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Abstract:

Myotonic dystrophy type 1 (DM1) is a rare neuromuscular disease in children causing sleep and respiratory disorders that are poorly described in the literature compared to adult forms.

This retrospective observational study was performed at the Armand Trousseau University Hospital, *Assistance Publique-Hôpitaux de Paris* (APHP), Paris, France. We retrospectively collected data from lung function tests, nocturnal gas exchange recordings, and polysomnography of 24 children with DM1.

39% of the children with DM1 reported respiratory symptoms indicative of sleep disordered breathing. Three patients (12%) presented with a restrictive respiratory pattern, 10 (42%) with a sleep apnoea syndrome, mainly of obstructive origin (2/10 with severe obstructive sleep apnea syndrome), and 11 (45%) with nocturnal alveolar hypoventilation. Non-invasive ventilation (NIV) was indicated in 9 (37.5%) children, although tolerance was poor. No significant deterioration in respiratory function or nocturnal gas exchange was observed during the NIV-free period.

This study provides new and useful insights into DM1 disease evolution in children to better adapt for respiratory follow-up and management. This highlights the need for future research to better understand the origin of respiratory and sleep disorders in patients with DM1.

Keywords: Myotonic dystrophy type 1, respiratory function, sleep, evolution, children

Introduction

Myotonic dystrophy type 1 (DM1) is a multi-systemic genetic disease with muscular, central nervous system, cardiac, and respiratory involvement [1]. Its worldwide incidence is one per 8000 births, and its prevalence is estimated to be two–14 per 100,000 [2,3]. It is an autosomal dominant disease linked to abnormal expansion of the CTG triplet (> 50 triplets) in the non-coding region of the *DMPK* gene (dystrophia myotonica protein kinase) [4]. The size of the expansion varies between subjects and tissues and tends to increase with age, which partly explains the evolution of the disease [1,5]. There are five different forms of DM1 classified according to the age at onset and the number of triplet repetitions: congenital (>1000 CGT), infantile (1-10 years), juvenile (10-20 years), adult-onset and late-onset. The number of triplets varies from 1000 to 300 CGT for infantile and juvenile forms, to 100 to 1000 for the adult-onset form and 50 to 150 CGT for the late-onset subtype; it decreases according to the form as well as the severity of the symptoms [6]. Muscle involvement is associated with myotonia and muscle weakness and may affect skeletal muscles as well as smooth muscles. Neurological impairment is characterised by cognitive and intellectual deficits [7,8]. Cardiac involvement is frequent, independent of the form, and mainly consists of conduction disorders. Patients may also present with swallowing disorders related to weakness of the oropharyngeal muscles and/or bulbar and gastrointestinal dysfunctions. Infantile and juvenile forms are most often diagnosed in the presence of learning difficulties at school age, variably associated with intellectual deficits and significant fatigue [1].

Respiratory impairment in DM1 patients is multifactorial and progressive. It results from respiratory muscle dystrophy which leads to a restrictive respiratory pattern and an increased risk of pulmonary infections. The degradation of respiratory function seems to be slower in patients with DM1 than in those with other neuromuscular diseases (Duchenne muscular

dystrophy and spinal muscular amyotrophy) [9]. Currently, the recommendation is to monitor lung function tests (LFTs) without precision on frequency [10,11].

Approximately 30% of DM1children report sleep related symptoms, such as hypersomnia, nocturnal awakenings, excessive daytime sleepiness, and fatigability [12,13]. These symptoms should not be overlooked because of their impact on learning and development, which are already impaired in these children. In DM1, the mechanisms of sleep alteration remain poorly understood and seem to be related to both respiratory muscle function impairment that can lead to nocturnal hypoventilation, central nervous system alterations that lead to central apnoea, and modification of sleep architecture [11,14]. A prospective study investigating sleep characteristics in 21 children with DM1 showed that 66% of the patients had such type of sleep disorders [15]. Studies on adults have shown a higher apnoea/hypopnea index with central and obstructive sleep apnoea, a decrease in sleep efficiency, an increase in the percentage of rapid eye movement (REM) sleep, and the prevalence of periodic limb movements in DM1 patients compared to control groups [14,16,17]. The consequence of these impairments is nocturnal alveolar hypoventilation, which could be the origin of the symptoms [11,18].

Currently, the respiratory management of DM1 patients is based on the implementation of non-invasive ventilation (NIV) or continuous positive airway pressure (CPAP), as well as airway secretion management when needed [10]. There are no specific recommendations regarding when to start NIV in DM1 children. However, respiratory impairment and its evolution appears to differ from other neuromuscular diseases. Meanwhile, NIV is known to improve nocturnal gas exchange, quality of life, and life span in children with other neuromuscular diseases [19], although no studies have been conducted in children with DM1. Moreover, studies have mainly been performed in adults with DM1, with limited literature on

children [15]. This study aimed to describe respiratory and sleep disorders and their evolution in children with DM1.

Materials and Method

This retrospective observational study was performed at the Armand Trousseau University Hospital, *Assistance Publique-Hôpitaux de Paris* (APHP), Paris, France. Children aged between zero and 18 years, presenting with DM1 and visiting the reference centre for rare lung diseases (RespiRare®) and the neuromuscular disease reference centre between January 2009 and December 2020 were included. The study was approved by the institutional review board of the French Learned Society for Respiratory Medicine, *Société de Pneumologie de Langue Française* (SPLF), which waived the need for patient consent (CEPRO 2021-018).

Procedure

Data were retrieved from patients' electronic medical records, including clinical information, spirometry, nocturnal gas exchange, and polysomnography (PSG) recordings. Pulmonary function tests were interpreted according to recommendations from the European Respiratory Society (ERS) Global Lung Function Initiative (GLI, http://gli-calculator.ersnet.org/) for spirometry. Merkus et al. was used for Rint, and Zapletal et al. for plethysmography, and presented as a percentage predicted [20–22].

Nocturnal gas exchange and polysomnography were performed in a hospital setting. Two devices were used for nocturnal gas exchange recordings: TCM4® (Radiometer, Copenhagen, Denmark) or SENTEC® (ResMed, Saint-Priest, France). PSG recordings used the CID102L8 (CIDELEC™, Saint Gemmes sur Loire, France). The sensors used during recordings were as follows: electroencephalogram (EEG), electrooculogram (EOG), chin electromyogram (EMG), chest and abdominal belts, nasal pressure, pulse oximetry, actimeter, and suprasternal

sensor for sound and pressure/effort. Sleep stages, arousals, and respiratory events were scored manually by experienced physicians, using the American Academy of Sleep Medicine (AASM) recommendations [23].

Statistical Analyses

Quantitative variables that were not normally distributed were expressed as median and interquartile range ([IQR]). We used Fisher's exact test for the comparison between matched qualitative variables, Wilcoxon signed ranks test, and Mann–Whitney test to compare quantitative variables, and Pearson's test for the comparison of independent quantitative variables. Statistical significance was set at $P \leq 0.05$. Statistical analyses were performed using BiostaTGV (http://biostatgv.sentiweb.fr/).

Results

Patients

A total of 24 children with DM1 were included in this study. All patients were Caucasian. The general characteristics of the study population are presented in **Table 1**. The median [IQR] age at the inclusion and length of follow-up were 9.9 [8.2; 14.3] years and 3.75 [1.35; 4.45] years, respectively. Among the five children (22%) with a history of cardiac involvement, four had an atrioventricular block, and one had chronic heart failure (left ventricular function, 45%). No history of recurrent lower or upper respiratory infections was observed. The parents of 10 (40%) children observed concentration and attention difficulties, and 6 (25%) children received a treatment with methylphenidate for this indication.

Lung function tests

A total of 86 spirometry measurements were attempted in 21 patients (87%), with a median [IQR] of 3 [2;4] tests per patient. Only three patients (14.3%), aged 12.5, 14.5 and 15.5 years, were able to achieve complete spirometry measurements, including total lung capacity (TLC), forced expiratory volume in one second (FEV_1), slow vital capacity (SVC), forced vital capacity (FVC), functional residual capacity (FRC), interrupter resistance (Rint), and maximum expiratory and inspiratory pressure (MEP and MIP, respectively). Spirometry results are presented in **Table 2** and their evolution is shown in **Figure 1.**

Three patients (12%) aged 12, 12.7 and 17.6 years displayed a restrictive pattern with TLC < 80% of predictive value and SVC and/or FVC < 80% of predictive value [22]. Two of them had a congenital form and one had an infantile form. None of the patients showed an obstructive spirometry pattern.

No significant decline in spirometry was found during the patients' follow-up, which ranged from 2.5 to 3.5 years. The median [IQR] differences in MIP, MEP and the percentage of predictive value of TLC and FVC between the first and last measures were -2 [-8; +4]% for TLC (p = 0.75), -4 [-8; 5]% for FVC (p=0.72), -2 [-6.5;7.5]cmH_2O for MEP (p=1), and +8 [2;21.5]cmH_2O for MIP (p=0.1).

Sleep studies

Sleep-related complaints were reported in 9/23 patients, with missing information for one child. The main clinical symptoms were daytime sleepiness and fatigability (reported by five and four patients, respectively); three patients reported snoring and one reported nocturnal awakenings. The remainder of the patients were asymptomatic.

Nocturnal gas exchange was recorded in all the patients as part of their systematic follow-up. A total of 77 recordings were collected during spontaneous ventilation and 14 under NIV. The median [IQR] age at first recording was 9.9 [8.2;14.5] years with 3 [1; 5.25] recordings per

patient. In the 16/24 children with more than one recording, the interval between recordings was 8 [6;9] months. The results of nocturnal recordings in spontaneous ventilation are shown in **Table 3** and the evolution of the median transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) is shown in **Figure 2.** There was no statistical difference between patient with congenital and patients with infantile/juvenile forms in terms of mean PtcCO2 (p=0.52), % of total sleep time (TST) spent with a PtcCO2 > 50 mmHg (p=0.64) or mean PtcO2 (p=0.20).

During their follow-up, 16/24 (66%) patients had at least two nocturnal recordings during spontaneous ventilation. The results of repeated gas exchange measurements are shown in **Figure 3** and were stable for all children during follow-up.

A PSG was performed during spontaneous ventilation in 10 children (41%). Indications included daytime sleepiness with or without fatigability (n=5), snoring (n=2), hypercapnia on nocturnal gas exchange recordings (n=1), and nocturnal awakenings (n=2). Sleep architecture could not always be evaluated because the patients refused to have EEG sensors installed (n=3). PSG recordings showed normal sleep architecture in all seven children with a median [IQR] for sleep efficiency of 90 [89;92]%. Sleep stages distribution was as follow: 19 [16.5;22.5]% REM sleep, 22.5 [20;26.5]% deep sleep, and 56 [55;59.5]% for light sleep. The PSG results are listed in **Table 4**. The evaluation for periodic limb movements of sleep was performed in only two patients and was positive in one without any reported symptoms (index 26/h).

Two out of 10 patients presented with mild, 6/10 with moderate, and 2/10 with severe obstructive SAS (OSAS), according to the AASM definition [23]. Two patients had mixed SAS with a central apnoea index (CAI) of 1 /h and 1.5/h. The description of symptoms according to SAS severity is shown in **Table 5**.

Eleven (45%) patients had nocturnal alveolar hypoventilation, defined as a mean $PtcCO_2$ > 50 mmHg for > 25% of TST, diagnosed at a median age of 11.5 [9.5;13.8] years. Two of these

patients were diagnosed with severe OSAS (apnoea hypopnea index (AHI) of 13.1/h and 30.4/h).

We did not identify an association between the symptoms of OSAS and restrictive syndrome on LFTs or nocturnal alveolar hypoventilation (p=0.5 and p=0.68, respectively). There was no significant difference in the mean nocturnal $PtcCO_2$ between the nine symptomatic and 14 asymptomatic patients (p=0.1). The median [IQR] of mean nocturnal $PtcCO_2$ was 48 [44.5;50]mmHg for asymptomatic patients and 49 [46;51]mmHg for symptomatic patients.

Respiratory management

Nine patients (37,5%) had an indication for NIV. The median age at ventilatory support initiation was 16 years, and the youngest patient was 9.5 years old. All patients presented with nocturnal alveolar hypoventilation, and three had associated clinical signs of sleep-disordered breathing. Tolerance and observance were adequate in 2 patients with severe OSAS, while the seven remaining patients refused or prematurely stopped the treatment. For five patients with pre- and post-NIV measurements, the median of mean nocturnal $PtcCO_2$ decreased from 51 [50;54]mmHg to 38 [38;39]mmHg under NIV (p=0.057).

Discussion

In this study, we describe respiratory and sleep disorders in 24 children with DM1, as well as their evolution and management. Analyses of nocturnal gas exchange recordings showed frequent hypercapnia. Considering a cut off $PtcCO_2$ value of 25% of TST spent > 50 mmHg, nocturnal alveolar hypoventilation was identified in 45% of the patients included in this study. This contrasts with the small number (12%) of patients presenting with a restrictive pattern on LFTs. Both nocturnal gas exchange and LFT results were stable throughout the follow-up

period. Severe OSAS was diagnosed in 20% of patients for whom a PSG was performed (2/10 patients).

Spirometry

Among the patients included in this study, FVC and FEV_1 measurements were obtained in only 52% of the 21 children who attempted spirometry, with a median age for the first measurement of 13.5 and 13.2 years, respectively. During the follow-up, there was an inter-individual variability in these measurements, with a tendency for some results to improve with age. This would indicate that technique execution is more reliable and reproducible with older rather than younger children. The recommendations for the management of children with DM1 are to perform spirometry as soon as the child's cooperation allows it. However, in children with DM1, several factors hinder the performance and interpretation of LFTs, such as orofacial muscle weakness, lack of understanding of the technique, and fear of examination (confinement in a narrow room, nasal pinch) in children who may present attention, concentration, and intellectual deficits [24]. To the best of our knowledge, these difficulties have not been described in paediatric studies. Several studies have shown that the measurement of nasal sniff inspiratory pressure (SNIP) could be a viable marker of respiratory muscle impairment and is more easily achievable in patients with neuromuscular diseases and cognitive impairments [25,26].

Three patients (12%) had a restrictive pattern All MEP and MIP measurements were impaired. Our results are in line with those reported in a study of 314 children, which showed restrictive pattern in only 27.2% of patients, with a median FVC of 79 ± 19% [27]. In adults, a restrictive pattern is frequently observed, and a recent retrospective study of 110 patients (median age 43 years) with different forms of DM1 (68% adult forms) showed an FVC <80% in 77% of the patients [28]. The other parameters of LFTs, notably MEP and MIP, have not

been described in previous paediatric studies, but an adult review of the literature reports that MEP and MIP are also systematically impaired measures (median MEP, 43cmH_2O; median MIP, 62cmH_2O) [29,30].

Interestingly, we observed no significant difference in LFTs between the beginning and end of the follow-up. To the best of our knowledge, no study to date has investigated the evolution of spirometry results in children. Adult studies also found stability in lung function, and a study following adult patients with DM1 over five years showed that there was no decline in FVC, including in patients with a restrictive syndrome [31]. These results may suggest a slow decrease in respiratory function and should encourage studies based on prospective longitudinal follow-up of patients during and after their progression to adulthood.

Study of sleep and nocturnal gas exchange

In our study, 39% of patients had clinical symptoms suggestive of sleep-disordered breathing, with daytime sleepiness and fatigue being the most frequently reported. There were no significant differences in nocturnal gas exchange between symptomatic and asymptomatic patients. Our results are consistent with quality of life studies performed in children [12,13,27]. Indeed, a study of 17 children showed that 35.5% had an abnormal Epworth score, which was not significantly related to the presence of intellectual deficit or PSG abnormalities [12]. These symptoms are non-specific and may result from sleep impairment, muscle weakness, or neurological factors. Eleven (45%) children had nocturnal alveolar hypoventilation according to the criteria usually used in patients with neuromuscular disease, and $PtcCO_2$ was stable during follow-up [32]. Only 45% of the patients were symptomatic. Nocturnal alveolar hypoventilation is well described in adult patients with DM1 and frequently leads to NIV initiation. This appears to be related to the loss of respiratory muscle function and the presence of a pulmonary restrictive pattern, leading to nocturnal alveolar

hypoventilation. However, an increasing number of researchers have hypothesised that alveolar hypoventilation could result from central nervous system dysfunction[31,33]. One study demonstrated a decrease in ventilatory response to CO_2 in DM1 adult patients [34]. Certain studies suggest that DM1 should be considered a neurological as well as a neuromuscular disease [35]. In terms of brain structure, neuroimaging has shown lesions of the white matter in all cerebral lobes, the brain stem, and the corpus callosum, as well as a reduction in grey matter [36]. At the tissue level, neurofibrillary degeneration has been demonstrated without the identification of a precise cerebral region based on post-mortem studies. However, immunoreactivity studies have shown a reduction in serotonergic and catecholaminergic neurones in the bulbar region and brain stem, respectively. This supports the hypothesis of a ventilator drive and chemosensitivity to CO_2 impairment [35,37,38].

Only three patients reported snoring, which is considered a more specific symptom of OSAS [39]. Two patients presented with severe OSAS, and one had moderate OSAS. Our study could not identify a link between nocturnal alveolar hypoventilation and sleep-disordered breathing symptoms, probably because of the small sample size. Several studies have attempted to explain excessive daytime sleepiness and have suggested that a primary disturbance of the central nervous system may be responsible [14,17].

Ten PSGs were performed during spontaneous ventilation in 10 patients, identifying two severe, six moderate, and two mild OSAS. Few studies have reported PSG results in children with DM1. In 2006, Quera-Salva et al. reported, in a study with 21 children, a 29% frequency of SAS, with a high proportion of central events (on average 44.5 versus 21.1 obstructive events on the whole recording) but with normal sleep architecture. That study also showed that 38% of DM1 children had periodic limb movements during sleep [15]. However, that study used previous definitions of respiratory events, which could explain the difference from the results reported in our study. In adult studies, OSAS was frequently associated with

central apnoea. A retrospective study of 36 patients with an adult form found 28% of OSAS, 32% central apnoea, and 40% of mixed respiratory events, with a median CAI of 5 +/- 8.9/h [18]. The authors hypothesised that the excessive daytime sleepiness described by patients with DM1 was the result of fragmentation and dysregulation of sleep (due to central nervous system impairment), with an increase in REM sleep, apnoea, and periodic limb movements [14,16,40]. However, this is contrary to our study, in which the percentage of REM sleep was normal and the majority of respiratory events were obstructive. Thus, the sleep profile of children with DM1 appears to differ from that of adults. Several causes should be investigated, including weakness of the orofacial muscles, velar insufficiency, and common causes of OSAS in children, such as adenoidal or tonsillar hypertrophy, maxillofacial malformations, and dental articulation disorders. Ear, nose, and throat (ENT) and orthodontic evaluation in cases of OSAS-related symptoms are essential.

Management

Nine patients had an indication of NIV, 80% for nocturnal alveolar hypoventilation, and 20% for severe OSAS. Under NIV, capnia normalisation was observed. Six patients accepted the implementation of NIV, but three patients interrupted it, and one had poor compliance despite an effect on mean nocturnal $PtcCO_2$. Two patients with severe OSAS showed good compliance with an improvement in their clinical symptomatology (less daytime sleepiness). Several prospective studies in adults have reported a significant discontinuation rate for NIV or CPAP in patients with DM1. Sansone et al. reported that 50% of adult DM1 patients used NIV less than 4h/night and 15% completely discontinued the treatment [11].

Study limitations

Our study is limited by its retrospective nature (missing data, particularly on sleep-disordered breathing symptoms and their evolution throughout the follow-up, and on ENT and orthodontic explorations), the heterogeneity of the follow-up, and the small number of patients because of its mono-centric character.

Conclusion

Few studies have focused on the respiratory function and sleep disturbances in children with DM1. Our results show that restrictive pattern on LFTs is rarely present in children with DM1, and that nocturnal hypercapnia remains fairly stable across follow-up, is rarely associated with significant OSAS and most of the time asymptomatic. This provides new and useful insights into disease evolution to better adapt patients' respiratory follow-up and management. This also highlights the need for future research to better understand the origins of respiratory and sleep disorders in DM1 patients. In particular, a clinical score should be developed to guide explorations, define thresholds of hypercapnia and nocturnal alveolar hypoventilation specific to DM1 patients. Additionally, CO_2 response tests could be considered in case of nocturnal alveolar hypoventilation in the absence of severe OSAS.

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[41] Recommandations HAS obesite enfant et adolescent n.d.

Table 1. General patient characteristics of the 24 study children

	n (%)	Missing data
Sex (female/male)	9 (37%)/15 (63%)	-
Form of the disease		-
Congenital	16 (67%)	
Infantile/Juvenile	8 (33%)	
Cardiac involvement	5 (22%)	1/24
Scoliosis	6 (27%)	2/24
Asthma	1 (4%)	1/24
Obesity	1 (4%)	-
Treatment for ADD	6 (25%)	4/24

Obesity is defined as a body mass index (BMI) > International Obesity TaskForce (IOTF) 30 according to the National Health Nutrition Program recommended by the *Haute Autorité de Santé* (HAS) [41]; ADD: attention deficit disorder.

Table 2. Spirometry results of 21 study children

	% of children with at least one successful measure	Median age at 1st successful measure (years)	Median [IQR]	Median [IQR] (% of normal value)	Min - Max (% of predictive value)
TLC (L)	62%	13	3.52 [2.7;4.2]	84 [76;90]	40 - 102
FEV_1 (L)	52%	13.2	2.6 [1.9;3]	88.5 [85;96]	26 - 104
SVC (L)	71%	14.1	2.6 [1.6;3.1]	78 [68;88]	14 - 109
FVC (L)	62%	13.5	2.9 [2.4;3.2]	81 [73;87]	22 - 95
MEP (cmH_2O)	52%	14	23 [19.5;32]	22 [18.5;33]	8 - 56
MIP (cmH_2O)	52%	15	-25 [-35;-20]	33 [21;44]	13 -109

TLC, Total Lung Capacity; FEV_1, Forced Expiratory Volume per second; SVC, Slow Vital Capacity; FVC, Forced Vital Capacity; MEP and MIP, Maximum expiratory and inspiratory pressure; Max, maximum; Min, minimum; L, litres.

Table 3. Results of nocturnal gas exchange recordings in spontaneous ventilation in 24 study children (n=77).

	Median [IQR]	Min – Max
Mean $PtcCO_2$ (mmHg)	49 [46;51]	37 – 61
$PtcCO_2$ maximal (mmHg)	52 [50;54]	39 – 64
% of nocturnal time recording with $PtcCO_2$ > 50 mmHg	31.5 [0.75;70]	0 – 100
Difference $PtcCO_2$ min – max (mmHg)	7 [5;10]	1 – 16
Mean $PtcO_2$ (mmHg)	77 [72.5;80]	59 – 93
Minimal $PtcO_2$ (mmHg)	66 [61.5;73]	50 – 87
Difference $PtcO_2$ min – max (mmHg)	18 [13;22]	8 – 45
Mean Saturation O_2 (%)	96 [96;97]	94 – 99
Desaturation index (n/h)	5 [2;9]	0 – 28

$PtcCO_2$, transcutaneous partial pressure of carbon dioxide; $PtcO_2$, transcutaneous partial pressure of dioxygen. O_2, Dioxygen; [IQR], interquartile range; max, maximum; min, minimum.

Table 4. Results of polysomnography recordings in spontaneous ventilation in 10 study children.

	Median [IQR]	**Min-Max**
AHI (/h)	8.5 [7.3;9.9]	3.9 - 30.4
CAI (/h)	0.6 [0.25;0.83]	0 - 1.5
OAHI (/h)	7.9 [7.3;9.1]	3.5 - 29.6
REI (/h)	12.3 [10.2;15]	4.7 - 39.8
Desaturation index (/h)	7.7 [2.7;11.4]	1.3 - 25.9
Mean $PtcCO_2$ (cmH_2O)	48 [44;51]	44 - 54
% of TST with $PtcCO_2$ > 50 mmH_2O	30 [0;66]	0 - 100

$PtcCO_2$, transcutaneous partial pressure of carbon dioxide; AHI, Apnoea-Hypopnoea Index; CAI, central apnoea index; OAHI, Obstructive Aponea Hypopnea Index; REI, Respiratory Event Index; TST, total sleep time; Min, minimum; Max, maximum.

Table 5. Repartition of symptoms according to SAS severity.

	Mild SAS n=2	Moderate SAS n=6	Severe SAS n=2
Snoring (n= 3)	0	2	1
Fatigability (n=4)	2	2	0
Daytime sleepiness (n=5)	1	2	2
Night Awakenings (n=1)	0	1	0
Asymptomatic (n=14)	0	1	0

SAS: Sleep Apnoea Syndrome

Figure legends:

Figure 1. Longitudinal evolution of spirometry. TLC, Total Lung Capacity; SVC, Slow Vital Capacity; FVC, Forced Vital Capacity; MEP, Maximum expiratory pressure.

Figure 2. Mean nocturnal $PtcCO_2$ evolution in spontaneous ventilation. $PtcCO_2$, transcutaneous partial pressure of carbon dioxide.

Figure 3. Evolution of the mean $PtcCO_2$ every 2 years in spontaneous ventilation. $PtcCO_2$, transcutaneous partial pressure of carbon dioxide