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SLEEP (M THORPY AND M BILLIARD, SECTION EDITORS)

Sleep Disordered Breathing in Duchenne Muscular Dystrophy

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Abstract This review aims to explain the inevitable imbalance between respiratory load, drive, and muscular force that occurs in the natural aging of Duchenne muscular dystrophy and that predisposes these patients to sleep disordered breathing (SDB). In DMD, SDB is characterized by oxygen desaturation, apneas, hypercapnia, and hypoventilation during sleep and ultimately develops into respiratory failure during wakefulness. It can be present in all age groups. Young patients risk obstructive apneas because of weight gain, secondary to progressive physical inactivity and prolonged corticosteroid therapy; older patients hypoventilate and desaturate because of respiratory muscle weakness, in particular the diaphragm. These conditions are further exacerbated during REM sleep, the phase of maximal muscle hypotonia during which the diaphragm has to provide most of the ventilation. Evidence is given to the daytime predictors of early symptoms of SDB, important indicators for the proper time to initiate mechanical ventilation.

Keywords Duchenne muscular dystrophy · Sleep disordered breathing · Diaphragm · NIV · Daytime predictors · Control of breathing

This article is part of the Topical Collection on *Sleep*.

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Introduction

Sleep is an actively regulated physiological process essential for the whole human being. The most important function of sleep is to allow the brain to reorganize its neuronal activity to the point that "sleep is of the brain, by the brain and for the brain" [1]. Sleep-induced alterations occur not only to brain activity but also to other physiological processes like heart rate, blood pressure, sympathetic nerve activity, body temperature, sexual arousal, and respiration.

Sleep disorders are chronic conditions and are frequently comorbid with other syndromes and conditions [2]. Patients with neuromuscular diseases are especially prone to sleep disordered breathing (SDB), being in turn a strong contributor to the morbidity of the disease itself establishing a dangerous vicious cycle.

The aim of the present review is to explain the mechanisms of this vicious cycle in Duchenne muscular dystrophy (DMD). It also provides a brief description on how it can be potentially treated and eventually predicted. In this review, priority is given to the specific studies dealing only with DMD instead of nonspecific studies including several neuromuscular disorders other than DMD.

Normal Sleep in Humans

There are three states of being: wakefulness, rapid eye movement (REM) sleep, and non-REM (NREM) sleep.

In more recent literature, NREM sleep is composed of three different stages (previous classifications defined four different stages) each characterized by unique and specific brain wave patterns and muscular tone. NREM sleep starts with a short period of stage 1 characterized by alpha waves and is the transitional stage between wakefulness and sleep. Stage 2 is

the first unequivocal stage of sleep that is mainly characterized by theta waves. Stage 3 is referred to as slow-wave sleep or deep sleep and is characterized by the presence of delta waves. Stage 3 sleep combines the previous classifications of stages 3 and 4. NREM sleep constitutes 75–80% of total sleep time. The remaining 20–25% of sleep time consists of REM sleep that normally follows NREM stage 3 and is characterized by bursts of rapid eye movements, EEG desynchronization, and loss of muscle tone and reflexes. REM sleep is not a homogenous state. It comprises a phase wherein bursts of rapid eye movements occur and a tonic phase characterized by no eye movements, skeletal muscle atonia, and a desynchronized low-voltage EEG pattern [3].

During sleep, a regular cyclic alternation of REM and NREM phases occurs throughout the night and is associated with dynamic and physiological changes in systemic processes and bodily functions [1, 2, 4, 5]. Sleep architecture commonly occurs in sleep cycles where the first sleep cycle lasts between 70 and 100 min, and the remaining sleep cycles last roughly 90 min each. Every sleep cycle finishes with REM sleep. In the first sleep cycle, the REM stage may only last a moment or a few minutes, but as the sleep cycles progress through the night, stage 3 sleep is progressively replaced by REM sleep and, in the final sleep, cycles may replace it entirely, i.e., REM follows directly stage 2 [6].

The Control of Breathing

The respiratory muscles do not have an intrinsic rhythmicity being totally dependent on the efferent impulses coming from the respiratory center. The respiratory control of breathing is composed of two mechanisms that are anatomically distinct but functionally integrated. The first mechanism is a suprapontine control system that includes both voluntary and behavioral influences together with the wakefulness drive to breathe. The second mechanism is an autonomic metabolic and mechanical control, therefore completely involuntary. These mechanisms are both integrated in the respiratory center from which they modulate output in order to meet the ventilatory demands [7, 8].

In the transition from wakefulness to sleep, the suprapontine input is suppressed. During sleep, respiration is entirely regulated by metabolic factors alone that in healthy subjects guarantee adequate gas exchange and provide a stable respiratory pattern [8–10]. More in detail, a supraspinal inhibition of γ-motoneurons and presynaptic afferent terminals from muscle spindles occurs during REM sleep with relatively preserved α-motoneurons [8, 10].

The metabolic control of breathing is modulated and regulated by chemoreceptors, whereas the mechanical control is modulated and regulated by mechanoreceptors [11].

There are two types of chemoreceptors: the peripheral and the central ones. Peripheral chemoreceptors are located in the carotid sinus and in the aortic body, and they respond to changes of arterial partial pressure of oxygen (PaO_2) [12]. The more PaO_2 decreases, the more the afferent activity from the carotid body increases, making respiratory rate increase in order to augment minute ventilation. This is known as the hypoxic ventilatory response. This hypoxic response becomes lower with deeper sleep. Also, the arousal response to breathing resistance becomes lower in NREM stage 3 [13].

Central chemoreceptors are located in the medulla oblongata and in the midbrain. They are sensitive to changes in pH and also indirectly to arterial partial pressure variations of carbon dioxide ($PaCO_2$). A decreasing arterial pH triggers these chemoreceptors to make minute ventilation increase, with corresponding decrease in $PaCO_2$ that, in turn, prompts an increment of pH. When pH rises, a compensatory reduction of minute ventilation makes $PaCO_2$ increase to reduce pH back to physiological levels. This is known as the hypercapnic ventilatory response [14, 15].

Peripheral chemoreceptors also respond to $PaCO_2$ changes, with carotid body also being sensitive to changes in pH, but to a lesser extent and more rapidly compared to the central ones.

Carbon dioxide (CO_2)-induced hypercapnia does not induce changes in the corticomotor excitability of either the diaphragm or the genioglossus [15, 16].

Mechanoreceptors are located in the airway smooth muscles, in the alveoli, and in the respiratory muscles, being sensitive to lung stretch, increased interstitial fluid volume, and muscle fiber tension, respectively [14]. In tracheostomized patients or in the case of increased airway resistance, the fall in ventilation and the rise in end-tidal pCO_2 during sleep are not altered. This indicates that chemoreceptors, rather than mechanoreceptors, are the primary controls of ventilation during sleep [17–19].

Cough reflex is suppressed during sleep [20]. Normal sleep is characterized by episodes of spontaneous arousal so that the suprapontine control system can return to control ventilation making the ventilatory drive increase in order to rapidly reduce $PaCO_2$ back to wakefulness values [14, 21].

Sleep and Breathing

From a ventilatory point of view, sleep induces changes in the respiratory muscles in terms of electrical activity, fiber shortening, and action.

Different patterns characterize every sleep phase. During NREM sleep, the electrical activity of intercostal muscles increases by a means of 34% compared to wakefulness status, whereas the electrical activity of the diaphragm does not change [8, 22, 23, 24•]. As a consequence, ribcage contribution to tidal volume progressively increases with the deepness

of NREM sleep and abdominal expansion decreases (Fig. 1) [8, 22, 23, 25, 26]. Trans-diaphragmatic pressure (P_{DI}) increases by 20% in NREM sleep compared to the wakefulness state. This implies that the contraction of the diaphragm becomes more efficient, as it generates higher pressure with the same level of electrical activation [22].

During REM sleep, there is a change in the distribution of the respiratory effort among respiratory muscles [23, 27]. In fact, the electrical activity of lower lateral external intercostal muscles is inhibited [24•] and ribcage expansion, in turn, falls (Fig. 1) [8, 22, 23, 25, 26]. Parasternal intercostal muscles and the diaphragm, in both its costal and crural part, remain fully active [24•]. The diaphragmatic electrical activity substantially increases, while P_{DI} decreases which implies that the efficiency of the diaphragm is reduced during REM sleep. This is confirmed by the fact that during REM sleep, tidal volume reduces, indicating that the action of the diaphragm is less effective than during the awake state [8, 25, 26, 28].

While diaphragmatic shortening does not change from wakefulness to sleep, the shortening of parasternal intercostal muscles decreases in both NREM and REM sleep despite the preservation of their electrical activity [24•]. The lesser contractility of parasternal intercostal muscles, i.e., reduced shortening per unit of electrical activity, and the differences in diaphragmatic efficiency may be attributed to the mechanical advantage/disadvantage of the overall changes in chest wall mechanics during sleep [8, 22, 24•]. The activation of intercostal muscles during NREM sleep may optimize the morphology of the diaphragm by increasing its length and/or radius of curvature [8, 22, 28]. During the REM sleep phase, the contraction of the diaphragm further increases making pleural pressure decrease. Intercostal muscles are inhibited with the exception of parasternal intercostal muscles. This means that parasternal intercostal muscles alone are not able to counteract the effects of the increased contraction of the diaphragm that is partially wasted in distorting the chest wall resulting in thoraco-abdominal asynchrony [8, 22, 24•, 28].

Taken together, these data show that (1) phrenic and parasternal motoneurons are spared by REM-related inhibition, (2) parasternal intercostal muscles remain active to provide ventilation also during REM sleep, and (3) parasternal intercostal muscles are essential inspiratory muscles like the diaphragm [9, 24•].

Pharyngeal and upper airway muscle tone is reduced during sleep, particularly during REM phase, making upper airway resistance increase [8, 14, 22, 29–31].

The result of sleep-induced motor inhibition of respiratory and airway muscles, the so-called REM "atonia," is hypoventilation. Inspiratory flow, an index of inspiratory drive, minute ventilation, and its two components, namely breathing frequency and tidal volume, become faster and more irregular. The result is hypoventilation during sleep in particular during REM phase [8, 23, 25, 28, 30, 32–34].

Sleep Disordered Breathing

Several disorders affect sleep and are among the most commonly overlooked health problems that hinder daily activities and functions. The cumulative effect of these disorders may lead to a wide range of health problems such as hypertension, diabetes, obesity, depression, heart attack, and stroke [30, 35].

Among sleep disorders, sleep-related breathing disorders refer to four different types: (1) obstructive sleep apnea syndrome, (2) central sleep apnea syndrome, (3) sleep-related hypoventilation disorder, and (4) sleep-related hypoxemia disorder [36, 37].

Symptoms of SDB are excessive daytime sleepiness, fatigue, exertional dyspnea, decreased concentration, morning headaches, and mood changes [30, 38]. SDB may turn into deficient ventilation resulting in hypoxemia (reduced oxygen

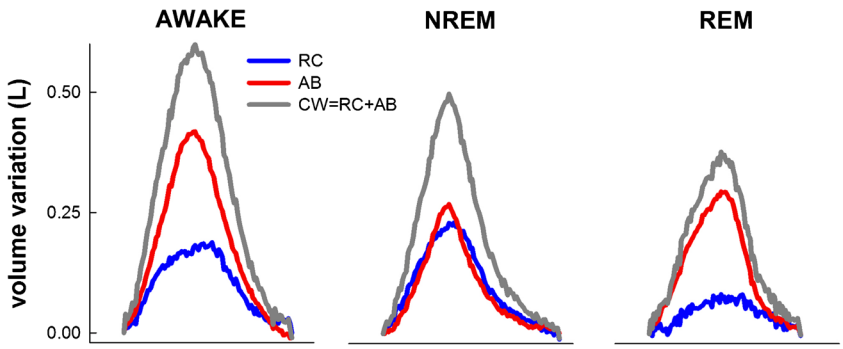

Fig. 1 Representative breaths during wakefulness spontaneous quiet breathing in supine position (AWAKE, *left panel*), non-REM sleep (NREM, *middle panel*), and REM sleep (*right panel*) phases of a healthy subject. The volume variations of the chest wall (CW, *gray*) and its two compartments, the ribcage (RC, *blue*) and the abdomen (AB, *red*), are reported. Passing from the awake status to non-REM sleep, the contribution of the ribcage to tidal volume increases with a corresponding reduction of abdominal contribution. During the REM sleep phase on the other hand, there is an inversion in the thoraco-abdominal contribution to tidal volume with breathing becoming almost completely abdominal (diaphragmatic) with a fall of thoracic expansion. During sleep the action of the diaphragm is lower than wakefulness

content in the blood, i.e., nocturnal SpO_2 [oxyhemoglobin saturation] ≤90% for more than 5 min with a nadir ≤85 or 30% of total sleep time spent with an SpO_2 of 90%), hypercapnia (increased levels of CO_2 in the blood >45 mmHg) or both [35, 36].

Obstructive sleep apnea (OSA) and hypopneas are the most common disorders. They are respectively defined as complete or partial episodes of collapse of the pharyngeal airway resulting from relaxation of the soft tissue in the rear of the throat. Apneas/hypopneas create an obstruction to the air passing through the airway, and vigorous respiratory efforts are present. The direct consequence is the fall of blood oxygenation that leads to arousal accompanied by snorts or gasps when the patient manages to overcome the obstruction and resume breathing [12, 34, 39].

Central sleep apnea is due to a temporary reduction or cessation of central respiratory drive, the cause of which is occasionally unclear and labeled "idiopathic." Patients consequently stop breathing until chemo-sensitivity increases to trigger hyperventilation in order to force $PaCO_2$ below the apneic threshold [14, 35, 40, 41].

Apneas therefore fragmentize sleep in response to the breathing pauses, and this leads to excessive daytime sleepiness, reduced concentration, and mood changes [14, 39].

The sleep-induced hypoventilation and hypoxemia may be primary, as a consequence of blunted central/peripheral chemo-responsiveness, or because of a congenital condition. It may also be comorbid with different medical conditions including neuromuscular disorders. They impair the patient's ability to breathe in terms of either dysfunction of respiratory motor innervation or respiratory muscle weakness. [36, 42].

Duchenne Muscular Dystrophy

Among the inherited diseases, DMD is the most common and severe form of myopathy in children that affects 1 out of 3600–6000 male births. It is caused by mutations in the dystrophin gene, resulting in progressive weakness and debilitation of all striated musculature, beginning with limb muscles and ending with respiratory muscles [43–45]. DMD patients experience progressive motor impairment, loss of ambulation before teen ages, severe, and ultimately cardiac and/or breathing failure, which is the ultimate cause of death [46–49].

Although no therapy is available, DMD patients' life expectancy has significantly improved up to the fourth decade thanks to a comprehensive and structured therapeutic approach particularly targeted to respiratory care [50–57]. With the progression of the disease, in fact, respiratory muscles are affected and DMD patients are characterized by reduced force of their respiratory muscles. This leads to poor spirometry, restrictive lung pattern, rapid and shallow breathing, ineffective cough, SDB, and ultimately respiratory failure [58–67].

In particular, the diaphragm progressively shows increasing thickness that may indicate pseudo-hypertrophy due to infiltration of connective tissue and fat deposition [68]. It becomes progressively weak to the point that in the end, it paradoxically moves upwards leading to progressively reduced abdominal contribution to tidal volume in supine position (Fig. 2) [61]. The weakness of the diaphragm is the main cause of (1) reduced tidal volume and hypoventilation, (2) nocturnal desaturation, and (3) inefficient cough [61, 69–70].

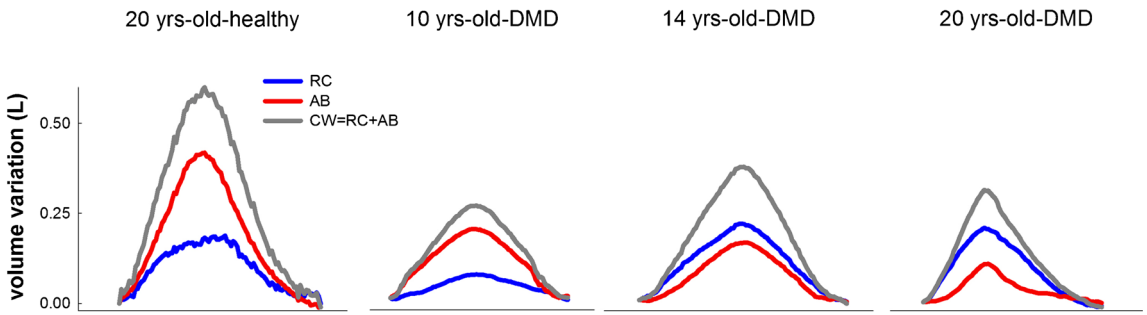

Fig. 2 Representative breaths during wakefulness spontaneous quiet breathing in supine position of a 20-year-old healthy subject, a 10-year-old Duchenne muscular dystrophy (DMD) patient who spent 100% of the nighttime with an oxyhemoglobin saturation (SpO_2) > 95%, a 14-year-old DMD patient who spent 91% of the nighttime with SpO_2 > 95% and 9% with 91 > SpO_2 > 95%, and a 20 year-old DMD patient who spent 4% of the nighttime with SpO_2 > 95%, 95% with 91 < SpO_2 < 95%, and 1% with SpO_2 < 90%. The volume variations of the chest wall (CW, *gray*) and its two compartments, the ribcage (RC, *blue*) and the abdomen (AB, *red*), are reported. Tidal volume in DMD is always lower than the healthy subject: At the age of 10 years, it is lower because of younger age; it slightly increases at the age of 14 and then it decreases at the age of 20, indicating the onset of a restricted pattern with the progression of the disease. Tidal volume is predominantly abdominal in the healthy subject and in the DMD boy; it becomes equally distributed between the ribcage and the abdomen in the DMD teenager, and finally, it is predominantly thoracic in the adult DMD. This indicates that in childhood, like in healthy subject, the diaphragm is the leading respiratory muscle and after it progressively becomes weaker with the evolution of the disease until ribcage muscles lead inspiration

Sleep Disordered Breathing in DMD

Respiratory failure is still the most common cause of death in DMD [45–47, 50–59]. Its evolution typically evolves in four stages: (1) SDB without hypercapnia, (2) hypercapnia and/or hypoxemia only during REM phase, (3) hypercapnia and/or hypoxemia also during NREM, and ultimately (4) diurnal chronic respiratory insufficiency [54, 56, 71–74].

Nocturnal oxygen desaturation is associated with a worse prognosis [75]. Unfortunately, the onset of respiratory insufficiency can be subtle in DMD to the point that patients and their parents are not aware that they are losing respiratory muscle strength and that the quality of their sleep is low. Unfortunately, the characteristics of DMD make these patients prone to develop nocturnal hypoventilation and therefore SDB. Nocturnal hypoventilation can be the consequence of either decreased ventilatory drive or worsening mechanics or a combination of the two.

In DMD, SDB has both nonobstructive and obstructive origins when respiratory, upper airway, and facial muscles become affected by the disease.

With the progression of DMD, functional residual capacity (FRC), and therefore the provision of oxygen in the alveoli, is reduced. This is also favored by the supine position that is known, per se, to reduce FRC [76, 77]. As a result, CO_2 levels rise with ensuing of nocturnal hypoxemia [78–80]. The combination of such restrictive lung patterns with respiratory muscle weakness and severe scoliosis, typical of DMD, results in chronic nocturnal hypoventilation that causes pulmonary micro-atelectasis [61, 63, 66, 81–84]. This may lead to a ventilation-perfusion mismatch resulting in a pulmonary shunt, i.e., one or more areas with perfusion but no ventilation, another contributor of hypoxemia [85].

The progressively DMD-induced diaphragmatic weakness [61, 69] plays a big part in nocturnal hypoventilation for two reasons: (1) passing from orthostatism to clinostatism, the diaphragm becomes the respiratory muscle that leads inspiration and guarantees 70% of tidal volume [86–88]; (2) it is almost the only muscle to remain active during REM sleep after intercostal muscles' depression [8, 22, 24•, 25, 26]. Therefore, when an "old" DMD patient lies in bed and reaches the REM sleep phase, his severely compromised diaphragm may not be able to adequately sustain the ventilatory demands. As a result, the most notable changes in DMD occur during REM sleep in terms of both poor tidal volume and hypoxemia [27, 79, 89].

REM timing in DMD shows a higher latency. This tendency of REM suppression may represent a compensatory mechanism to avoid the sleep phase during which patients are most vulnerable to oxygen desaturation [90••]. This seems confirmed by the fact that in four DMD patients, the reduction of the total time spent in REM sleep through protriptyline treatment was effective towards diminishing the related hypoxaemia and episodes of desaturation [91].

Other compensative and adaptive mechanisms, i.e., recruitment of sternocleidomastoid or other inspiratory extra-diaphragmatic muscles, are reported in patients with paralysis of the diaphragm [18, 92, 93]. These evidences suggest brainstem reorganization during REM sleep to cope with the paralysis of the diaphragm. There are no studies reporting similar compensative mechanisms in DMD.

DMD also involves facial and airway muscles, and this contributes to limit the oropharyngeal lumen therefore promoting obstructive sleep apneas particularly in the presence of obesity. The presence of OSA positively and strongly correlates with the body mass index in young boys with DMD [79, 94••]. Obesity therefore is a further predisposing factor of obstructive apneas, and it is common in DMD teenagers because of the forced progressive physical inactivity and of the long-term use of corticosteroid therapy [85, 95–97].

DMD patients can also develop macroglossia, a further contributor to obstructive events [18, 74]. Scoliosis is yet another severe feature of DMD that aggravates with age and is shown to worsen sleep quality, efficiency, architecture, and REM duration [98].

The more airway resistance increases and scoliosis degenerates, the higher the load for the already weak respiratory muscles. This further worsens hypoventilation and REM hypoxemia therefore ensuing a fatal vicious circle in DMD [71, 99].

SDB in DMD starts in the form of recurrent OSA, while in the second decade of life, it is mainly due to nocturnal hypoventilation and "pseudo-central apneas" secondary to respiratory muscle involvement. Hence, apneas in DMD evolve from obstructive to apparently central [38, 100]. The ventilatory pump becomes so weak that it is not able to produce the pressure swings needed to open the closed pharynx. In this way, the obstructive apnea is mislabeled as central: a pseudo-central apnea [90••, 101, 102].

Although DMD is a peripheral and not a central neuromuscular disease, central sleep apneas are also reported in young patients [74, 94••, 103]. In order to investigate the problematic presence of central apneas in DMD, invasive techniques, like gastro-esophageal catheters, should be used during sleep to measure the respiratory swings of pressure during efforts [104]; otherwise, it is more likely that OSA would be mistaken for central apnea [101].

A possible consequence of nocturnal hypoventilation, hypoxemia, and hypercapnia is that both peripheral and central respiratory chemoreceptors could become less sharp. This depresses the respiratory drive and determines a state of chronic alveolar hypoventilation that further worsens respiratory failure [85, 99]. Figure 3 summarizes the mechanisms that lead to SDB in Duchenne patients.

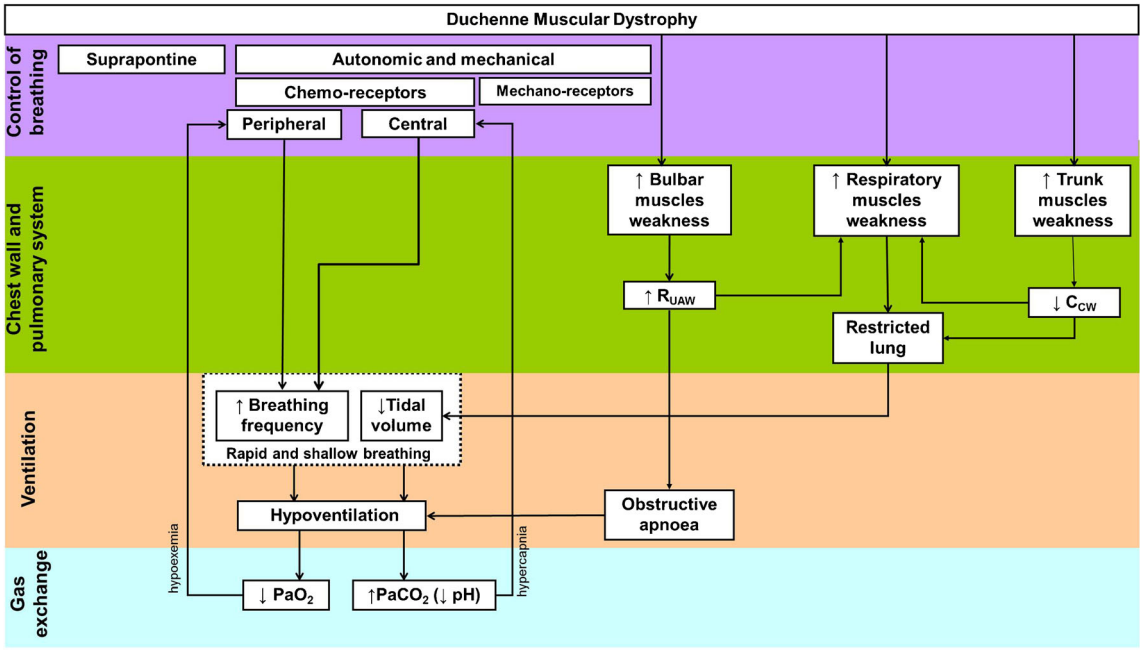

Fig. 3 Schematic diagram summarizing the generalized causes of sleep disordered breathing in Duchenne muscular dystrophy. R_{UAW} upper airways resistance, C_{CW} chest wall compliance, PaO_2 partial pressure of oxygen in arterial blood, $PaCO_2$ partial pressure of carbon dioxide in arterial blood. *Upwards arrow* (↑) indicates increment, and downwards arrow (↓) indicates decrement

Nocturnal Noninvasive Mechanical Ventilation

Sleep disorders, namely hypoxemia, sleep fragmentation, and daytime sleep-induced impaired functions, are potentially treatable.

Supplementary oxygen therapy was the first solution applied in early 1990s. There is no doubt that it improves hypoxemia, but it is now used with great care because it may also depress the central respiratory drive, therefore prolonging apneas and exacerbating the risk of CO_2 retention [8, 51, 55, 105–107].

To treat the SDB-induced hypoxemia, noninvasive ventilation (NIV) is needed. According to the internationally recognized guidelines, in fact, the structured approach to respiratory management in DMD comprises, among other treatments, the use of NIV to deal with nocturnal hypoventilation, SDB, and ultimately with respiratory failure [51, 54, 108, 109].

The earliest forms of NIV used negative pressures such as the "iron lung," the rocking bed, and the abdominal cuirass. These forms of negative pressure ventilation brought the intrinsic complication of developing upper airway obstruction therefore leading to OSA with consequent episodes of arterial oxygen desaturation [110].

Nasal intermittent positive pressure ventilation (NIPPV) is largely used and has proven to be an efficient and beneficial treatment in DMD, able to increase survival in hypercapnic patients and improve arterial O_2 and CO_2 tensions [57].

It is also preferable to invasive mechanical ventilation requiring tracheostomy. In fact, the combination of NIV with cough aids leads to a lower hospitalization rate than invasive ventilation [111, 112]. The mechanisms of beneficial impact of NIV in daytime blood gases include resting of respiratory muscles [113, 114], recruitment of lung volume therefore reversing atelectasis, reset of the respiratory drive at the level of chemoreceptors, and delay daytime hypercapnia [60, 115, 116]. NIPPV should be started as an in-patient, and then it is well tolerated and easy to handle at home by the family [8].

Nasal continuous positive airway pressure has a limited application in DMD, because it just keeps the upper airway open without ventilating the patient. The problem is that when a DMD patient needs NIV, his respiratory muscles are weak to the point that they are not able to provide adequate ventilation [85].

Daytime Predictors of SDB and Indicators of NIV in DMD

Almost all the symptoms of SDB may be easily attributed to DMD per se with the risk to further delay the diagnosis of SDB [38, 117]. The fact that nocturnal hypoventilation occurs earlier than daytime awake respiratory impairment [71, 100] means that the first sign of respiratory failure in DMD starts during sleep, particularly during REM phase.

For this reason, nocturnal monitoring is necessary in these patients, as it may provide not only early detection of respiratory involvement but also becomes an important indication to intervene. It is still under debate, in fact, the proper time to initiate NIV in order to achieve maximal benefit: if it is started too early, there is the risk to induce atrophy in the diaphragm [118]; if it is started too late, respiratory failure can occur earlier leading to premature death risk [119].

Table 1 Relationship between daytime respiratory function and nocturnal indexes in DMD

Paper	No. of DMD patients	Age mean (range)	Main findings
Smith 1988 [71]	14	18 (15–22)	DeSat compared to Sat characterized by • ↓ MEP
Manni 1989 [80]	11	16 (10–20)	Inverse relationship of both FRC and RV with SpO_2
Baydur 1990 [112]	17		indicator of *nocturnal* NIV • VC = 0.5–0.7 L indicator of *full-time* NIV • VC < 0.3 L
Manni 1991 [79]	9	16 (10–20)	correlation of FRC with mean SpO_2 during REM and with SpO_2 drop during apneas
Kerr 1994 [27]	11	10 (4–16)	assumption: "Patients with NREM abnormalities have severe respiratory dysfunction; whereas those without show adequate respiratory function"
Barbè 1994 [74]	6	18 (12–22)	AHI correlates with daytime PaO_2 and FEV_1/FVC
Phillips 1999 [75]	19	2 groups: Sat: (16.5–24) DeSat: (14–19.5)	No differences found between DeSat and Sat in terms of spirometry and respiratory muscles strength
Hukins 2000 [72]	19	18 ± 3.9	- Relationship between FEV_1 and FVC to $PaCO_2$, PaO_2 and base excess; - indicator of sleep hypoventilation: • FEV_1 < 40% (91% sensitive, 50% specific)
Kirk 2000 [121]	11	(9–21)	No relationship found between FVC and the presence/severity of SDB
Suresh 2005 [100]	32	10 (2–16)	No relationship found between FVC and the presence of SDB
Toussaint 2007 [73]	114	3 groups: Normocapnic: 16.5 ± 3 Nocturnal hypercapnia: 17.9 ± 3 Diurnal hypercapnia: 23.1 ± 5	predictor of *nocturnal* hypercapnia: • VC ≤ 1.82 L (87% sensitive, 51% specific) • MIP ≤ 39 cmH_2O (71% sensitive, 54% specific) • RSBi > 0.07 min^{-1} mL^{-1} (71% sensitive, 73% specific) predictors of *diurnal* hypercapnia: • VC ≤ 0.68 L (90% sensitive, 95% specific) • MIP ≤ 22 cmH_2O (92% sensitive, 87% specific) • V_T/VC > 0.33 (77% sensitive, 95% specific)
Hahn 2009 [122]	46	17.7 ± 5.3	- With the increasing use of NIV: ↓ FVC and ↑ TT_{MUS} - FVC is sensitive to recognize patients who need NIV - TT_{MUS} helps to justify the extent of need for NIV: TT_{MUS} > 0.23 in DMD ventilated 8–20 h; TT_{MUS} > 0.37 in DMD ventilated >20 h/day.
LoMauro 2010 [61]	66	(5–22)	DeSat compared to Sat characterized by • ↓ $\%AB_{QB}$
Hamada 2011 [123]	83	3 groups: No NIV: 17.8 ± 5 Nocturnal NIV: 22.3 ± 5 Full-time NIV: 30.2 ± 6	indicators of *nocturnal* NIV: • RR/VC ≥ 0.024 min^{-1} mL^{-1} (85% sensitive, 89% specific) • RSBi ≥ 0.024 min^{-1} mL^{-1} (81% sensitive, 90% specific) • VC ≤ 770 mL(85% sensitive, 89% specific) indicators of *full-time* NIV: • RR/VC ≥ 0.071 min^{-1} mL^{-1} (86% sensitive, 95% specific) • RSBi ≥ 0.153 min^{-1} mL^{-1} (81% sensitive, 90% specific) • VC ≤ 370 mL(78% sensitive, 85% specific)
Romei 2012 [70]	40	2 groups: Sat: 17.7 ± 2 DeSat:18.5 ± 4	discriminators of nocturnal desaturation: • $\%AB_{IC}$ < 25% (62% sensitive, 79% specific) • $\%AB_{QB}$ < 36.2% (76% sensitive, 58% specific) • FEV_1 < 33.5% (75% sensitive, 66.6% specific)

Table 1 (continued)

Paper	No. of DMD patients	Age mean (range)	Main findings
Sawnani 2015 [94••]	111	11 (5–18)	for every ↓ 10% predicted of FVC, MIP and MEP the odds of nocturnal hypoventilation respectively ↑ by 20%, 24% and 22%

Downwards arrow (↑) indicates increase. Upwards arrow (↓) indicates decrease

SpO_2 oxyhemoglobin saturation, *FRC* functional residual capacity, *(F)VC* (forced) vital capacity, *NIV* noninvasive ventilation, *REM* rapid eye movement sleep phase, *NREM* nonrapid eye movement sleep phase, PaO_2 arterial partial pressure of oxygen, *AHI* apnea/hypoapnea index, FEV_1 forced expiratory volume in 1 s, *MIP* maximal inspiratory pressure, *MEP* maximal expiratory pressure, V_T tidal volume, TT_{MUS} tension time index of the respiratory muscles, *RR* respiratory rate, *RSBi* rapid and shallow breathing index, $\%AB_{IC}$ supine percentage contribution of the abdomen during an inspiratory capacity, $\%AB_{QB}$ supine percentage contribution of the abdomen during quiet breathing, pCO_2 partial pressure of carbon dioxide, *DeSat* patients who desaturate in the night, *Sat* patients who do not desaturate in the night

Polysomnography (PSG) is a comprehensive, multiparametric test used as a diagnostic tool in sleep medicine to study the physiological changes that occur during sleep. The functions monitored by PSG are cerebral cortical activity (electroencephalogram), eye movements, muscle activity mainly of mylohyoid (electromyography), cardiac activity (electrocardiogram), respiratory airflow, thoraco-abdominal movements, and peripheral pulse oximetry [120]. PSG is expensive, it needs complicated instruments, it presents logistic difficulties, and it is not universally available in the normal clinical practice. For this reason, simpler, specific, surrogate, and easy-to-obtain daytime indexes of SDB and of NIV use are needed. Such daytime predictors of severe nocturnal hypoventilation and/or hypoxemia may permit the identification of those patients most at risk of severe hypoxemia, particularly during respiratory tract infections, when airway obstruction increases and thoracic compliance decreases [71], on whom PSG becomes justified and therefore mandatory [72].

Hypercapnia and hypoxemia can be respectively detected by measuring $PaCO_2$ and PaO_2. These techniques have two disadvantages: they are invasive and they are measured during wakefulness, therefore not reflecting the sleep condition. Overnight transcutaneous pCO_2 measurement and pulse oximetry are noninvasive techniques. The former slightly overestimates $PaCO_2$ and it concordantly increases, while SpO_2 decreases during REM hypoventilation [72]. The latter can be less sensitive particularly in early stages of DMD [56]. In order to identify clinical factors associated with the onset of SDB, it is important to test the concordance between laboratory PSG and portable monitoring systems [107, 121].

All the studies specific for DMD that are present in the literature and that contain both sleep characterization and daytime respiratory function are reported in Table 1. Some authors did not to find any relationship, whereas others found useful information like daytime predictors of SDB and indicators for the extent of need for NIV.

In order to find the optimum timing for starting NIV and to delay respiratory failure in DMD, it is important to measure respiratory function in terms of spirometry, lung volumes, respiratory muscles strength, and resting breathing patterns.

Among all the considered parameters, three of them should be put in evidence:

1. Vital capacity: it is the most informative parameter, but spirometry requires repetition of maximal efforts that can fatigue the weak respiratory muscles, particularly in old DMD patients.
2. Rapid and shallow breathing index: it is nonvolitional and it can be considered a global index of ventilatory pump weakness ("shallow") and increased ventilatory drive ("rapid"). It requires the use of a mouthpiece that can be problematic in the presence of macroglossia and cheek muscles weakness.
3. The abdominal contribution to tidal volume in supine position: it is nonvolitional, it does not need mouthpiece and it is a specific index of the action of the diaphragm.

To be noted that DMD being a degenerative progressive disease, it is extremely important to consider homogeneous age groups. The use of a wide range of ages, in fact, carries the risk of hiding important features by grouping together young and old patients, with the former to introduce positive bias due to their relatively less compromised condition.

Table 2 reports the international guidelines for the criterion of establishing nocturnal and daytime NIV in DMD.

Table 2 International guidelines of the criterion for establishing nocturnal and daytime noninvasive ventilation in DMD

Guideline	Indications
Finder 2004 [51]	Criterion for establishing *nocturnal* NIV • pCO_2 > 50 mmHg or awake SpO_2 < 92%
Birnkrant 2010 [54]	Criterion for establishing *nocturnal* NIV • FVC < 30% • Baseline SpO_2 < 95% and/or blood or end-tidal pCO_2 < 45 mmHg Criterion for establishing *daytime* NIV • Symptoms of hypoventilation with baseline SpO_2 < 95% and/or blood or end-tidal pCO_2 < 45 mmHg

SpO_2 oxyhemoglobin saturation, *FVC* forced vital capacity, *NIV* noninvasive ventilation, pCO_2 partial pressure of carbon dioxide

Animal Model

Mdx mouse is an important, reliable, murine model for physiological studies of DMD, particularly for the diaphragm. While the degeneration of limb muscles of *mdx* mice does not parallel patients', their diaphragm closely mirrors the pathophysiology, fibrosis, and severe functional deficit of DMD patients [124, 125].

Experimental protocols comprising intermittently induced episodes of hypoxia are used in animal models to simulate sleep apnea. It has been shown that exposure to episodic hypoxia may result in a 30% reduction in diaphragmatic strength in *mdx* mice and that respiratory dysfunctions are more severe in older *mdx* mice [126, 127].

The function of sternohyoid muscle, a pharyngeal dilator important for the control of airway patency, is compromised (in terms of poor force, work, and power) in *mdx* mice, but shows an apparent tolerance to acute hypoxic stress [128].

Another interesting study reveals that peripheral chemosensory response is reduced in *mdx* mice and that *mdx* mice show dysfunction of the carotid body [129].

Conclusion

SDB is expected in the natural history of DMD, and it ultimately results into respiratory failure during wakefulness. SDB can be present in all ages: young patients are placed at risk of obstructive apnea; older patients hypoventilate and desaturate during sleep because of the impairment of their respiratory muscles, in particular the diaphragm. This is further exacerbated during REM sleep, the phase of maximal muscle hypotonia during which the diaphragm has to carry the entirety of ventilation.

Daytime predictors of early symptoms of SDB and of the proper time to initiate mechanical ventilation can be found in spirometry and in the breathing pattern at rest.

"To sleep, perchance to dream. Ay, there's the rub"
(Shakespeare, Hamlet. Act 3, Scene 1, Page 3)

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Compliance with Ethical Standards

Conflict of Interest Antonella Lo Mauro, Maria Grazia D'Angelo, and Andrea Aliverti declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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