ERJ Express. Published on July 26, 2006 as doi: 10.1183/09031936.06.00004906

Diurnal ventilation via mouthpiece: survival in end-stage Duchenne patients.

Michel Toussaint, Marc Steens, Geert Wasteels, Philippe Soudon

Institution: All authors from Ziekenhuis Inkendaal, 1602 Vlezenbeek, Belgium

Study institution:

Acute Neurorespiratory Rehabilitation Unit, Neuromuscular Excellency Centre VUB-Inkendaal and Centre for Home Mechanical Ventilation, Z.H. Inkendaal Rehabilitation Hospital,

Inkendaalstraat, 1, B-1602 Vlezenbeek (Brussels) Belgium

Corresponding author: Michel Toussaint

michel.toussaint@inkendaal.be

Tel: +32 2 531 51 11

Fax: +32 2 531 53 01

Short title: Mouthpiece diurnal ventilation in Duchenne

Keywords: duchenne, mouthpiece, neuromuscular, non-invasive, survival, ventilation

Abstract

OBJECTIVE: To assess the impact of diurnal mouthpiece ventilation (MIPPV) as the extension of the nocturnal ventilation (NIPPV) in Duchenne muscular dystrophy (DMD).

PATIENTS: Forty two DMD patients, aged 15-33 years, normocapnic at night with NIPPV, receiving MIPPV since end-diurnal hypercapnia appeared.

MEASUREMENTS: Transcutaneous CO2 tension (TcCO2) was prospectively monitored at the end of the day, before and after MIPPV initiation. Vital capacity (VC), breathing pattern and maximal inspiratory strength were measured. Patients were asked to score the presence (1 point) or absence (0 point) of seven respiratory-linked symptoms before and after MIPPV establishment.

RESULTS: One year, three year, five year and seven year survival rates reached 88%, 77%, 58% and 51% respectively. The mean survival was 31 years. VC stabilized during five years with MIPPV. Symptom scores significantly decreased and TcCO2 normalized during the day (61.5±16.7 to 43.5±5.5 mmHg). No accident and minor side effects were observed in this 184 cumulated patient-years study.

CONCLUSIONS: Daytime mouthpiece ventilation is safe, prolongs survival and stabilizes the vital capacity in Duchenne patients. It is recommended on condition that patients are equipped with a self-supporting harness.

Introduction

Respiratory insufficiency appears in the course of Duchenne Muscular Dystrophy (DMD), first during sleep [1] and at a later stage during the day [2]. With progressive respiratory failure, ventilation needs to be assisted. Invasive or non-invasive assisted mechanical ventilation are successful treatment options [3]. The duration and settings of ventilation aim at achieving optimal blood gases 24h/24. Nasal intermittent positive pressure ventilation (NIPPV) at night initially produces 24h effective blood-gas improvement for several years [4]. In end-stage DMD patients, however, nocturnal NIPPV needs to be progressively used during the daytime as increasing ventilatory dependency develops [5]. At this moment, tracheostomy is proposed in many countries at the expense of complications and social disability [6]. When offered the choice, patients however prefer non-invasive techniques of ventilation [7]. One option for prolonging NIPPV in the daytime is the use of the nasal mask as for NIPPV which however may interfere with the patient's social activity. Assisted ventilation during the day using mouthpiece intermittent positive pressure ventilation (MIPPV) is another, yet poorly explored option. Historically, it appeared in 1957 for daytime ventilation and in 1964 for nocturnal support in post-polio patients [6] and later in Duchenne patients [8]. Mouthpiece ventilation was reported safe and comfortable for wheelchair use, aesthetic and easily applicable. It is inexpensive and confirmed as a user-friendly system during social activities such as eating and speaking [9]. Surprisingly, this technology is not commonly used, and the long-term survival for daytime use is poorly documented in end-stage DMD patients [10]. It is empirically driven as no evidence-based guidelines exist as to when and how to start it. The aim of the present study was to investigate the feasibility of MIPPV as an extension of nocturnal NIPPV

in Duchenne patients and the impact of establishing MIPPV on survival and on disease progression.

Material and methods

Patients

From 1st June 1996 to 31st December 2005, forty-five consecutive DMD patients, normocapnic at night with NIPPV, were considered for daytime MIPPV since they presented additional diurnal hypercapnia. They were all wheelchair-bound before the age of 12. The diagnosis of DMD was made according to the standard criteria available before 1998 [11]. All these patients benefited from home respiratory therapy by intrapulmonary percussive ventilation to prevent low chest infections and to treat them at home when present [12]. All the patients were trained in cough assistance techniques by abdominal-thoracic manual compression and by air-stacking mixed by experienced therapists from the Centre. The efficiency of these techniques was assessed in all patients every 6 months by measurement of the peak expiratory cough flow (PCF) improvement obtained during the manoeuvres. Mechanical cough assistance by Cough-Assist® was available from 2002 for hospitalized patients and three patients (7%) benefited from this technique at home from 2004. One patient had impaired cognitive level and two others had recurrent aspiration and ineffective cough, even when cough was assisted. They all three underwent tracheostomy and were excluded from further analysis. The local Ethics Committee approved the ventilation protocol, and informed consent was obtained from the 42 DMD patients prior to study inclusion coinciding with MIPPV establishment.

Study design

This prospective cohort study investigates (1) the long-term impact of daytime MIPPV on survival and lung function and (2) the short-term and long-term impacts of daytime MIPPV on daytime CO2 tension and related symptoms.

Ventilation protocol

A strict protocol for mechanical ventilation was used (figure 1), based on transcutaneous CO2 monitoring (TcCO2) during sleep (22PM-7AM) preceded by the monitoring of the last two hours of the day in waking patients (20-22 PM). End-diurnal TcCO2 concludes a full day of spontaneous respiration. It should assess the ability to sustain spontaneous ventilation during a full day [13]. Based on TcCO2 measurements, ventilation prescription was decided by the last author of this study, without knowledge of other test results.

In stage 0, 24h/24 normocapnic patients were not ventilated (figure 1A). In stage 1, nasal NIPPV was introduced since nocturnal TcCO2 surpassed 45mmHg, avoiding extension of nocturnal hypercapnia to the daytime with associated clinical deterioration [14] (figure 1B). Stage 2 was defined by end diurnal TcCO2 above 45mmHg measured with autonomous ventilation before resuming NIPPV (figure 1C). Diurnal hypercapnia was the criterion for introducing diurnal MIPPV since it highlighted the inability to breathe completely unassisted during the day between two nights of effective nasal ventilation. Patients were discharged home after two learning days in the hospital. In this study, patients were prospectively included and studied since they presented diurnal hypercapnia despite nocturnal NIPPV. Data when starting nocturnal NIPPV were retrospectively retrieved. Pure bulbar muscle

dysfunction was an exclusion criterion for starting MIPPV, but decrease in swallowing speed was not.

Monitoring and equipment

Transcutaneous CO2 tension (TcCO2) was non-invasively recorded (TCM3® Radiometer, Copenhagen, Denmark). The best of 3 vital capacities (VC) was recorded; the spontaneous respiratory rate (RR), tidal volume (VT) and minute ventilation (VE) at rest were averaged over a full minute of quiet breathing (5410 Ohmeda, Louisville, USA). Predicted values for VC were calculated using reference values proposed by the European Respiratory Society [15]. Maximal inspiratory pressure (MIP) was measured according to the technique of Black and Hyatt [16] (Microloop®, Micro Medical Limited, Rochester, UK). Alveolar minute ventilation (VE alv) was calculated by the technique of Harris and collaborators [17]. Patients were asked to confirm the presence (1 point) or the absence (0 point) of seven respiratory-linked symptoms: chronic secretions, dyspnoea, loss of appetite and weight, depression, intellectual fatigue or trouble of concentration, headaches and swallowing troubles [18]. A score of 7/7 points was given for 7 present symptoms and a score of 0/7 was given if no symptom was present. Symptoms were quoted when starting MIPPV and one year later. TcCO2 and symptom scores were not recorded during the day when nocturnal NIPPV started. Free time was recorded as the maximal time in one continuous shot of unassisted breath per 24h.

Mouthpiece ventilation

The rigid plastic-made mouthpiece (Mouthpiece angled, Respironics, Murrysville, USA) is inserted in a short tubing held by a rigid Acrylonitrile Butadiene Styrene (ABS) piece constructed by the third author (figure 2). ABS support is placed on patients' shoulders

aiming at following body movements. This self-supporting system should ensure the stability of the mouthpiece, even when the patient does not hold it in his mouth. Volumetric ventilators, also used for the NIPPV, were placed with an additional battery on the wheelchair: 15 Eole3 (Saime, Savigny le Temple, France), 12 PLV100 (Lifecare, Lafayette, USA), 1 Legendair and 6 Airox Home 1 (BIO MS, Pau, France), 4 EV801 (Dräger, Lübeck, Germany), and 4 Breas PV501 (Breas, Molnlycke, Sweden).

Analysis

Survival was calculated by Kaplan-Meier analysis (Medcalc®). Lung function and body characteristics were compared by one-way analysis of variance (ANOVA). Student-Newman-Keuls test was used for all post ANOVA comparisons between NIPPV, MIPPV and 1, 3, 5 and 7 years MIPPV follow-up. Paired t test compared diurnal TcCO2 and symptom scores before and after MIPPV. Significance was accepted for $p<0.05$.

Results

MIPPV started 4.1±2.5 years after NIPPV implementation. Figure 3 shows 1 yr, 3 yr, 5 yr and 7 yr MIPPV survival rates reaching 88%, 77%, 58% and 51% respectively. Patients' characteristics are presented in table 1. Lung function significantly lowered between NIPPV and MIPPV initiations but VC was not different during the five first years with MIPPV despite a significant decrease in MIP within 3 years. Figure 4 shows significant daytime TcCO2 improvements with MIPPV. Normocapnia remained constant during the study. Symptoms scores decreased after establishing MIPPV. Appetite improved in 7/12, dyspnoea disappeared in 8/11 and swallowing improved in 6/7 patients. Eleven patients died. Their characteristics measured before death are shown on table 2. Five patients died from cardiac

failure by low output syndrome (LOS), 2 from sudden death during the night, 3 from acute respiratory failure (ARF), and 1 (# 11) underwent tracheostomy during an acute respiratory infection after using MIPPV during 2.3 years. He died from tracheal bleeding three months later. Among the three patients with ARF, subject # 4 presented decrease in swallowing speed. He died at home after 1.6 years MIPPV from pneumonia since bulbar weakness developed. Subject # 5 dramatically lost weight and became very weak. He died at home during a chest infection. Subject # 7 died after 2.1 years MIPPV during an emergency tracheal endoscopy. Since assisted cough by manual chest compression was ineffective in patients # 4, 5 and 7 (table 2), we believe that we probably could have helped these patients if the Cough-Assist® device had been available in Europe before 2002. In our experience, Cough-assist® is effective in +/- 80% of the subjects in whom manual cough techniques have become useless. The loss of mouthpiece out of the mouth did not result in additional adverse events. Assist control mode of ventilation was used in 39 and control mode in 3 patients. Ventilator setting remained the same during night and day. Ventilator mean frequency was 19±3 rates per minute and the mean tidal volume was 688±19 ml.

Discussion

On the long-term, daytime mouthpiece ventilation provided 50% survival at 31 years of age and stabilized lung function for five years in DMD patients reaching diurnal hypercapnia after 4.1 yr NIPPV. On the short-term, TcCO2 and symptoms scores improved. Although an open study, the results presented here demonstrate that mouthpiece interface is an option to ventilate DMD patients during the day. These results are difficult to compare with controlled tracheostomized groups because the indications and clinical conditions for tracheostomy are not the same as for MIPPV [19]. In our experience, since patients were well informed about

mouthpiece technology, they all chose MIPPV instead of daytime ventilation via nasal mask [20] or via tracheostomy [21].

Impact on survival

This inception cohort study analysed DMD patients at a later stage of disease progression than previous published studies: the stage of diurnal hypercapnia. This stage is logically expected after a period of several years with nocturnal NIPPV [5, 19, 20]. This specific context makes historical comparisons difficult.

In Duchenne dystrophy, survival without mechanical assistance was consistently reported at the beginning of the third decade (19.3yr [20]; 20yr [22] and 21yr [23]). Undoubtedly NIPPV has been an important advance in prolonging life. Previous studies related spectacular improvement in DMD survival probability with NIPPV confined to the night only. The groups of Yasuma [24] and Eagle [20] reported 50% survival at 25.3 and 30.4 years respectively. Despite retrospective, these NIPPV series are interesting since they considered all DMD patients from birth, even those not reaching the criterion for starting mechanical ventilation. Using similar parameters, our data are comparable with those of Simonds et al. [10] and Bach et al. [25]. In the latter, similar techniques of ventilation were used (volumetric respirators, nasal mask plus mouthpiece, night-time and daytime ventilation) in a similar DMD population. Their patients started nocturnal ventilation at a similar age of 18.6 versus 19.4 here. The mean (50%) survival age was 26.4 vs 32.5. The proportion of survivors above 25 years was 75% vs 83%. The mean use of NIPPV plus MIPPV was 7.8 years vs 8.6 years here. Instructive is the comparison of our data with those of Simonds et al. [10]. In both studies, patients were ventilated at the point of diurnal hypercapnia measured by TcCO2, but, with Simonds, patients started nocturnal NIPPV when, in the present study they would be offered diurnal

MIPPV. Interestingly, the 5-yr survival was 70% in both studies. Important differences however distinguish this study from that of Simonds. First, nocturnal NIPPV was established earlier (at nocturnal hypercapnia) than in Simonds' experience (at diurnal hypercapnia). Recent data of the same group confirm the appropriateness of the early approach [14]. Secondly, the natural illness evolution by Simonds' patients seemed clearly more severe than here, perhaps related to the absence of early assisted ventilation. In their experience, NIPPV was implemented at very low vital capacities (range 0-600 vs 240-1240 ml here), with diurnal TcCO2 at 77 mmHg (10.3 KPa) vs 62 mmHg. In the present study, delayed diurnal hypercapnia at higher VC suggests a slower deterioration of the respiratory function with earlier NIPPV.

The 50% survival was 31 years. The average age of 32.5 among those patients using MIPPV for 7 years or more suggests that MIPPV indeed prolonged life. This is important because NIPPV is now considered so effective [19] that almost 3/4 DMD patients are expected to survive for 5 more years with NIPPV [10], giving them the chance to prolong life to later and unexplored respiratory stages than previously investigated. In this study, 64% patients died from cardiac failure (table 2). This confirms that cardiac failure represents the major cause of death in DMD patients with prolonged ventilation. All the patients with cardiomyopathy were treated with β-blockers and ACE inhibitors when the left ejection fraction was less than 50%. Perhaps here the widespread use of cardiac medications improved cardiac management and could influence the survival rate of the present DMD population.

The living place was not very different between the 11/42 dead patients versus 31/42 survivors: 27% vs 19% lived in institution, 73% vs 71% lived at home, and 0% vs 10% lived in a nursing home respectively. This clearly illustrates the difficulty of all ventilated patients in staying at home because of lack of financial and family-based resources.

Impact on lung function

Deterioration in respiratory function is related to muscle strength [23]. In DMD patients, vital capacity is reported to decline at a higher rate in the last years of life [26]. Interestingly, VC was previously reported to decline less [27] or even to stabilize [28] with NIPPV. In this study, the annual decline of vital capacity was 118ml with nocturnal NIPPV. As a similar result VC stabilized for more than 5 years with daytime MIPPV (decline of 24ml/yr, NS) despite significant decline in MIP within 3 years. Lowering VC decrease can be explained by resting respiratory muscle or by reducing mechanical load, but, up to now, no data are available to confirm these hypotheses. Anyway, reducing the impact of the disease progression on lung function is of clinical importance in ventilator free time preservation on the long-term. A free time as little as 30-60 minutes makes sense in the management of these patients, their families and caregivers. It provides ventilator free autonomy for daily activities like transfers from bed to the wheelchair/toilets, for taking a bath or a shower, for drinking or eating without respiratory mechanical support. It also reduces the fear of suffocating in case of ventilator failure, which is not negligible.

Impact on diurnal hypercapnia

In this study, MIPPV significantly improved end-diurnal CO2 tension (figure 4). As similarly reported with NIPPV [10, 29], this improvement remained constant on the long-term during the full follow-up for all the subjects with SaO2 >95% and diurnal TcCO2 <45mmHg.

Impact on the symptoms

In 1999, after this study started, the American Thoracic Society (ATS) proposed a constant awake PCO2>50mmHg and/or SaO2<92% in restrictive disorders as criterion to start diurnal ventilation when nocturnal NIPPV is not sufficient [5]. In this study, no patient met these “a

posteriori" ATS criteria. They were soon included for starting diurnal ventilation since they presented diurnal TcCO2>45mmHg. At this moment, we observed that symptoms were already present in 40/42 patients and that a symptom score higher or equal to 3/7 was quoted in 27/42 patients. The presence of the symptoms suggests physiological changes along with impending need for additional daytime ventilation. Symptoms perhaps signal the presence of a high cost of energy expenditure spent in maintaining normocapnia probably leading to further clinical deterioration. This hypothesis, however, needs further investigation. As it was demonstrated with NIPPV, DMD patients may benefit from daytime ventilation before further worsening [14]. Controlled investigations however are needed to help clinicians in deciding when to start daytime ventilation, perhaps by the use of a simple symptom score. To our surprise, swallowing problems and aspirations were reversible in 6/7 patients despite initially looking like bulbar impairment. This temporary recovery suggests that swallowing problems were related to the respiratory worsening rather than to pure bulbar involvement. In such similar cases, we strongly recommend a trial with mouthpiece ventilation before considering tracheostomy. Compared with previous study reporting more than 30% DMD patients disrupting NIPPV for tracheostomy [29], two patients (5%) were candidates for tracheostomy in the present experience.

Mouthpiece safety and tolerance

In very weak Duchenne patients, it was thought that the risk of releasing the mouthpiece due to orbicularis oris muscle weakness [5] was so important that MIPPV safety was uncertain. This study contradicts this view and demonstrates that appropriate self-supporting system minimizes efforts to hold the piece and prevents accidents due to disconnection (figure 2). Leaks around the mouth were largely present, but patients knowingly controlled the leaks and pursed the lips at regular intervals (once every two or three breaths, sometimes only twice per

minute) as they felt it necessary to be fully inflated in response to their needs. For a prolonged period of release, patients hold their mouthpiece in contact with their cheek to avoid low pressure alarm. No patient except subject 2 presented orthodontic disorders. This contradicts another experience reported after prolonged use of the mouthpiece [8].

With tracheostomy and nasal ventilation, patients are expected to take air at each insufflation. With diurnal mouthpiece, we observed that patients managed ventilation differently. When starting MIPPV, some patients took air 1 time on 4 insufflations and this proportion increased with disease progression. Others took air at each insufflation, but they produced voluntary massive inspiratory leaks. They pursed the lips 1 or 2 times per minute. With illness progression, they decreased the quantity of leaks and increased the frequency of lip pursing. This finding means that recording the ventilator's clock alone may provide wrong information on how patients are ventilated. For this reason, the only method to assess the free time is to stop ventilation and to record how long the patients can breathe without machine. In the practice, patients were questioned on the time they could breathe unassisted and they were invited to show their free time. The test was stopped when patients expressed the need to start ventilation again. The majority of them could not reach O2 desaturation in the trial. At the time of study inclusion, MIPPV was prescribed for 2 hours after lunch, and patients were asked to progressively increase ventilation support with years. As shown on table 1, the surprising finding was that patients naturally spend more time with respirator than prescribed and thus MIPPV was found addictive for most of them. This can be explained for the reasons described above. Nevertheless, we changed our approach and we are now looking for a better respect of the prescription.

In conclusion, mouthpiece ventilation during the day as an extension of nocturnal ventilation is safe and provides reliable survival in end stage Duchenne patients. These patients benefit

from the treatment as judged by release of diurnal hypercapnia, by improvement of the major respiratory-related symptoms and by long-term vital capacity stabilization. Daytime ventilation via mouthpiece can be recommended on condition that patients are equipped with a self-supporting harness around the neck and that they can accede to non-invasive techniques for airway clearance.

Acknowledgments

The authors thank Thierry Troosters, PhD (Katholieke Universiteit Leuven, Belgium) and Dilys de Guigné (Moulins, France) for their friendly help.

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	NIPPV	MIPPV	1yr	3yr	5yr	7yr	ANOVA
n	42	42	35	28	17	13	
age (y) **	19.4 ± 4.2	23.5 ± 4.4	24.8 ± 4.7	27.1 ± 5.0	29.2 ± 4.9	32.5 ± 4.4	a c d e
height (cm)	164 ± 8	164 ± 8	163 ± 8	163 ± 8	163 ± 8	164 ± 8	-
weight (kg)	52 ± 15	47 ± 16	49 ± 13	49 ± 13	47 ± 11	46 ± 12	-
BMI	19.2 ± 4.5	17.6 ± 5.2	18.5 ± 4.3	18.3 ± 4.5	17.7 ± 4.0	17.1 ± 4.5	-
VC (ml) **	1016 ± 399	534 ± 200	582 ± 198	488 ± 178	412 ± 173	354 ± 129	a f
VC% predicted **	21 ± 8	11 ± 4	13 ± 4	11 ± 4	9 ± 4	8 ± 3	a
MIP (cmH2O) **	29 ± 11	16 ± 5	15 ± 5	12 ± 5	8 ± 3	6 ± 2	a c d e
VT (ml) **	281 ± 87	217 ± 64	199 ± 46	181 ± 57	168 ± 58	137 ± 75	a e
RR (/m) *	21±5	24±6	24±5	25±6	26±6	26±5	a
VE (ml) **	5692 ± 1657	5027 ± 1339	4688 ± 1271	4466 ± 1525	4292 ± 1458	3396 ± 1772	a e
VE alv (ml) **	3398 ± 1058	2792 ± 916	2509 ± 848	2263 ± 1011	2057 ± 1112	1391 ± 1278	a e f
Free time (hours) **	24.0 ± 0	15.7 ± 1.1	2.9 ± 1.8	2.1 ± 1.8	1.2 ± 1.6	0.5 ± 0.6	a b c d e
Diurnal TcCO2 (mmHg)	-	62 ± 17	43 ± 10	39 ± 10	39 ± 10	43 ± 12	b

Table 1: Characteristics by ventilation stages with spirometric data and free time.

NIPPV: start nocturnal Nasal Intermittent Positive Pressure Ventilation; MIPPV: start diurnal Mouthpiece Intermittent Positive Pressure Ventilation; 1, 3, 5, 7yr: Years of follow-up with MIPPV; BMI: Body Mass Index; VC: Vital Capacity; MIP: Maximal Inspiratory Pressure; VT: Tidal Volume; RR: Respiratory Rate; VE: spontaneous minute Expiratory Ventilation, VE alv: alveolar minute ventilation.

ANOVA (analysis of variance): *: $p=0.005$; **: $p<0.001$
Student-Newman-Keuls comparison test ($p<0.05$): a: NIPPV/MIPPV; b: MIPPV/1yr; c: MIPPV/3yr; d: MIPPV/5yr; e: MIPPV/7yr; f: 1yr/7yr.

#	Death		Delay	Lung		Heart	PCF		Living
	Cause	Age (years)	N-MIPPV (years)	VC (ml)	MIP (cmH2O)	LEF (%)	Spont (L/min)	Assisted (L/min)	place
1	LOS	27.8	3.0	240	8	24	36	127	Inst
2	LOS	35.8	2.8	370	7	29	66	114	Inst
3	LOS	21.3	0.8	300	6	29	48	176	Inst
4	ARF	22.7	7.5	250	8	56	52	154	Fam
5	ARF	25.3	0.7	430	14	48	89	145	Fam
6	SUD	24.2	1.7	630	18	45	123	310	Fam
7	ARF	21.4	2.6	520	14	43	93	156	Fam
8	SUD	27.0	3.5	760	20	39	128	256	Fam
9	LOS	24.4	5.9	290	11	33	48	218	Fam
10	LOS	24.4	1.1	1140	23	30	160	240	Fam
11*	TRACH	21.2	0.2	386	18	34	38	187	Fam
mea n		25.0	2.7	483	13	37	80	189	
sd		4.2	2.3	272	6	10	42	60	

Table 2: Last individual cardio-pulmonary characteristics measured within 6 months before death in 11 patients who died with diurnal MIPPV.

* Patient undergoing tracheostomy; LOS: low output syndrome; ARF: acute respiratory failure; SUD: sudden death; TRACH: tracheostomy complication; LEF: left ejection fraction; (PCF): peak cough flows are measured spontaneously (Spont) and assisted (Assisted) with air-stacking combined with manual chest compression; Fam: living with family; Inst: living in institution.

Legends of the figures

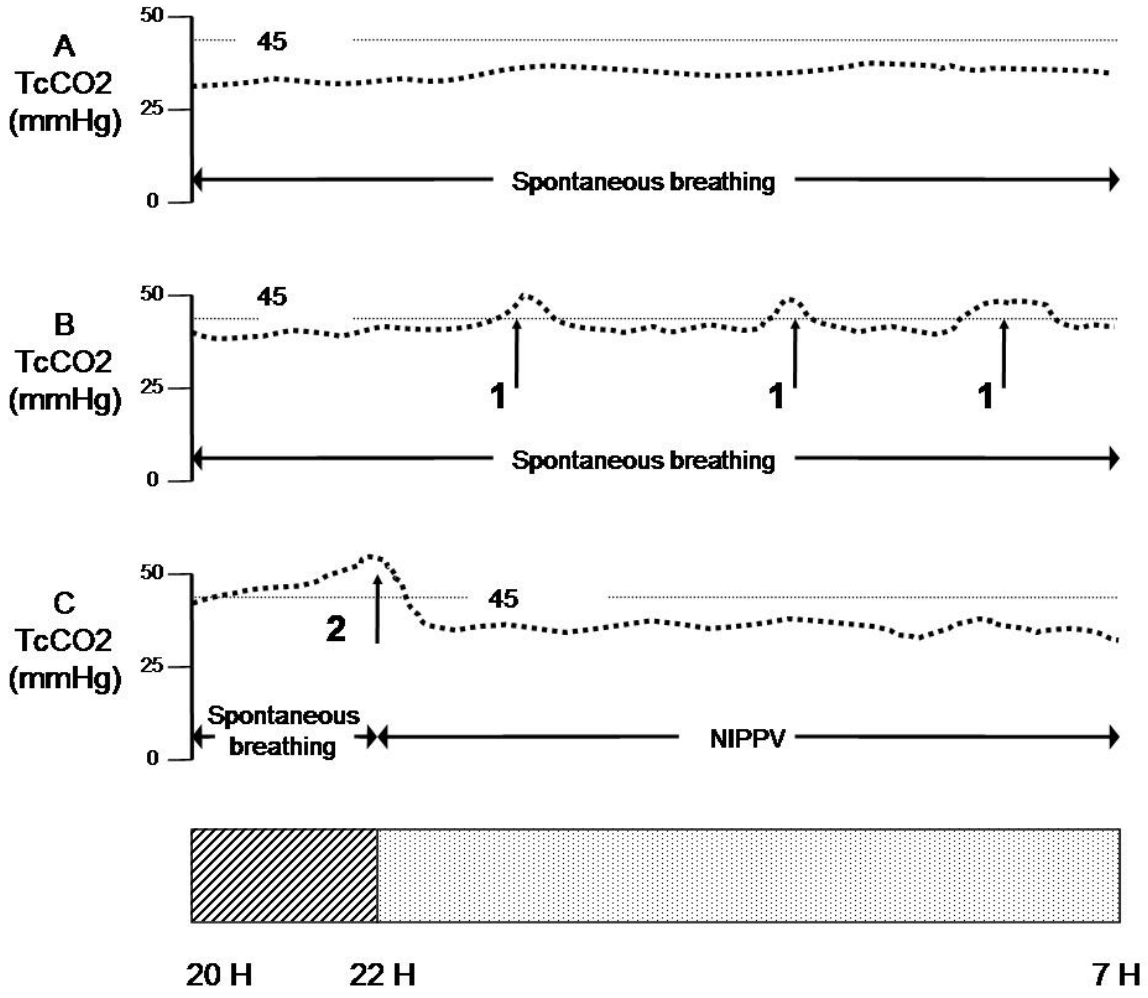

Figure 1: Schematic transcutaneous CO2 tension monitoring at the time of inclusion in stages 0, 1 and 2 of ventilatory support.

A. Stage 0: spontaneous ventilation
B. Stage 1: start nocturnal intermittent positive pressure ventilation (NIPPV)
C. Stage 2: start mouthpiece intermittent positive pressure ventilation (MIPPV)
TcCO2: Transcutaneous CO2 tension; 1: sleep-related TcCO2>45mmHg; 2: end diurnal TcCO2>45mmHg

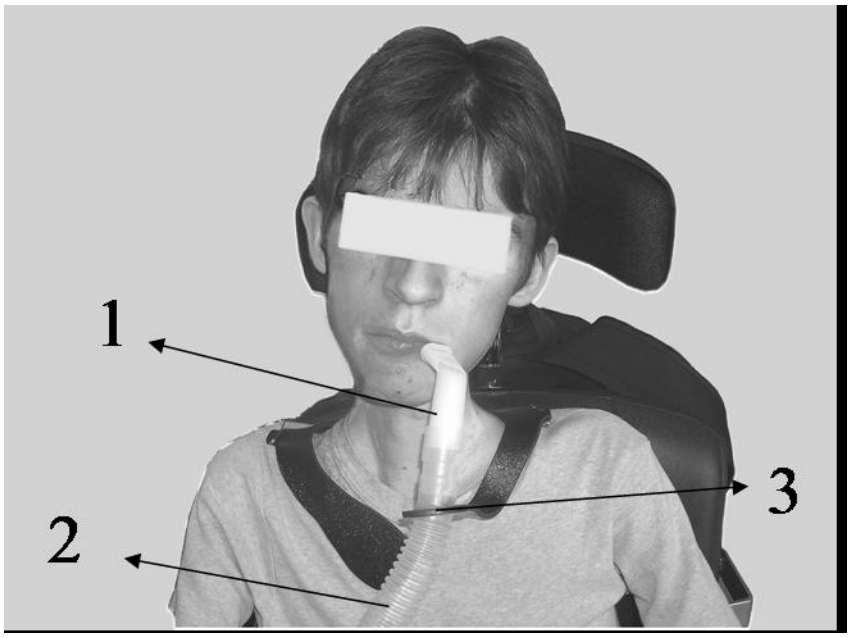

Figure 2: The mouthpiece self-supporting system

(1) Rigid plastic mouthpiece
(2) Short tubing
(3) Fixation on the shoulders

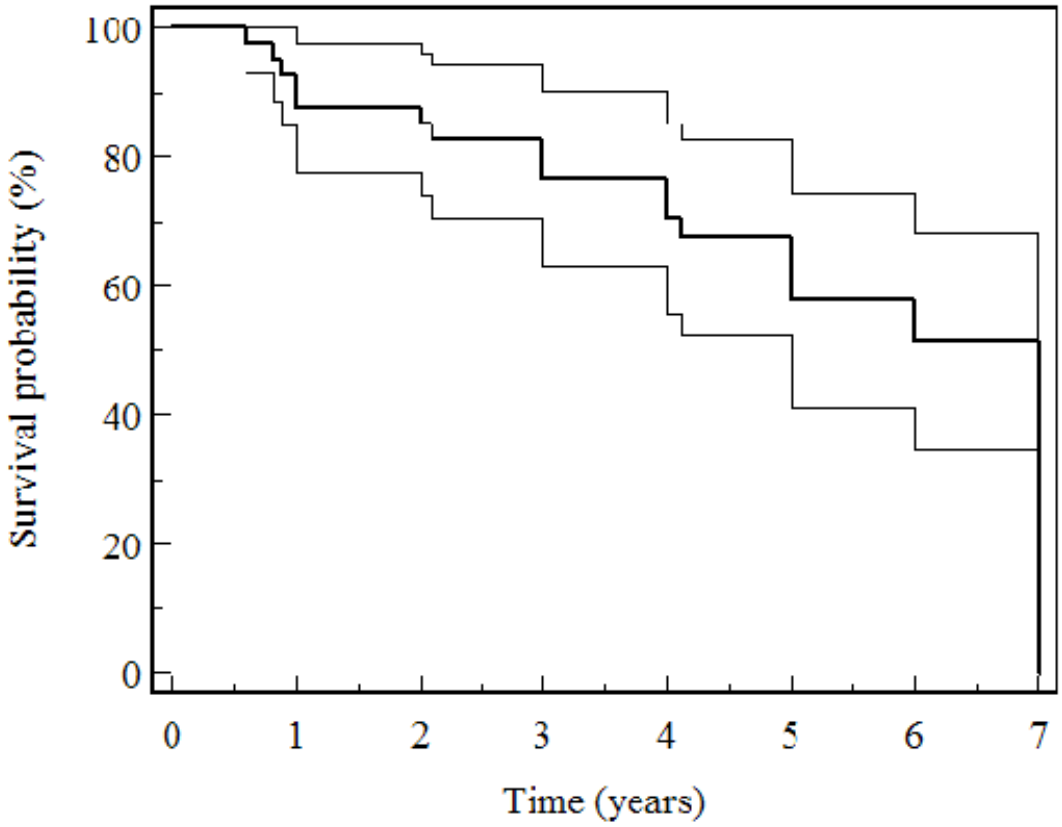

Figure 3: Survival curve (including 95% Confidence Interval) of daytime ventilation via mouthpiece in Duchenne patients.

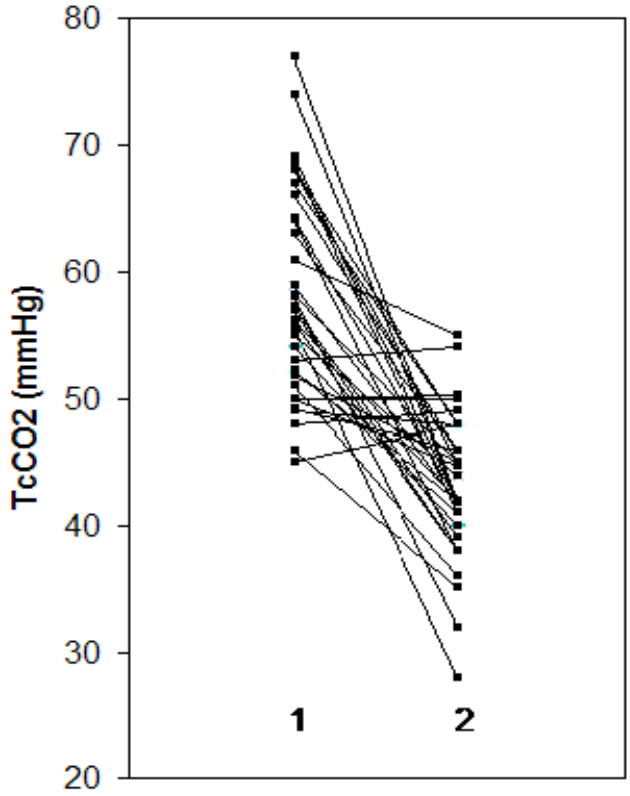

Figure 4: Impact of daytime ventilation via mouthpiece on transcutaneous CO2 tension (TcCO2)
(1) Before starting and (2) +6 months after starting daytime mouthpiece ventilation