects, indicating that the increased upper airway collapsibility may be due to anatomic or structural causes, such as a reduced baseline lung volume through reduced traction and stability of the upper airway (16, 17) and increased cervical vascular volume (59).

Macroglossia, which has been rarely reported in muscular dystrophies (60) and more commonly reported in infantile Pompe disease (61), may also contribute to the pathogenesis of obstructive sleep apnea in neuromuscular diseases.

**Central Sleep Apnea, Periodic Breathing, and Cheyne-Stokes Breathing**

Central sleep disturbance in neuromuscular disorders is due either to Cheyne-Stokes breathing in association with cardiomyopathy, as can be seen in the dystrophies (62), or to an instability in control of breathing due to diaphragm weakness, as has been proposed in myotonic dystrophy, spinal cord injury, or
the postpolio syndrome (20, 46, 63). An important differentiating factor between Cheyne-Stokes breathing due to heart failure and periodic breathing due to instability in the control of breathing may be a cycle length greater than 40 seconds in heart failure, corresponding to the prolonged circulation time (36, 64).

In the setting of cervical (C5–C7) spinal cord injury, 63% of subjects had central apneas and 88% had periodic breathing, perhaps reflecting an increased plant gain, whereas in thoracic spinal cord injury (T1–T6), 13% had central sleep apnea and 38% had periodic breathing (63).

There is a potential concern of positive pressure ventilation in preload-dependent individuals with impaired cardiac function. For instance, a randomized trial documented an increase in mortality in subjects with DMD randomized to the noninvasive ventilation arm (65). One explanation was a possible bias such that a higher proportion of subjects with left ventricular dysfunction were randomized to noninvasive ventilation. A parallel observation was made in the CANPAP (Canadian Continuous Positive Airway Pressure) study, in which subjects randomized to continuous positive airway pressure for central apnea and heart failure had an early survival disadvantage (66).

**Pitfalls in the Identification of Sleep-disordered Breathing**

Diaphragm and respiratory muscle involvement in neuromuscular diseases often hinders the identification of the precise etiology of sleep-disordered breathing, particularly in the absence of direct or indirect measurement of inspiratory effort (e.g., diaphragm EMG, esophageal or supraglottic pressure monitoring, pulse transit time).

Obstructive apneas may be misclassified as central in neuromuscular disease due to the inability of weak respiratory muscles to expand the chest or abdomen against an occluded airway. In that context, some measurement of respiratory effort is necessary to ensure that obstruction is not present (67), as has been demonstrated in DMD, where continued submental EMG activity was noted during inspiration throughout apparent central apneas (68). Furthermore, paradoxical movement of the chest and abdomen, which is used to define obstructive events (36), occurs in neuromuscular disease in the absence of airway narrowing (69).

Conversely, during a clear obstructive event documented by esophageal pressure monitoring, paradox may not be seen in the presence of muscular weakness (67).

Compounding those issues, pseudocentral/diaphragmatic events can be misclassified as obstructive. Specifically, a much lower prevalence of obstructive sleep apnea in neuromuscular diseases is seen in studies that objectively classify obstructive versus nonobstructive events with the use of diaphragmatic EMG or esophageal monitoring (18, 22, 47).

Finally, there is a complex interplay between features of neuromuscular diseases that may facilitate airway obstruction (such as bulbar dysfunction, pharyngeal neuropathy or hypotonia, reduced lung volumes, and macroGLOSSIA) and the neuromuscular weakness which, when it involves the respiratory muscles, reduces the ability to generate the negative pressure necessary for airway collapse and promotes instead REM-related pseudocentral events (55). Ultimately, the neuromuscular weakness and the REM-related pseudocentral events may predominate, with a time course that depends on features of the disease and the tempo of progression to respiratory muscle impairment. This interplay may explain that obstructive sleep apneas are more frequent in neuromuscular subjects with a higher vital capacity (20), that obstructive events decrease in frequency in proportion to the duration of ALS (53), anecdotal evidence of resolution of snoring with neuromuscular disease progression, the absence of obstructive apnea in ALS associated with orthopnea (55), and the bimodal distribution of disease (obstructive events early in the course of the disease and REM-related pseudocentral events later on) in more slowly progressive disorders (such as DMD and acid maltase deficiency) (33, 43–45).

**Possible Compensatory Mechanisms**

Compensatory mechanisms may mitigate diaphragm weakness. For instance, recruitment of accessory respiratory muscles in NREM prevents oxygen desaturation in long-standing poliomyelitis (70). This recruitment is evidenced by inspiratory activity of the genioglossus, intercostal, and sternomastoid muscles and expiratory activity of abdominal muscles (22, 70). REM sleep may also be reduced or even completely absent with diaphragm dysfunction, thereby reducing the vulnerable period during which sleep-disordered breathing is more likely to occur (22, 71). Last, preserved phasic sternomastoid activation during REM sleep can prolong REM sleep and protect against hypoventilation (71). Activation of the sternomastoid or genioglossus muscles during phasic or tonic REM sleep may occur in up to 39% of subjects with diverse chronic neuromuscular conditions (20, 22).

This unusual but potentially protective loss of normal REM atonia has been reported in ALS as early as 1979 (72). There are even reports of frank REM behavior disorder in ALS (73, 74), myotonic dystrophy (75), spinal muscular atrophy (76), and the Guillain-Barré syndrome (77).

**Sleep-disordered Breathing Events Associated with Noninvasive Ventilation**

Sleep-disordered breathing specifically attributed to the use of noninvasive ventilation is not limited to subjects with neuromuscular diseases but is important to consider in this review because a neuromuscular disorder is a common indication for home use of noninvasive ventilation. For instance, in a European survey, a neuromuscular disorder was an indication for about 80% of Danish noninvasive ventilation users (78). The discussion that follows is predominantly based on evidence from neuromuscular diseases (Table 2).

**Air Leaks**

Air leaks are found in 34% of subjects undergoing noninvasive ventilation, are associated with hypercapnia in neuromuscular diseases, may account for asynchronies such as autotriggering and prolonged insufflation (79), and affect the quality of sleep (80). Air leaks can be recognized by a fall in the pressure signal, amputation of the expiratory flow signal, two-sloped aspect of the inspiratory flow curve, increased inspiratory time, and decrease in belt signals (81). Air leaks may respond to the addition of a chin strap or better mask adjustment (41).

**Asynchrony**

Although patient–ventilator asynchrony is predominantly reported with application of
invasive and noninvasive ventilation in the acute care setting (82), there is considerable evidence it also occurs with noninvasive ventilation in the chronic outpatient setting in up to 58% of cases and has been specifically documented in neuromuscular diseases, where it can cause increased arousals, desaturations, impaired sleep architecture, and reduced adherence to the intervention (79, 83–87).

Ineffective effort. Ineffective effort describes an effort to breathe without subsequent breath delivery from the noninvasive device. Ineffective effort may represent the most common cause of asynchrony with noninvasive ventilation in neuromuscular diseases, found in 45% of cases, such that an ineffective triggering index (representing the proportion of ineffective breaths relative to the total) of greater than 10% was found in 20% (85). Ineffective effort occurs predominately in NREM sleep, particularly stage N1–2 sleep, and is associated with increased arousals (79, 86), reduced REM sleep (86), and reduced tolerance of noninvasive ventilation (85). Although one study has shown no association with desaturations (79), another did show association (87). Although this type of event can be expected in obstructive lung disease from the threshold load imposed by increased intrinsic positive end-expiratory pressure, one study has shown that it occurs with equal frequency in obstructive and restrictive lung disease (85).

In neuromuscular diseases, ineffective breathing may be uncommon due to failure to trigger the device and more usually associated with higher levels of pressure support and higher respiratory rate, both of which can cause dynamic hyperinflation (85–87). Ineffective triggering can be recognized on a polysomnogram by a respiratory effort (identified on the flow, thoracic belt, and abdominal belt signals) that is not associated with pressure delivery from the device (88). Ineffective triggering may resolve by decreasing the pressure support level or adjusting the end-expiratory pressure to a level closer to the dynamic end-expiratory pressure (86).

Autotriggering. Autotriggering refers to breath delivery from the noninvasive device in excess of the subject’s respiratory rate. An autotriggering index (representing the proportion of ineffective relative to total breaths) of greater than 10% was found in 30% of subjects with chronic respiratory failure (85). Autotriggering was the most common asynchrony in neuromuscular diseases in one study (79). It occurs mostly in NREM sleep, especially stage N1–2 sleep, and is usually associated with increased arousals (79) and reduced adherence to the device (85). Autotriggering can be due to air leaks, excessive water condensation in the circuit, and cardiac oscillations (89). It can be identified as at least three successive breaths delivered by the device in excess of the subject’s respiratory rate and may respond to mask adjustments, draining the circuit, and adjusting the trigger sensitivity (79).

Prolonged insufflation. Prolonged insufflation represents extension of breath delivered by the device beyond the subject’s desired inspiratory time (79). This event is more common in NREM sleep, perhaps slightly more in stage N3 sleep relative to stages N1 and N2, is usually not associated with desaturations or arousals, and may be more common with a mode of ventilation that targets a certain lung volume, though also seen with time-cycled ventilation (79).

Central Sleep Apnea
Overassistance and excessive pressure support with noninvasive ventilation may draw the PaCO2 below a hypopapnic apneic threshold and trigger central apneas (90). Ineffective breathing and central apneas were the most common problems arising in the course of noninvasive ventilation for neuromuscular diseases in one study, with a central apnea index greater than 5 found in one-third of subjects (86). Although central apnea due to overassistance is most common in NREM sleep, it is also associated with a reduction in REM sleep (86). This type of central apnea can be corrected by a strategy that reduces the pressure support (86).

Glottic Closure
Glottic closure from adduction of the vocal cords is an exaggerated protective laryngeal reflex originating from bronchopulmonary receptors (91). Although glottic closure occasionally occurs during wake in ALS or myotonic dystrophy (81), this section specifically addresses its occurrence in the course of noninvasive ventilation, which was first reported in congenital myopathy (92). In normal sleeping subjects, progressive glottic closure in proportion to an increase in volume ventilation may limit the expected increase in tidal volume (93). In pressure-limited modes of ventilation, glottic closure occurs more consistently with controlled breaths rather than spontaneous breaths (94, 95). Therefore, unlike the oropharyngeal obstruction of obstructive sleep apnea, glottic closure usually occurs in the absence of inspiratory effort and in the context of machine-delivered breaths. Glottic closure is worse in stage N2 sleep relative to stage N3, is associated with hyperventilation and lower PaCO2, and improves with CO2 administration (93) or use of a spontaneous mode (or reduced back-up rate) (94, 95).

The Role of Polysomnography
Polysomnography plays a vital role in the evaluation and management of neuromuscular diseases. From a diagnostic perspective, practice parameters of the American Academy of Sleep Medicine consider that “for patients with neuromuscular disorders and sleep related symptoms, polysomnography is routinely indicated to evaluate symptoms of sleep disorders that are not adequately diagnosed by obtaining a sleep history, assessing sleep hygiene, and reviewing sleep diaries” (96). From a therapeutic perspective, a best clinical practice report advised that noninvasive positive pressure titration with attended polysomnography “is the recommended method to determine an effective level of nocturnal ventilatory support in patients with chronic alveolar hypoventilation” and “allows definitive identification of an adequate level of ventilator support for patients with neuromuscular disease in whom noninvasive positive pressure ventilation treatment is planned” (97). Specifically, polysomnography plays a central role for the correct classification of respiratory events (36), for the identification of events that may be triggered by noninvasive ventilation (81, 88), and for the implementation of an effective titration strategy (86, 97).

Classification of Events
The pitfalls in the identification of sleep-disordered breathing highlight the increased possibility of misclassification of sleep-disordered events in neuromuscular diseases, with a possible bias toward labeling pseudocentral events as obstructive and a consequent risk of inadequate treatment of
the sleep-disordered breathing (98). The American Academy of Sleep Medicine provides some guidance as to the scoring of sleep-disordered breathing events, including central hypopneas (36). For instance, even without direct measurement of inspiratory effort, events are likely to be obstructive if there is flow limitation on a pressure-transduced channel, phase opposition in the thoracic and abdominal belt signals, or snoring, or if arousals terminate the events (36). Events are more likely to be central if they are associated with periodic breathing and if arousals occur at the peak of ventilation as opposed to the resumption of ventilation. Central sleep apnea is usually associated with a proportional and simultaneous decrease in thoracic and abdominal belt signals without phase opposition (81). In contrast, pseudocentral events and hypventilation due to neuromuscular disease is suspected when events occur predominantly during phase REM sleep with asymmetric greater decrease in the thoracic belt excursion relative to the abdominal belt (Figure 3) (15). An additional clue to a neuromuscular cause to the sleep-disordered breathing events is positional variability in events and desaturations in cases with differential diaphragm impairment, such that sleep-disordered events are more prominent in a lateral decubitus position with the least affected side down.

**Identification of Sleep-disordered Breathing Triggered by Noninvasive Ventilation**

The European SomnoNIV group ascribes an important role for the sleep laboratory in the identification and scoring of respiratory events occurring in the context of noninvasive ventilation (40, 88, 99). These studies provide a framework for standardization of reporting and comparison of findings. The group proposes a systematic analysis for detection of events such as air leaks, decrease in ventilator drive, glottic closure, asynchrony, or combination of events (81, 88). This analysis can be readily obtained from signals obtained during a standard polysomnography, such as the device pressure signal, flow signal, abdominal and thoracic belts, and saturation levels, and can provide sufficient and specific information for the detection of device-associated sleep-disordered events (Table 2) (81, 88). Capnography (to detect hypoventilation), pulse transit time (a surrogate marker of inspiratory muscle effort), and device-specific software (which can include measures of parameters such as rate, leaks, minute ventilation, tidal volume, percent of patient-triggered breaths) may provide additional important information (40, 88, 99, 100).

**Positive Airway Pressure Titratin**

Although the goal of noninvasive ventilation is not necessarily to normalize the nocturnal PaCO₂ (86), 53% of neuromuscular subjects on nocturnal ventilation still have nocturnal hypventilation (37). Guidelines to address obstructive sleep-disordered breathing, hypventilation events, and asynchrony on polysomnography have been published (97). Suggested recommendations from those guidelines are to use a back-up rate on a bilevel device, control obstructive sleep events first then hypventilation (as assessed by desaturations or hypercapnia on a transcutaneous CO₂ monitor), and improve synchrony by adjusting the inspiratory time to between 30 to 40% of the total cycle time. Generally, subjects with neuromuscular disorders prefer a longer inspiratory time within this range and may be more comfortable with a slower rise time to the set pressure (97).

One study compared a usual to a physiologic approach during a titration study in subjects with neuromuscular disease. The physiologic approach selected sufficient inspiratory pressure to reduce the tidal swings in transdiaphragmatic pressures by 40 to 80% and applied an external positive end-expiratory airway equal to about 80% of the dynamic positive end-expiratory pressure (86). Although both approaches improved daytime blood gases and successfully unloaded the inspiratory muscles, the physiologic approach additionally improved sleep efficiency and reduced ineffective breathing, with a corresponding increase in the percentage of REM sleep (86).

In conditions where obstructive sleep apnea and hypventilation from diaphragm dysfunction coexist, as may occur in DMD and acid maltase deficiency, there may be competition between the higher expiratory pressure to control obstructive sleep apnea and the higher pressure support required to control hypventilation (101). The resolution of these issues may require maintaining or increasing the pressure support with increasing expiratory positive airway pressure while monitoring capnometric readings and avoiding central apneas from overventilation (101).

Automatic servoventilation devices are used for the management of sleep-disordered breathing in heart failure with instability in the control of breathing (102). These devices may have variable inspiratory pressure support to compensate for periodic and Cheyne-Stokes breathing, automatic adjustments of the back-up rate for central events, and variable expiratory airway pressure based on algorithms that distinguish an open from an obstructed airway. These types of devices may trigger events such as glottic closure (103) and may not address concomitant hypventilation in subjects with neuromuscular disease and cardiomyopathy. Therefore, the sleep laboratory still has an important role in identification of these events, with titration options including setting an appropriate minimal pressure support (to address hypventilation), setting a minimal end-expiratory pressure, and changing mask device to a nasal mask (for possible glottic closure) (103).

Finally, there are devices that target a preset tidal volume or alveolar ventilation and automatically adjust the pressure support, which would otherwise be empirically adjusted in progressive neuromuscular diseases. However, some studies show that volume-targeted devices can cause repetitive arousals attributed to rapid changes in inspiratory pressure (104), increase asynchronies such as prolonged inspiration (79), reduce total sleep time and stage N2 sleep, and increase wake after sleep onset and awakenings (40). The sleep laboratory may therefore help identify and troubleshoot those events.

**Conclusions**

Hypoventilation and nocturnal desaturation in neuromuscular diseases are due to the combined effects of reduced lung volumes during supine sleep and sleep-disordered breathing subsuming phasic REM-related pseudocentral events, desaturations, hypventilation, obstructive, and central sleep events. Although noninvasive ventilation reverses these events and can
improve survival and quality of life, it can also be associated with sleep-disordered events including air leaks, ventilator–patient asynchrony, central events, and glottic closure that contribute to desaturations, arousals, impaired sleep architecture, and poor adherence. Polysomnography using conventionally available parameters is an important tool for accurate classification of sleep-disordered breathing, identification of events triggered by noninvasive ventilation, and titration to appropriate settings.

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**References**


