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Sleep-disordered breathing and effects of non-invasive ventilation on objective sleep and nocturnal respiration in patients with myotonic dystrophy type I

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Abstract

Patients with myotonic dystrophy type I (DM1) may develop nocturnal hypoventilation, requiring non-invasive ventilation. Data on long-term adherence to non-invasive ventilation, or sleep and ventilation outcomes are scarce. We retrospectively collected baseline polysomnography and capnometry results from 36 adult patients with sleep-related symptoms (42.9 ± 12.5 years, 20 female), plus follow-up sleep study records from those treated with non-invasive ventilation. Sleep-disordered breathing was found in 33 patients (91.7%) including 8 (22.2%) with daytime hypercapnia. Twenty-six patients (72.2%) showed nocturnal hypoventilation on transcutaneous capnometry. The sensitivity of oximetry to detect nocturnal hypoventilation was only 0.38. Twenty-eight patients (77.8%) showed sleep apnea, which was predominantly obstructive ($n = 8$), central ($n = 9$), or "mixed" ($n = 11$). Thirty-two patients were initiated on non-invasive ventilation which significantly improved ventilation and oxygenation in the first night of treatment. Follow-up revealed stable normoxia and normocapnia without deterioration of sleep outcomes for up to 52 months. Adherence to treatment was low to moderate, with substantial inter-individual variability.

Sleep disordered breathing is highly prevalent in adult DM1 patients complaining of daytime sleepiness, and non-invasive ventilation significantly, rapidly and persistently improves nocturnal gas exchange. Capnometry is superior to oximetry for detection of nocturnal hypoventilation. Adherence to non-invasive ventilation remains a major issue in DM1, and long-term treatment benefits should be individually assessed.

Keywords: Myotonic dystrophy type 1; Sleep-disordered breathing; Hypoventilation; Capnometry; Non-invasive ventilation.

1. Introduction

Myotonic dystrophy type I (DM1; Online Mendelian Inheritance in Man® ID 160900) is a hereditary multi-system disorder characterized by myopathic facies, distal muscle wasting, myotonia, bilateral cataract, endocrine and cardiac conduction abnormalities. The prevalence of DM1 in industrialized countries is 3–15/100,000. DM1 follows an autosomal dominant trait and is caused by an expansion of a trinucleotide CTG-repeat in the 3′-untranslated region of the DMPK gene on chromosome 19 [1].

Non-restorative sleep and excessive daytime sleepiness (EDS) are common in DM1 patients and may have a number of different aetiologies, including sleep-disordered breathing (SDB), restless legs syndrome, periodic limb movements and hypersomnolence of central origin [2–5]. SDB in DM1 includes obstructive sleep apnea (OSA), central sleep apnea (CSA) and nocturnal hypoventilation (NH) which is caused by respiratory muscle weakness (RMW) [6].

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Non-invasive ventilation (NIV) is indicated when NH or daytime hypercapnia are accompanied by sleep-related symptoms [7,8]. Data on treatment effects in DM1 is conflicting since substantial problems may hamper initiation and, in particular, long-term maintenance of nocturnal NIV in clinical practice. Both mask intolerance and insufficient adherence to treatment are common, and treatment benefits may be blurred by co-existing daytime sleepiness independent of SDB [1–8]. Prevalence of NH or respiratory failure in DM1 has been reported to be 18% and 27%, respectively [4,5], but NH has not yet been evaluated using overnight capnometry. Oximetric measures have been shown to have low sensitivity for the detection of NH in patients with various NMD. Therefore, capnometry may facilitate early identification of patients for whom NIV is indicated [9]. Of note, mortality benefit from early initiation of NIV has been described for patients with rapidly progressive NMD [10,11]. In addition, carbon dioxide monitoring allows for assessment of alveolar ventilation on follow-up studies in patients receiving home ventilatory support, and persistent normoventilation has been shown to positively affect objective sleep outcomes and even survival in patients with NMD [11,12].

This retrospective study investigated the diagnostic utility of transcutaneous capnometry for identification of NH in patients with DM1 and evaluated short-term and long-term effects of NIV on nocturnal ventilation and objective sleep outcomes in this condition.

2. Material and methods

2.1. Patients

Thirty-six patients with genetically-proven DM1 were included. Patients consecutively attended our sleep laboratory for first-ever diagnostic sleep studies between 1 January 2009 and 1 April 2017. All patients complained of non-restorative sleep and daytime sleepiness. In addition, sleep studies were initiated if symptoms and signs of diaphragmatic weakness were present (exertional dyspnea, orthopnea, forced vital capacity [FVC] < 70% of predicted). Initial daytime blood gas analysis had not revealed daytime hypercapnia in any of the patients. Patients were not selected from a larger database. The study was approved by the local ethics authority (Ethikkommission der Westfälischen Wilhelms-Universität Münster und der Ärztekammer Westfalen-Lippe).

2.2. Sleep studies

Diagnostic sleep studies were performed using full polysomnography (PSG, Nihon Kohden, Rosbach, Germany) according to standard recommendations [6]. Sleep stages and sleep-associated events were manually scored from PSG recordings. We documented respiratory parameters including the apnea-hypopnea index (AHI), oxygen saturation (SpO_2), and oxygen desaturation index (ODI). Given that all patients complained of daytime symptoms, sleep apnea was defined as an AHI > 5/h [6]. An obstructive apnea was scored when nasal flow amplitude decreased by ≥90% for ≥10 s with thoraco-abdominal effort constantly present. A central apnea was scored when flow amplitude decreased by ≥90% for ≥10 s in the absence of any respiratory effort. If thoracic or abdominal excursions recurred during an initially central apnea the event was classified as a mixed type apnea. Central sleep apnea (CSA) was diagnosed if both the AHI and central apnea index (cAI) were >5/h with >50% of all apneas being central in origin. Overnight transcutaneous capnometry (Sentec, Therwil, Switzerland) was performed with each PSG [13]. Nocturnal hypercapnia was diagnosed when transcutaneous carbon dioxide tension ($tcCO_2$) was either ≥50 mmHg or increased from the awake supine value by >10 mmHg during sleep [13,14]. For comparison between different methods of NH detection, diagnosis of hypoventilation was also based on oximetry parameters (e.g. nocturnal $SpO_2 \leq 88\%$ for ≥5 consecutive minutes [15], mean nocturnal $SpO_2 < 90\%$ [16] and/or $SpO_2 < 90\%$ during ≥10% of the recording time [17]. Early morning blood gas analysis was conducted in all subjects using blood drawn from the arterialized earlobe.

In patients in whom NIV was initiated, the effects of treatment on objective sleep quality measures and nocturnal respiration were evaluated and long-term effects were determined by analyzing sleep studies that were regularly scheduled every six months. Sleep outcomes included sleep efficiency, percentage of slow wave sleep (SWS) and rapid eye movement (REM) sleep, index of sleep stage changes, arousal index, respiratory arousal index, and time spent awake after onset of sleep (WASO).

2.3. Clinical assessment

Demographic data, body mass index (BMI), neurological status and detailed information on sleep-related complaints were obtained from clinical records. Severity of motor symptoms was categorized using the Muscular Impairment Rating Scale (MIRS) which comprises four categories as follows: (1) No muscular impairment; (2) Minimal signs (myotonia, facial weakness, neck flexor weakness, nasal speech, no distal weakness except isolated digit flexor weakness); (3) Distal weakness (no proximal weakness except isolated elbow extensor weakness); (4) Mild to moderate proximal weakness; (5), Severe proximal weakness [18]. Sleep-related symptoms were self-reported using the Epworth Sleepiness Scale (ESS; [19]) and the Pittsburgh Sleep Quality Index (PSQI; [20]). The ESS is an eight-item Likert scale rating sleep propensity in everyday situations. Scores >10 are considered indicative of EDS [19]. The PSQI rates sleep quality during the last 4 weeks by generating a global score and seven component scores reflecting sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, daytime dysfunction and overall sleep quality. A cut-off score of 5 reliably distinguishes between ‘good sleepers’ (≤5) and ‘bad sleepers’ (>5). Self-reported fatigue was measured using the Fatigue Severity Scale (FSS), which generates a total score ranging from 1

Table 1
Patient clinical and demographic data at baseline (T0).

	Patients (n = 36)
Age, years	41.2 ± 11.7
Female,% patients	55.6
BMI, kg/m²	25.8 ± 7.0
MIRS score	3.0 ± 0.69
Upright FVC, L	2.7 ± 0.9
Supine FVC, L	2.1 ± 0.8
FVC,% predicted	67.4 ± 16.5
ΔFVC,%	23.7 ± 17.5

Notes. Clinical and demographic data at baseline (T0). Values are depicted as mean and standard deviation, or percentage of patients.
BMI, body mass index; FVC, forced vital capacity; ΔFVC, positional drop of FVC; MIRS, Muscular Impairment Rating Scale.

to 7; scores >4 indicate significant fatigue [21]. Capillary blood gas analysis was performed according to standard recommendations [14,22].

2.4. Statistical methods

Statistical data analysis was performed using SPSS® v25.0 (IBM Inc., Armonk, NY). Parametric data are presented as mean ± standard deviation, and the *t*-test for independent samples was used. Paired *t*-test was used for paired values. For non-parametric data, the Mann–Whitney U test or the Kruskal–Wallis test was used for group comparisons as appropriate. Categorical variables were analysed using the χ^2 test. Pearson's correlation coefficient was used for associations between continuous variables. For multiple testing Bonferroni's correction was applied. Sensitivity was calculated for oximetry-based diagnosis in detecting hypoventilation. *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Demographics and disease characteristics

Diagnostic sleep study results at baseline were available in all 36 patients with DM1 (Table 1). No patients had previously been treated with continuous positive airway pressure (CPAP) treatment or NIV. The MIRS score was ≥3 in 27 patients; the MIRS score did not correlate with age, and no gender difference was found (data not shown).

3.2. Sleep-related symptoms

Eleven patients (28.9%) had EDS based on an ESS score of >10, more than half of all patients specified reduced sleep quality (PSQI global score >5), and nearly half had significant fatigue (FSS score >4) (Table 2). Neither ESS score, PSQI global score nor FSS score correlated with objective sleep or respiratory measures (data not shown). Restless legs syndrome was diagnosed in 10 out of 36 patients.

3.3. Sleep-disordered breathing at baseline

Thirty-three patients (91.7%) showed SDB, and eight (22.2%) also had daytime hypercapnia on early morning blood gas analysis (pCO_2 > 45 mmHg). Twenty-six patients (72.2%) showed NH on capnometry (maximum $ptcCO_2$ > 50 mmHg or $\Delta tcCO_2$ > 10 mmHg). Maximum nocturnal $tcCO_2$ was 52.2 ± 6.4 mmHg, and mean difference from baseline to maximum $tcCO_2$ was 8.6 ± 4.0 mmHg. Based on the above capnographic definition of NH, the sensitivity of pulse oximetry (SpO_2 ≤88% for ≥5 min, mean SpO_2 < 90% or SpO_2 < 90% for ≥10% of the recording time) to identify patients with NH was 0.38.

Sleep apnea (AHI ≥5/h) was found in 28 patients (77.8%), with predominant OSA and CSA present in 8 and 9 patients, respectively; 11 patients had a mixed sleep apnea pattern. In patients with OSA, the AHI did not significantly differ between genders, and was not correlated with age or BMI. NH and OSA coincided in 7 patients and another 7 subjects had both NH and predominant CSA.

3.4. Sleep outcomes at baseline

Sleep and respiratory parameters at baseline are shown in Table 2. Correlation analysis showed that the index of sleep stage changes was significantly associated with AHI, mean SpO_2, minimum SpO_2 and time with SpO_2 < 90% (r-values of 0.43, –0.54, –0.47 and 0.45, respectively; all p < 0.05). Sleep efficiency, percentage of different sleep stages, and WASO did not significantly differ between DM1 patients with and without SDB (data not shown). Both the arousal index (AI) and the respiratory arousal index (RAI) were significantly higher in patients with predominant CSA (with or without NH) compared to those with OSA or without sleep apnea (AI: 22.9 ± 11.8/h vs. 13.3 ± 8.3/h; p = 0.03; RAI: 14.2 ± 11.0/h vs. 2.6 ± 3.8/h; p < 0.001). In contrast, arousal indices did not significantly differ when patients with and without OSA were compared (AI: 19.2 ± 12.2/h vs.13.3 ± 8.3/h; p = 0.24; RAI: 10.7 ± 10.7/h vs.2.6 ± 3.8/h; p = 0.09). Sleep efficiency, WASO, percentage of REM sleep and SWS were not significantly affected by the presence of either CSA or OSA. Diagnostic PSG revealed that only two patients (with RLS) showed periodic limb movements (PLM) in sleep (PLM index > 15/h).

3.5. Impact of NIV on respiration, sleep architecture, and sleep quality

NIV was successfully initiated in 32 out of 33 patients with SDB (1 patient declined NIV after the first night) using a spontaneous/timed (S/T) bi-level mode (minimum IPAP 8.5 ± 1.6 cmH_2O, maximum IPAP 18.7 ± 2.2 cmH_2O, backup respiratory rate 13.6 ± 1.6/min). NIV incuded average volume-assured pressure support (AVAPS®, Philips Respironics) in 30 subjects with NH, and the simple S/T mode was used in two patients with isolated CSA. In patients without SDB or any other medical disorder possibly

Table 2
Symptom scores and respiratory and sleep parameters on polysomnography at baseline and during follow-up.

	Baseline ($n=36$)	T1 ($n=32$)	T2 ($n=23$)	T3 ($n=20$)	T4 ($n=12$)
Symptom scales					
ESS score	8.6 ± 4.6		8.3 ± 4.6	8 ± 2.8	9.6 ± 2.6
ESS score > 10% patients	28.9		29.4	16.7	30.0
PSQI[#]	6.4 ± 3.4		4.4 ± 2.5	4.8 ± 2.5	6 ± 4.3
PSQI score > 5,% patients	55.6		27.3	22.2	40.0
FSS score[#]	4.1 ± 1.9		3.8 ± 2.1	3.4 ± 1.7	4.5 ± 2
FSS score > 4,% patients	47.1		45.5	42.9	60.0
Sleep parameters					
Sleep efficiency,%	78.0 ± 11.7	74.6 ± 14.2	73.2 ± 16.6	69.0 ± 15.7	75.4 ± 16.5
N3 sleep,% TST	27.2 ± 9.7	30.1 ± 9.6	30.8 ± 8.5	25.8 ± 8.3	29.2 ± 11.5
REM sleep,% TST	19.1 ± 7.1	18.5 ± 5.2	17.7 ± 6.8	17.4 ± 7.2	17.6 ± 7.5
WASO, min	77.3 ± 56.7	84.1 ± 50.9	102.1 ± 84.5	106.3 ± 65.5	87.8 ± 53.8
Index of sleep stage changes, /h TST	12.7 ± 4.7	16.1 ± 6.0	16.5 ± 6.6	16.2 ± 5.7	17.0 ± 3.6
Arousal index, /h	17.2 ± 10.7	12.8 ± 4.4	11.9 ± 6.3	17.1 ± 8.3	16.5 ± 13.1
Respiratory arousal index, /h	7.5 ± 9.3	1.5 ± 2.4*	1.8 ± 1.8	2.1 ± 2.6	0.7 ± 0.8
Respiratory parameters					
AHI, /h	16.0 ± 14.1	2.6 ± 3.0/h*	4 ± 4.4*	4.3 ± 4.6*	3.3 ± 4.2*
ODI, /h	15.2 ± 13.2	3.7 ± 3.4*	5.1 ± 4.4*	4.7 ± 3.8*	5.5 ± 9.3*
cAI, /h	5.0 ± 8.9	0.7 ± 1.6*	1.0 ± 2.1	2.0 ± 3.9	0.2 ± 0.4*
oAI, /h	3.9 ± 5.6	0.1 ± 0.2*	0.9 ± 1.9*	0.4 ± 1.1*	0.4 ± 0.9*
HI, /h	7.6 ± 8.2	1.8 ± 2.5*	2.6 ± 3.4	3 ± 2.5	1.1 ± 1.1
Mean SpO_2,%	91.7 ± 4.2	94.5 ± 3.2*	94.6 ± 2.7*	94.1 ± 2.8*	93.8 ± 2.8*
Minimum SpO_2%	78.2 ± 11.0	77.2 ± 10.0	80.7 ± 6.2	82.2 ± 6.5*	80.9 ± 5.5
Time with SpO_2 < 90%, min	114.9 ± 129.3	47.1 ± 74.6*	42.8 ± 64.4*	44.6 ± 63.9*	33.5 ± 56.6
Mean $tcCO_2$. mmHg	46.4 ± 5.3	39.5 ± 5.2*	37.9 ± 4.7*	40.6 ± 5.1*	40.1 ± 5.2*
Maximum $tcCO_2$, mmHg	52.3 ± 6.4	48.1 ± 5.4*	44.8 ± 4.2*	48.0 ± 5.0*	48.3 ± 7.3*
Maximum $tcCO_2$ ≥50 mmHg,% patients	66.7	42.9	18.2	45.0	45.5
$\Delta tcCO_2$ (mmHg)	9.1 ± 4.2	8.4 ± 4.3	5.4 ± 3.7*	6.8 ± 3.6*	6.8 ± 4*
$\Delta tcCO_2$ ≥ 10 mmHg,% patients	33.3	14.3	0	15.0	20.0
pCO_2 (mmHg)	41.5 ± 5.1	40 ± 4.5*	41.6 ± 4.3	41.8 ± 4.3	41.5 ± 3.6
pCO_2 ≥45 mmHg,% patients	22.2	7.1	30.4	26.3	8.3
pO_2 (mmHg)	79.2 ± 14.3	79.8 ± 17.3	72.5 ± 11.6	74.8 ± 11.1	76.6 ± 16.6
pO_2 < 80 mmHg,% patients	59.3	59.1	81.8	77.8	66.7
HCO_3^-, mmol/L	26 ± 2	26 ± 6	25 ± 2	26 ± 2	26 ± 2

Notes. Symptom scores and respiratory and sleep parameters on polysomnography at baseline and during follow-up. Values are depicted as mean and standard deviation or percentage of patients.
Analysis of variance for multiple measurements was also conducted and showed that respiratory outcomes did not significantly change when subsequent timepoints were compared among each other.
AHI, apnea-hypopnea index; cAI, central apnea index; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; HI, hypopnea index; N3, slow wave; oAI, obstructive apnea index; ODI, oxygen desaturation index; pCO_2. partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement; SpO_2, peripheral oxygen saturation; T1, first night of NIV; T2, first follow-up (mean 4.9 ± 2.4 months); T3, second follow-up (mean 12.1 ± 5.3 months); T4, third follow-up (mean 19.6 ± 10.6 months); $tcCO_2$, transcutaneous carbon dioxide tension; $\Delta tcCO_2$, difference between baseline and maximum $tcCO_2$; TST, total sleep time; WASO, wake after sleep onset.
[#] Data only available in 18/36 patients.
* $p<0.05$ for comparison between T0 and T1, T0 and T2, T0 and T3, or T0 and T4 using a paired *t*-test.

explaining EDS further diagnostic work-up included multiple sleep latency test, and stimulants were offered.

NIV was associated with significant improvement of ventilation and oxygenation, and significant reductions in the AHI and time spent with SpO_2 < 90% on the first night of treatment (T1) (Table 1). Up to three follow-up sleep studies per patient were included in data analysis (Table 2). The first follow-up (T2) was 4.9 ± 2.4 months after initiation of NIV ($n=23/32$), the second (T3) after 12.1 ± 5.3 months ($n=20/32$), and the third (T4) after 19.6 ± 10.6 months ($n=12/32$). Reasons for loss to follow-up included discontinuation of NIV due to treatment intolerance or lack of perceived benefit, unwillingness to attend subsequent inpatient sleep studies, and removal to another area. Treatment adherence rates were 45.0 ± 32.6% at T2, 29.6 ± 36.6% at T3, and 53.5 ± 42.1% at T4 (median use of NIV per day was 206, 159 and 320 min at T2, T3, and T4, respectively). At T1, ventilation and oxygenation measures showed significant improvement compared to baseline values including AHI, ODI, mean SpO_2, desaturation time, mean and maximum $tcCO_2$ (Table 2). Follow-up sleep studies revealed stable normoxia and normocapnia (Fig. 1). Analysis of variance for multiple measurements revealed that respiratory measures did not significantly change when subsequent timepoints were compared among each other (data not shown). Adjustment of ventilator settings was considered necessary when hypercapnia and/or OSA (AHI > 5/h) were still present. However, modifications of pressure settings,

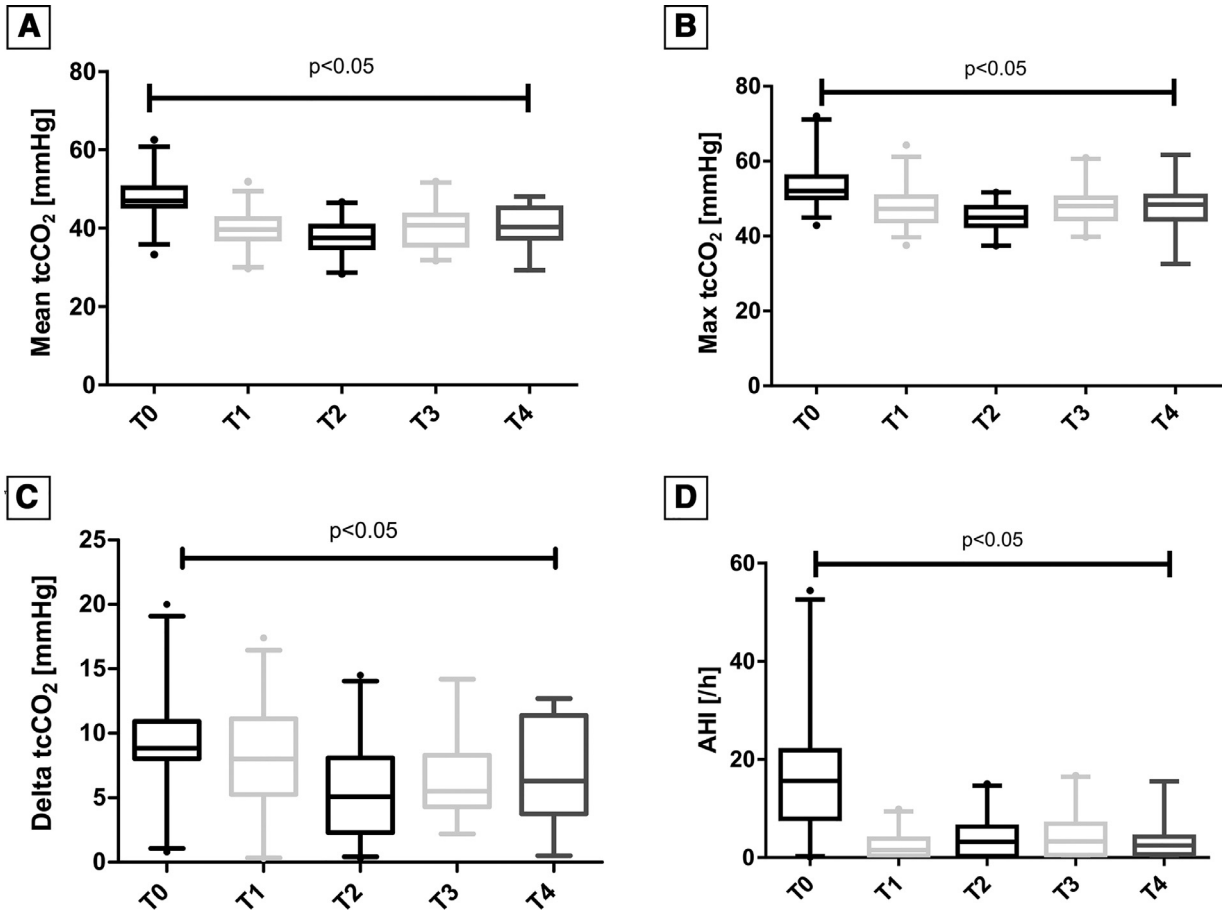

Fig. 1. Changes in objective respiratory parameters during follow-up. (**A**) Mean transcutaneous carbon dioxide tension ($tcCO_2$); (**B**) Maximum $TcCO_2$; (**C**) Difference between baseline and maximum $tcCO_2$ ($\Delta tcCO_2$) ; (**D**) Apnea-hypopnea index (AHI) per hour of total sleep time (TST). Box plots are given with the mid horizontal line showing the mean, boxes showing the upper and lower quartile, and whiskers showing the 5th and 95th percentiles (outliers are displayed as dots).

respiratory rate or tidal volume were marginal and were only required in 12 patients. After the first night of therapy, no significant changes in sleep efficiency, WASO, SWS percentage and REM sleep percentage were observed (Fig. 2). Only the respiratory arousal index was significantly reduced (Table 2). In addition, self-reported sleep outcomes did not significantly change from baseline to later timepoints (data not shown).

With regard to T2, T3 and T4, we conducted a subgroup analysis in order to further evaluate the impact of treatment adherence. At each of the above timepoints, patients were stratified according to the median use of NIV within the respective cohort (Supplemental Figs. 1 and 2). At T2, both respiratory parameters (including residual AHI, mean and maximum $tcCO_2$) and the respiratory arousal index were significantly better in patients with higher treatment adherence, i. e. who used NIV for more than the median duration per night (206 min). At following timepoints, differences were not consistent, probably reflecting that sample size was subsequently decreased. In patients with better treatment adherence at T2, capnometric measures at baseline (T0) showed more severe NH (however, lacking significance), and prevalence of early morning hypoxia (pO_2 < 80 mmHg) at T0 was significantly higher in this subgroup (Supplemental Table 1).

4. Discussion

In this study we found a high prevalence of NH in DM1 complaining of EDS, and NH would have been missed in the majority of cases if only overnight pulse oximetry had been performed. In addition, we found that NIV significantly improved NH on the first night of treatment and was associated with long-term normocapnia and normoxia without deterioration of sleep quality.

Daytime sleepiness and fatigue are reported by the majority of patients with DM1 and have been shown to occur very early in the course of the disease [23,24]. Hypersomnolence can be found in one-third of DM1 patients and correlates with the degree of motor impairment [23]. However, the ESS score does not accurately reflect daytime performance in DM1 patients [25], which is supported by the fact that it was not correlated with either SDB or the FSS score in our study population. It is a specific feature of DM1 that EDS may occur as a result of different etiologies. Among these, central nervous system (CNS) involvement

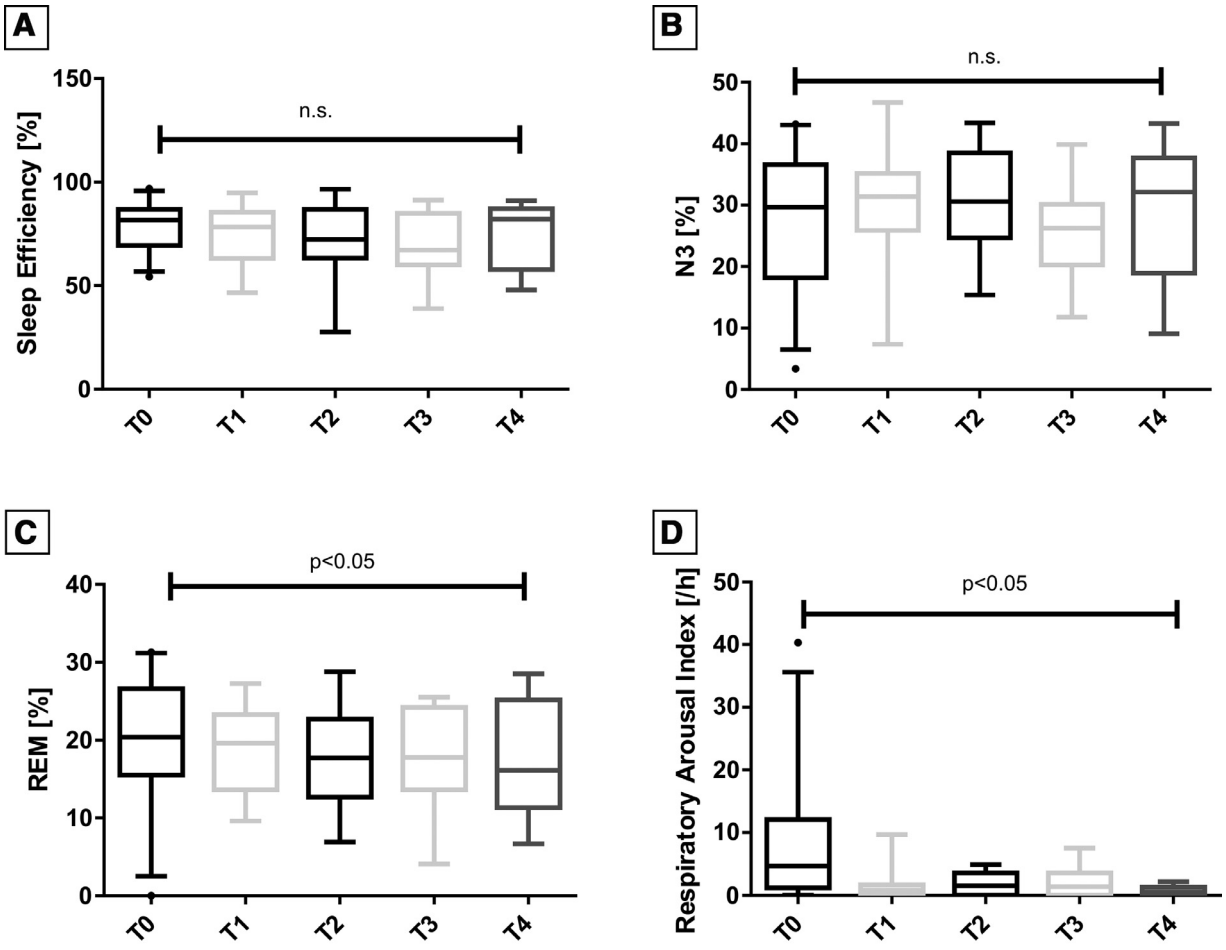

Fig. 2. Changes in objective sleep parameters during follow-up. (**A**) Sleep efficiency; (**B**) Percentage of slow wave (N3) sleep (as a percentage of total sleep time [TST]); (**C**) Percentage of rapid eye movement (REM) sleep (as a percentage of TST). (**D**) Respiratory arousal index (per hour of TST). Box plots are given with the mid horizontal line showing the mean, boxes showing the upper and lower quartile, and whiskers showing the 5th and 95th percentiles (outliers are displayed as dots).

has been postulated, possibly caused by degeneration of serotoninergic neurons within the dorsal raphe nuclei [26]. In addition, a subset of patients may even exhibit narcolepsy-like features, including decreased cerebrospinal fluid hypocretin levels and pathological findings on the multiple sleep latency test [27,28]. However, our study confirms that SDB is a common finding in DM1 patients complaining of daytime sleepiness, and that this may include NH, OSA and/or CSA [29,30]. The prevalence of SDB in our study population was high, and the presence of sleep-related symptoms can be considered a strong predictor of SDB in DM1.

This study is the first to include transcutaneous capnometry in the polysomnographic evaluation of DM1 patients. It shows that daytime blood gas analysis and nocturnal pulse oximetry may fail to identify patients with NH as defined by capnography. This is consistent with previous reports showing that capnometry is superior to pulse oximetry for identification of NMD patients in whom NH is present [9,13,14]. The fact that published studies report a lower prevalence of NH in DM1 patients can likely be attributed to the use of pulse oximetry alone [4,5]. As a result, transcutaneous capnometry is indispensable for baseline evaluation of DM1 patients with suspected SDB.

Our findings confirm that overlap of sleep apnea and NH is common in DM1 [2]. The prevalence of predominant CSA (25%) was unexpectedly high in this study. A previous study described CSA in 15% of patients with DM1 [2]. It is possible that patients in the current study had more advanced disease which might have increased the risk of CSA. However, data on the extent of cerebral white matter lesions reflecting CNS involvement were not available in these subjects. Interestingly, 7/9 patients with CSA also showed NH in our study. It can be hypothesized that CSA in DM1 is triggered by central respiratory instability which leads to transient hyperventilation overcompensating mild hypercapnia during sleep in patients with respiratory muscle weakness. In addition, hypoventilation has been shown to increase pulmonary artery pressure, which is known to further increase central respiratory drive [31].

NIV remains one of the few appropriate therapeutic options in DM1 patients with SDB. Thus, it is tempting to speculate that early initiation of NIV is as important in

DM1 as in other NMD where it has been shown to improve nocturnal gas exchange, objective sleep outcomes, quality of life, and even life span [7,10,32–34]. In fact, our data suggest long-term improvement of nocturnal respiration by NIV. However, this was not associated with improvement of objective sleep quality measures other than the respiratory arousal index. Similarly, a previous study showed that long-term NIV consistently improved nocturnal ventilation but not sleep outcomes in patients with late-onset Pompe disease [12]. In contrast to ALS, DM1 and Pompe disease are slowly progressive, and affected patients may develop NH very subtly which leads to no or only mild deterioration of sleep quality as long as RMW is still moderate. For patients with DM1 in particular, associated symptoms may often not be overt, or self-awareness of the problem may be limited. As a result, perceived treatment benefits and long-term adherence to NIV may be suboptimal in some patients with DM1 as was shown in our study (although clear improvements in respiratory indices were present). Due to slow disease progression, direct benefits of NIV on sleep, health-related quality of life and life span are difficult to demonstrate. An innovative study evaluated the effects of a 1-month withdrawal followed by a 1-month reinstitution of NIV in twelve DM1 patients diagnosed with stable respiratory failure [35]. In this cohort, sleep-related symptoms did not worsen during the withdrawal period and showed no improvement thereafter. This has given rise to the notion that initiation of NIV may not be beneficial in all patients with DM1 fulfilling standard indication criteria, especially in those with only few NH episodes, mild hypoxia, moderate daytime symptoms, and less severe motor impairment [35]. These patients may not gain sufficient subjective treatment benefits to sustain long-term adherence to NIV. However, a recent prospective study conducted in 218 DM1 patients showed that failure to regularly use NIV may indeed be associated with increased mortality suggesting “dose-dependent” effects of NIV [36]. Interestingly, the present study revealed that at baseline, both the extent of NH and the prevalence of early morning hypoxia ($pO_2 < 80$ mmHg) were higher in patients who showed better adherence to NIV at T2. Moreover, longer use of NIV may be associated with improved capnometric measures on follow-up sleep studies which possibly contributes to the effect of adherence on mortality. Thus, the indication for NIV in DM1 is a highly individual decision that requires balancing of objective measures and clinical complaints as well as regular re-evaluation of the benefits of treatment. A large-scale randomized controlled trial comprehensively assessing the benefits of NIV in DM1 patients with SDB is desirable.

Our study is limited by the fact that duration of follow-up substantially varied between patients. Thus, long-term data are still based on small sample sizes, making general conclusions difficult and highlighting the need for future studies. In addition, it may be considered a limitation of this study that a control group was not included. However, this study was not specifically designed as a case-control study since it did not aim to systematically investigate either prevalence of - or risk factors for - SDB in patients with DM1.

In conclusion, this study confirms that SDB is common in DM1 patients complaining of daytime symptoms, and sleep apnea and NH often coincide. Overnight transcutaneous capnometry is recommended for reliable detection of NH, and long-term NIV has the potential to establish normal nocturnal gas exchange. However, treatment adherence remains a major issue in DM1 and the true benefits of NIV have to be individually assessed. Long-term effects of NIV on both subjective and objective sleep outcomes or even mortality need to be addressed in future prospective trials.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.02.006.

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