Daytime predictors of sleep disordered breathing in children and adolescents with neuromuscular disorders

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Abstract

Sleep disordered breathing with or without nocturnal hypercapnic hypoventilation is a common complication of respiratory muscle weakness in childhood neuromuscular disorders. Nocturnal hypercapnic hypoventilation as a sign of respiratory muscle fatigue, portends a particularly poor prognosis. We aimed at identifying daytime predictors of sleep disordered breathing at its onset and sleep disordered breathing with nocturnal hypercapnic hypoventilation. Forty-nine children and adolescents (11.3 ± 4.4 years) with progressive neuromuscular disorders were studied with inspiratory vital capacity, peak inspiratory pressure, arterial blood gases, polysomnography, and a ten-item symptoms questionnaire. Daytime respiratory function was prospectively compared with polysomnographic variables. Sleep disordered breathing was found in 35/49 patients (71%). Twenty-four (49%) had sleep disordered breathing with nocturnal hypercapnic hypoventilation. Inspiratory vital capacity and peak inspiratory pressure, but not symptom score, correlated with sleep disordered breathing and severity of nocturnal hypercapnic hypoventilation. Sleep disordered breathing-onset was predicted by inspiratory vital capacity < 60% (sens. 97%, spec. 87%). Sleep disordered breathing with nocturnal hypercapnic hypoventilation was predicted by inspiratory vital capacity < 40% (sens. 96%, spec. 88%) and $PaCO_2 > 40$ mmHg (sens. 92%, spec. 72%,). Sleep disordered breathing can reliably be predicted from simple daytime respiratory function tests, which, if applied systematically, will improve recognition of nocturnal respiratory failure.
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Keywords: Nocturnal hypoventilation; Respiratory failure; Neuromuscular disorders; Sleep disordered breathing; Polysomnography; Children; Adolescents

1. Introduction

Sleep disordered breathing (SDB) is common in neuromuscular diseases [1,2]. The principle cause is disease-related loss of respiratory muscle function, which in the context of sleep-induced reduction of respiratory muscle tone and drop of central drive results in limited capacity to compensate for sleep-related drop of alveolar ventilation. SDB is particularly prevalent in rapid eye movement (REM) sleep [3–5], a period of maximal muscle atonia, and in the presence of diaphragm dysfunction [6]. It can manifest in different ways, depending on the relative contribution of upper airway or diaphragm dysfunction. Hypopneas with desaturations in REM sleep are most common, particularly at early disease stages. As disease progresses, hypercapnic alveolar hypoventilation, first in REM, then in non-REM

sleep prevails as the predominant marker of waning respiratory muscle force.

We have recently shown in adults with myopathic diseases that the degree of ventilatory restriction impacts directly on pattern and severity of SDB, and that nocturnal hypercapnic hypoventilation (NHHV) was prevalent at vital capacities below 40% predicted [7]. Because NHHV is likely to advance the development of cor pulmonale and daytime respiratory failure and may impact unfavorably on survival, timely recognition is important. Furthermore, as therapy in way of non-invasive ventilation may effectively normalize gas exchange and improve prognosis [8–11].

Unfortunately, SDB and NHHV are rarely apparent on daytime presentation. Symptoms may be subtle and non-specific. In children, failure to thrive may be the only indicator. High index of suspicion and polysomnographic evaluation, therefore, are required for a diagnosis [12].

We investigated lung and respiratory muscle function and respiration during sleep in children with neuromuscular diseases with the intent of identifying daytime predictors

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of SDB at its onset and for SDB with NHHV. We were particularly interested in establishing the predictive values of readily available function tests such as vital capacity, peak inspiratory muscle pressure, daytime blood gas analysis, and symptoms.

1.1. Patients and methods

1.1.1. Patients

Sixty-one children and adolescents (22 girls and 27 boys, aged 11.3 ± 4.4 (range 5–18 years)) were referred and prospectively evaluated between January 1997 to December 2000. Reasons for referral were assessment of respiratory function prior to corrective spinal surgery ($n = 6$), failure to thrive/suspected SDB ($n = 32$), or advanced clinical disease ($n = 23$). Twelve children were excluded from the study, five under the age of 6 years because reliable lung function test could not be obtained, seven because of acute respiratory failure necessitating emergent non-invasive ventilation. Eighteen patients had congenital muscular dystrophy (10.4 ± 4.1 years), seven had Duchenne muscular dystrophy (DMD, 14.6 ± 4.0 years), five had intermediate spinal muscular atrophy type I–II (SMA, 8.4 ± 1.1 years), seven had SMA type II (8.9 ± 2.5 years), four had limb girdle dystrophy (14.0 ± 3.7 years), three had juvenile type of acid maltase deficiency (11.7 ± 6.2 years), two had nemaline myopathy (6 and 14 years), two had hereditary motor and sensor neuropathy type I (11 and 12 years), and one subject had centronuclear myopathy (8 years). A pediatric neurologist had assessed all patients and the diagnosis had been confirmed at the histopathological, and where possible at the molecular level. Twenty-eight patients were wheelchair-bound. No patient was using ventilatory support before entering the study.

1.1.2. Lung function

Inspiratory vital capacity (IVC), forced expiratory lung volumes (FEV_1), forced vital capacity (FVC), and respiratory muscle function were measured with a hand-held spirometer/manometer (ZAN Meßgeräte, Obertulba, Germany). The best of three consistent efforts ($<5\%$ variability) was used. Predicted values were derived from published data [13]. Respiratory muscle function was assessed as peak inspiratory pressure (PIP). Arterial blood gas tensions were determined from the arterialized ear lobe blood in an automated blood gas analyzer (AVL 500, AVL LIST GmbH Medizintechnik, Graz, Austria) on the evening prior to polysomnography.

1.1.3. Polysomnography (PSG)

PSG was performed according to the standards of the American Thoracic Society [14]. Signals were recorded onto a computerized workstation (Compumedics, Melbourne, Australia). Transcutaneous carbon dioxide tension ($PtcCO_2$) was recorded simultaneously (Radiometer, Copenhagen, Denmark). No oxygen was supplemented.

Sleep stages and respiratory parameters were scored manually. Apnoeas were defined as >10 s cessation of airflow and respiratory effort (central) or >10 s cessation of airflow with persisting effort (obstructive). Hypopneas were defined as >10 s reduction of airflow or thoracoabdominal effort accompanied by $>3\%$ oxyhemoglobin desaturation or electroencephalographic (EEG) arousal of >3 s [15]. SDB was considered present if respiratory disturbance index (RDI) was above five events per hour of total sleep or above ten per hour of REM sleep. NHHV was defined as $PtcCO_2 > 50$ mmHg for $>50\%$ of total sleep time (TST) [16]. Respiratory failure (RF) was defined as daytime hypercapnia ($PaCO_2 \geq 45$ mmHg), repeatedly measured over a period of respiratory stability.

1.1.4. Symptoms

Subjects were asked to complete a ten-item questionnaire on quality of sleep, nocturnal breathing problems, nocturnal sweating, morning headaches, appetite, concentration, mood, daytime function and general well-being, frequency of chest infections, and dyspnea. The questions had to be answered along a ten point scoring scale, the high end indicating intense and the low end a few complaints. Maximal total score was 100 points.

1.1.5. Statistical analysis

Analysis was performed with Statistica 5.1 software package (StatSoft, Inc., Tulsa, OK). Correlations between parameters of daytime function and nocturnal gas exchange were analyzed using the Spearman's rank test. Group comparison was performed with the Mann–Whitney U-test. All results are presented as mean $\pm$ standard deviation. $P < 0.05$ was considered as significant. Multiple regression analysis was used to identify the major determinant of SDB, the dependent variable being percentage of TST spend with $PtcCO_2 > 50$ mmHg, the independent variables being age, IVC, and PIP. Receiver operator curves (ROCs) were constructed for each independent variable, cut-off points separating patients with and without SDB were calculated by bi-dimensional analysis and with equal sensitivity/specificity (ratio 1:1). The variable with the largest area under the curve (AUC) was considered the strongest predictor of SDB.

2. Results

2.1. Sleep disordered breathing

PSG identified SDB in 35 patients, two with obstructive hypopneas in REM sleep, nine with non-obstructive hypopneas and hypoventilation predominantly in REM sleep, and 24 with continuous sleep stage-independent NHHV. NHHV was accompanied by hypoxemia during 70–100% of sleep time and phasic desaturations particularly in REM sleep (Fig. 1). SDB resulted in slight increase of arousal index
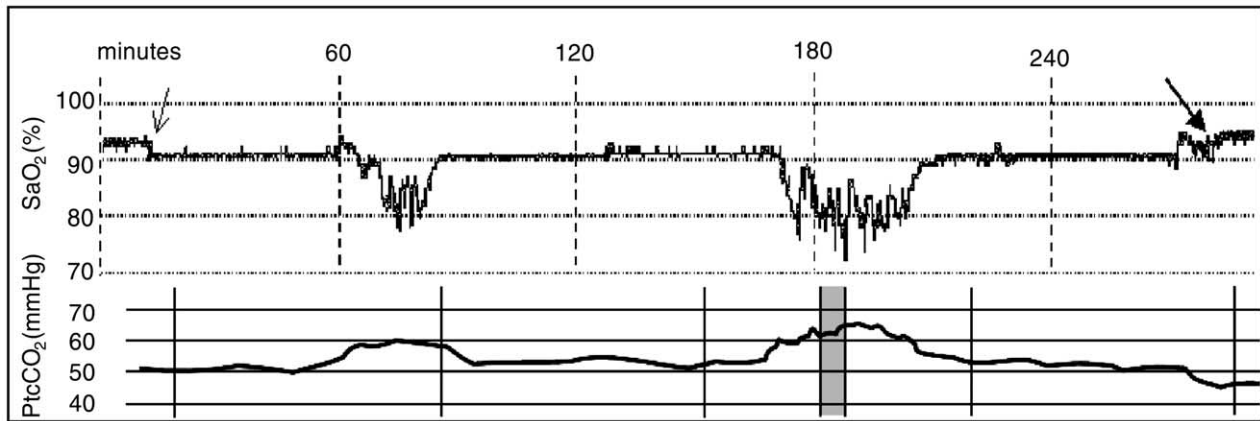
Fig. 1. Example from a 12 year old girl with congenital muscular dystrophy and IVC 28% predicted, PIP 2.2 kPa, $PaCO_2$ 48 mmHg and PaO_2 79 mmHg. The oxymetry and capnometry as a detail from a complete PSG are shown. The small arrow indicates the moment when the patient fell asleep and SaO_2 immediately fell from 94 to 91%. In the following 258 min sleep mean SaO_2 is 89% with further decrease to minimal 72% during REM sleep. Mean $PtcCO_2$ was mean 57 mmHg and maximum 68 mmHg. The large arrow indicates the start of non-invasive ventilation.

but no disruption of sleep architecture (awake: $5 \pm 2\%$, stage 1: $5 \pm 3\%$, stage 2: $45 \pm 10\%$, stage 3 and 4: $28 \pm 13\%$, and REM: $18 \pm 3\%$). Comparative data between patients with SDB and without are summarized in Table 1.

2.2. Symptoms

Total symptom score was slightly higher in patients with SDB than without (29.7 ± 18.2 vs. 19.1 ± 14.1 points, $P = 0.08$), and was highest in patients with obstructive sleep hypopnea (52.8 ± 13.6 vs. 24.4 ± 15.5 points in non-obstructive SDB, $P < 0.005$). Most common complaints were sleep disruption (4.4 ± 2.6 vs. 2.4 ± 2.2 points, $P < 0.005$), morning headaches (2.5 ± 2.7 vs. 0.8 ± 1.7 points, $P < 0.01$), daytime sleepiness (2.6 ± 3.0 vs. 0.8 ± 1.5 points, $P < 0.05$), and dyspnea (2.7 ± 2.7 vs. 0.9 ± 2.3 points, $P < 0.005$). Total symptom score correlated with RDI ($r = 0.51$, $P < 0.001$) but not with parameters of nocturnal gas exchange or IVC.

2.3. Daytime respiratory function

IVC and PIP were significantly lower in patients with SDB than those without (Table 2). IVC correlated with PIP ($R = 0.5$, $P < 0.001$), daytime PaO_2 ($R = 0.59$, $P < 0.0001$) and $PaCO_2$ ($R = -0.54$, $P < 0.0001$), and also with various parameters of nocturnal respiration. Average daytime gas exchange was well maintained in patients with and without SDB, but was significantly impaired in the subgroup with NHHV. This subgroup included seven children with $PCO_2 < 40$ mmHg, eight with PCO_2 41–44 mmHg, and nine with $PCO_2 > 45$ mmHg ($PaCO_2$ 52.3 ± 4.1 mmHg, PaO_2 71.0 ± 8.3 mmHg).

2.4. Predictors of SDB and NHHV

Multiple regression analysis identified IVC as the major determinant of SDB (adjusted $R^2 = 0.68$, $P < 0.0001$). Scatter plots and ROCs obtained for IVC yielded highly predictive threshold for SDB-onset (IVC < 60%) and SDB with NHHV (IVC < 40%) (Fig. 2A,B). $PaCO_2 > 40$ mmHg was also a highly predictive threshold for SDB with NHHV (Fig. 2C). PIP < 4 kPa predicted SDB-onset and PIP < 2.5 kPa predicted SDB with NHHV. Sensitivities, specificities, and AUC are summarized in Table 3. Symp-

Table 1
Nocturnal respiratory function[a]

Parameter	SDB	No SDB	P
Mean SaO_2 (%)	93.4 ± 5.2 (47–95)	97.4 ± 2.6 (96–98)	<0.001
$SaO_2 \leq 90\%$ (% of TST)	24.9 ± 35.1 (0–100)	0	<0.001
Minimum SaO_2 (%)	79.5 ± 11.2 (47–89)	92.2 ± 2.7 (91–96)	<0.001
Mean $PtcCO_2$ (mmHg)	49.5 ± 7.6 (40–70)	41.3 ± 3.0 (37–48)	<0.0001
$PtcCO_2 \geq 50$ mmHg (% of TST)	59.0 ± 7.6 (0–100)	0.7 ± 0.9 (0–5)	<0.001
REM-RDI (events/h REM)	6.6 ± 5.9 (3–73)	2.6 ± 1.0 (0–10)	<0.005
RDI (events/h)	6.6 ± 5.9 (0–20)	1.3 ± 1.6 (0–4)	<0.005
Arousal index	19.5 ± 10.1 (30–75)	11.7 ± 13.9 (3–39)	0.06

[a] SaO_2, oxyhemoglobin saturation; % of TST, percent of total sleep time; $PtcCO_2$, transcutaneous carbon dioxide; REM, rapid eye movement; RDI, respiratory disturbance index.

Table 2
Daytime respiratory function[a]

Parameter	SDB	No SDB	P
IVC (% predicted)	25.8 ± 11.8 (9–67)	80.3 ± 12.6 (62–95)	<0.0001
PIP (kPa)	2.6 ± 1.1 (0.8–5.0)	4.2 ± 1.9 (19–9.5)	<0.0001
PaO$_2$ (mmHg)	83.7 ± 13.5 (62–102)	97.2 ± 4.7 (86–106)	<0.005
PaCO$_2$ (mmHg)	42.3 ± 7.1 (32–59)	36.9 ± 3.2 (29–42)	<0.005
pH	7.38 ± 0.04	7.42 ± 0.03	<0.05
Base excess	0.5 ± 2.0	− 0.8 ± 1.4	<0.05

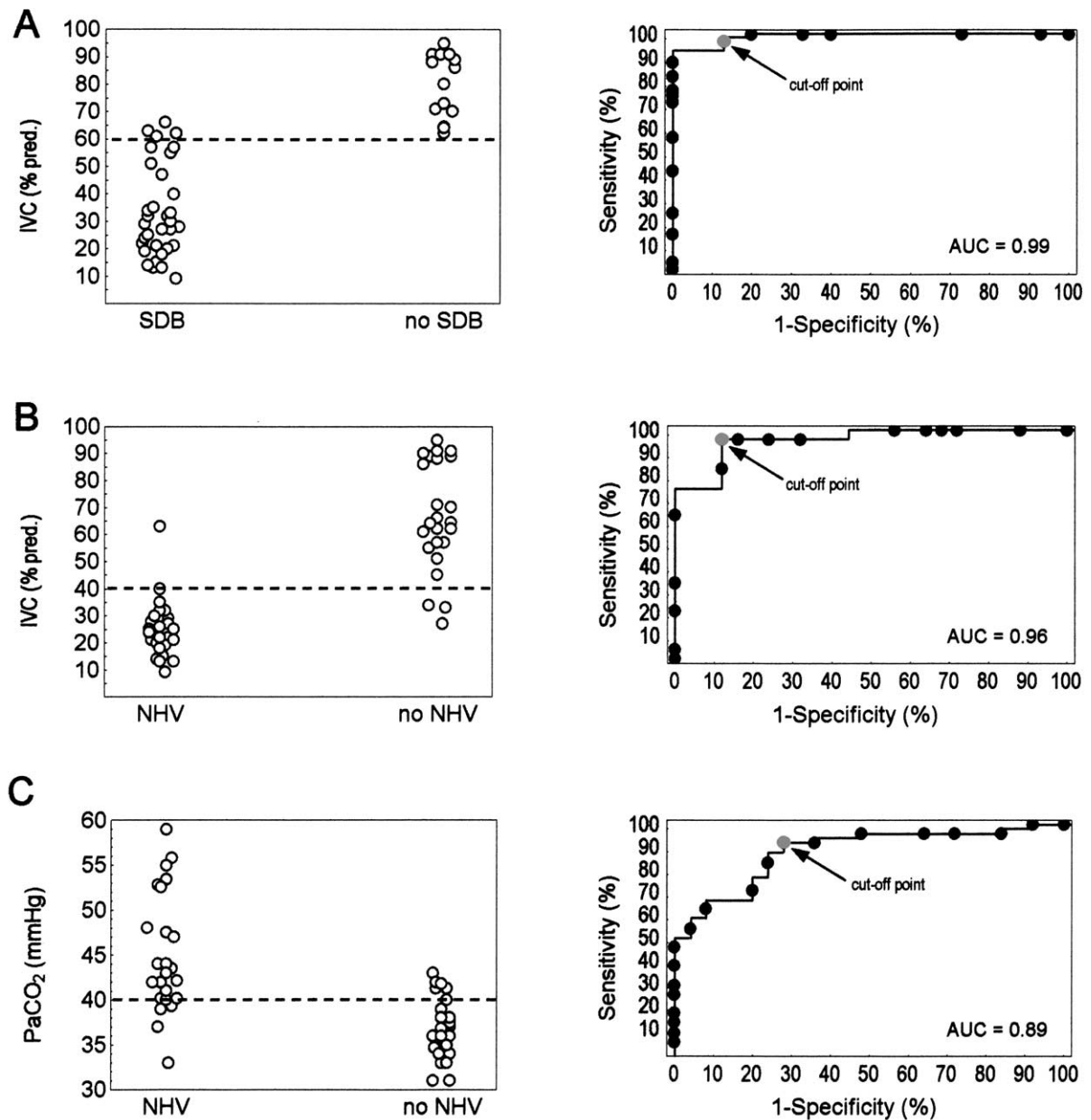[a] IVC, inspiratory vital capacity; PIP, peak inspiratory pressure.

Fig. 2. (A–C) On the *left*, raw data of IVC for patients with and without SDB (A) or NHHV (B) and raw data of PaCO$_2$ for patients with and without NHHV (C). On the *right*, the corresponding receiver operator curves with the area under the curve (AUC). The *dashed line* indicates the optimal cut-off point for the predictors calculated with bi-dimensional analysis.

Table 3
Predictors of SDB-onset and NHHV[a]

Parameter	Cut point	Sensitivity/specificity (%)	AUC (%)
SDB-onset			
IVC (% predicted)	< 60	97/87	99
PIP (kPa)	< 4	87/43	82
NHHV			
IVC (% predicted)	< 40	96/88	96
PIP (kPa)	< 2.5	72/83	79
$PaCO_2$ (mmHg)	> 40	92/72	89

[a] IVC, inspiratory vital capacity; PIP, peak inspiratory pressure; $PaCO_2$, arterial carbon dioxide tension; AUC, area under the curve.

toms (AUC < 67%) and base excess (AUC < 55%) had no predictive value for SDB-onset or SDB with NHHV.

3. Discussion

The present study demonstrates the significant interrelation between lung and respiratory muscle function and respiration during sleep in children with neuromuscular disorder (NMD), and identifies accurate daytime predictors of SDB at its onset and SDB with NHHV.

As previously shown in adult myopathic disease, IVC correlated closely with respiratory muscle pressures and gas exchange by day and night [7]. This close relation formed the basis for our assumption that daytime lung and respiratory muscle function were major determinants of SDB also. SDB in neuromuscular disease indicates an imbalance between ventilatory demand and respiratory muscle capacity and as such is associated with an unfavorable survival prognosis [17,18]. Continuous hypercapnic hypoventilation, in particular, is a sign of respiratory muscle fatigue in the setting of exhausted respiratory muscle reserves. Progression to chronic and acute on chronic RF is common if left untreated. Institution of non-invasive ventilatory support, therefore, is urgently indicated at this point [8].

Our study identified SDB with or without NHHV in 70% of patients, a prevalence rate similar to that reported in other neuromuscular disease cohorts [1,2]. Fifty-two percent of SDB patients had continuous NHHV. The findings were unexpected in the majority of cases, whose referral had, for the most part, not been symptom-triggered. Our symptoms questionnaire, derived from the typical symptoms complexes associated with the obstructive sleep apnea syndrome, was insensitive in identifying patients with SDB and NHHV. Although total score was slightly higher in patients with SDB than without, scores as such were low (<30% of maximal possible). Individual scores, particularly those for sleep disruption, morning headache, somnolence, or dyspnea were also low in both groups (<3/10). This low level of disturbance corresponded to an evident lack of sleep disruption on PSG, as indicated by near normal arousal

indices and normal sleep stage distribution on EEG profiles. Not surprisingly, therefore, symptoms did not correlate with vital capacity or nocturnal gas exchange. Although these data must be interpreted with caution as our questionnaire was not a validated one, our findings are supported by observations from obstructive sleep apneas syndromes showing strong correlations between symptoms scores and sleep disruption but not desaturation or level of hypoxemia [19].

Because SDB in NMD is rarely suspected on clinical examination, daytime predictors have been sought. Previous studies, most of them in adolescents with DMD and adults with various NMD, have identified various correlations between FVC and time in wheelchair, FVC and depth of nocturnal desaturation, or FEV_1 and length of desaturations, but relations have been inconsistent [1,20–22]. Our data, by contrast, obtained in a relative homogenous cohort of patients of largely myopathic NMD, showed high-grade correlations between vital capacity, PIP, daytime and nocturnal gas exchange, and SDB, particularly with regard to the degree of nocturnal hypoventilation. As in adults with acid maltase deficiency or other progressive neuromuscular disorders [6,7], SDB-onset was clearly defined by IVC < 60% predicted, and SDB with NHHV by IVC < 40% predicted. The exceptions were a DMD patient with severe sleep-induced upper airway obstruction and NHHV, despite IVC of 63%, and three SMA children (6–8 years) with IVC < 40% but no NHHV, in whom we suspect IVC may have been underestimated due to poor test cooperation. Our results in children complement the recently reported observation that FEV_1 < 40% correlated with percent sleep time spent at SaO_2 < 90% in DMD patients [23].

Given the close interrelation between vital capacity and gas exchange, daytime $PaCO_2$ > 40 mmHg also proved an excellent, if IVC-dependent, predictor of NHHV. Two-thirds (15/24) of our patients with continuous NHHV had normal daytime blood gases with a $PaCO_2$ < 44 mmHg. Average base excess, therefore, was normal in our patient cohort. Although normocapnia by convention is defined as $PaCO_2$ < 45 mmHg, clinical experience tells us that $PaCO_2$ in truly normal conditions is generally under 40–42 mmHg. Our data clearly show that $PaCO_2$ > 40 mmHg in NMD children should raise the suspicion of respiratory muscle fatigue and should prompt polysomnographic investigation, even if IVC is >40% predicted.

PIP, as in previous studies, correlated closely with lung function [24], but was not as accurately predictive of SDB as IVC or $PaCO_2$. This is explained by the much larger interindividual variability of even normal PIP measurements [25]. PIP < 2.5 kPa, nevertheless, was a reasonably sensitive and specific predictor for SDB, more so than the previously reported 6 kPa in ALS [17]. As PIP measurements are very useful from a pathogenetic point of view, they should be obtained in patients with neuromuscular disease.

In summary, we showed that SDB and SDB with NHHV

are common complications of neuromuscular disease in children, that they produce few symptoms of sleep disturbance, and in the majority of cases are associated with normal blood gases by day. We identified three simple tests, derived from readily available daytime lung and respiratory muscle function tests that are highly accurate in predicting the presence of SDB without or with nocturnal hypoventilation. These predictors may aid in identifying patients at risk, help with the appropriate scheduling of PSG for diagnostic confirmation, and assure timely institution of therapeutic non-invasive ventilation.

Acknowledgements

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