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SYMPTOMS, CLINICAL AND PHYSIOLOGICAL FINDINGS MOTIVATING HOME MECHANICAL VENTILATION IN PATIENTS WITH NEUROMUSCULAR DISEASES

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Objective: **To clarify the relationship between symptoms, clinical signs and physiological abnormalities that were motivating the initiation of home mechanical ventilation in patients suffering from neuromuscular diseases.**

Methods: **From The Swedish Home Mechanical Ventilation Register we identified 352 patients with neuromuscular diseases and we looked at circumstances (acute vs elective) and clinical motives for starting ventilatory support.**

Results: **Home mechanical ventilation was commenced electively in 268 patients (76%) and among these daytime sleepiness was the most common motive, being reported in 56% of the patients. In the 24 children with spinal muscular atrophy, however, 96% started ventilation electively and cough insufficiency was the most common motive. The patients were moderately hypercapnic ($PaCO_2$: 7.0 kPa, SD 1.3). None of the clinical motives were related to the $PaCO_2$ level. Average PaO_2 was above 8 kPa in all groups, but lowest in the patients with post-polio and dystrophia myotonica. Mean vital capacity was close to 40% of predicted, but significantly lower in the Duchenne patients (26% of predicted).**

Conclusion: **Daytime sleepiness was the most common clinical symptom motivating home mechanical ventilation in this group of patients with chronic hypercapnic respiratory insufficiency secondary to neuro/myopathies. Respiratory function testing is therefore suggested to be included in the diagnostic work up of daytime sleepiness in these patients.**

Key words: respiratory failure, non-invasive ventilation, invasive ventilation, symptoms and signs.

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INTRODUCTION

Home mechanical ventilation (HMV) in patients with chronic alveolar hypoventilation secondary to neuromuscular diseases (NMD) has become widely acceptable, as the provision of ventilatory support can provide symptomatic relief and increase life expectancy (1).

HMV can be applied as non-invasive ventilation (NIV) most often via a facemask, or as invasive ventilation via a tracheostomy. Generally, the use of NIV is much more prevalent than invasive ventilation. There are many reasons for this, some of which are that NIV is simpler and cheaper to administer and that most patients are ventilated initially during sleep only. Eventually, when the need for HMV exceeds 16–20/24 hours, some centres would consider a change to invasive ventilation, while others are more reluctant to take this step.

Encouraged by the increasing numbers of patients on HMV, a consensus report defining the clinical indications for NIV was published in 1999 (2), and there is a general agreement that both symptoms and physiological criteria should form the basis for commencing HMV. At the same time, we have a limited knowledge about the actual application and priority of the indications that result in the embarking on ventilatory support. Baseline clinical data have been reported prior to HMV; still, the mutual relevance of these data to the decision-making for initiating HMV has been stated only occasionally.

The purpose of this study was to rank 10 predefined clinical motives for starting HMV in patients with ventilatory impairment secondary to function-limiting NMD and to define the relationship between the motives on one hand and physiological criteria on the other.

METHODS

Our database was the Swedish Home Mechanical Ventilation Register (3). A closer description of the enlistment of patients in the register is given in (4). The accumulated number of patients in the register was 1519 as of January 1, 2003 and 1088 individuals were at that moment reported to be alive on a ventilator 6–24 hours a day, corresponding to a HMV treatment prevalence in Sweden of 12/100,000. For patients starting therapy after January 1, 1996 (prospective part of the register $n=970$), we have data on blood gases (spontaneous breathing, room air), vital capacity and symptoms and signs motivating HMV. Only patients starting after this date and presenting neuromuscular diseases as the cause of respiratory failure ($n=352$) were included in our analysis, which was comprised of the following diagnostic groups: (a) post-polio syndrome, (b) amyotrophic lateral sclerosis (ALS), (c) Duchenne muscular dystrophy (DMD), (d) dystrophia myotonica (DM), (e) spinal muscular atrophy (SMA) and (f) other neuro/myopathies. Identical register forms were used by all the participating physicians, who thus relied on the same pre-defined criteria framing 10 different clinical motives leading to HMV. In this study the umbrella term "motive" refers to symptoms, signs and physiological indices that in combination with additional evidence of respiratory muscle weakness were pieces of the puzzle in the process of launching domiciliary ventilatory support. The motives were stated in the elective patients only ($n=268$), as the symptom list may not be applicable to acutely ill patients. Elective

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patients were defined as individuals starting ventilatory support according to plan over days or weeks. Opposing this, acute patients presented a rapid worsening in their condition, often induced by an infection, leading to severe respiratory insufficiency requiring immediate medical attention.

Calculation of vital capacity in percent of the predicted value (VC%pred) in patients beyond 19 years of age was done according to Berglund et al. (5). In the rest of the patients we based this calculation on Zapletal et al. (6).

The Swedish Data Inspection Board approved the register and the Medical Ethics Committee at the University of Lund approved the study. All patients were given written information about the register and specifically asked by their physicians if they accepted registration. For statistical analysis between groups, we used analysis of variance and t-test for the continuous variables and χ^2 test for categorical data. Analyses were carried out with the computer program Statistica version 6.1. (StatSoft Inc, Tulsa, USA).

RESULTS

Of the 352 individuals, 268 (76%) started HMV under elective conditions, and the remaining 24% started HMV during an acute respiratory episode. The distribution of elective and acute launching of HMV varied between the diagnostic groups, most strikingly seen in the SMA group that started HMV electively more often than the other patients ($p < 0.05$). These data and demographic information are outlined in Table I. In the elective patients, tracheotomy was performed in 7 patients (2.7%) only, in contrast to 35 (43%) of the acute patients. The majority of the patients (>90%) were ventilated less than 12 hours per day.

The percentage distribution of the 10 different predefined motives that contributed to the decision of starting HMV in the different diagnostic groups is depicted in Table II. More than one motive could be attributed to each patient, which explains that the sum of motives exceeds 100%. Altogether, the most common motive was daytime sleepiness. Cough insufficiency was a more frequent motive in the children with SMA ($p < 0.01$) compared with the other groups; no other statistically significant differences were seen between the diagnostic groups. The mean (SD) age in the patients with and without daytime sleepiness was 53 (20) and 46 (24) respectively, ($p < 0.05$).

The daytime blood gas analyses and objective pulmonary function tests are displayed in Table III, demonstrating that most of the patients were moderately hypercapnic. There were no statistical differences in $PaCO_2$ levels between the diagnostic groups. The PaO_2 values differed significantly between the groups (analysis of variance) and t-test for each of the diagnosis groups vs all other patients showed that the PaO_2 values were lowest in the polio and DM group ($p < 0.05$) and the base excess values were lowest in the SMA group ($p < 0.05$). Vital capacity (VC) differed significantly between the groups and t-test showed that it was the DMD patients who presented significantly lower values ($p < 0.01$).

We looked specifically at the blood gases and pulmonary function tests for the 5 most common motives. These data are shown in Table IV, which contains information on patients with and without the listed motives. In the patients with daytime sleepiness compared with those not having daytime sleepiness, the only difference was seen in base excess (BE) ($p < 0.05$). In the patients with abnormal daytime blood gas tests as reported motive we confirmed worse PaO_2, $PaCO_2$ and BE values ($p < 0.01$ in all 3 parameters). In the patients with dyspnoea, the VC was better ($p < 0.05$) in spite of the same patients having worse blood gases (PaO_2: $p < 0.005$, BE: $p < 0.05$). Patients with cough insufficiency as motive had better blood gases (PaO_2, $PaCO_2$ and BE: $p < 0.01$) compared with the patients without this motive. Finally, in patients with and without headache, we found no statistically significant differences.

DISCUSSION

In this prospective register-based study, comprising 352 patients with chronic hypercapnic respiratory failure secondary to neurological diseases, we have shown that 24% of the patients started HMV in an acute situation. In the remaining 268 elective patients we found that the most common motive for starting HMV was daytime sleepiness, which was present in 56% of the patients, yet this was not associated with worse blood gases compared with the patients not complaining of daytime sleepiness. In most of the diagnostic groups the vital capacity was reduced to about 40% of the predicted value, whereas the DMD group exhibited a more substantial reduction to 26%. Hypercapnia was evident in all groups, in spite of PaO_2-levels well above 8 kPa.

A register-based study may be severely biased in case of under-reporting. The register receives reports from 35 clinics, 8 of whom are responsible for two-thirds of the entire registered population. We cannot claim total coverage of all small centres in Sweden, but their numerical contribution to our data would be negligible. Loss of data from the bigger centres may be a

Table I. *Demographic data of the 352 patients*

	Total	Post-polio	ALS	DMD	DM	SMA	Other
n	352	98	72	48	29	24	81
Elective	268 (76%)	78 (80%)	60 (83%)	35 (73%)	22 (76%)	23 (96%)*	50 (76%)
Age (years)		66 (60–72)	64 (57–71)	20 (15–25)	48 (34–55)	12 (5–23)	49 (25–60)
% Males	61	48	71	100	31	54	56

Elective = number and percentage of the patients that initiated HMV under elective conditions. Age is expressed as median value and (25–75% interquartile range). *Statistically significant difference ($p < 0.05$) for SMA compared with the rest of the patients.
ALS = amyotrophic lateral sclerosis; DMD = Duchenne muscular dystrophy; DM = dystrophia myotonica; SMA = spinal muscular atrophy.

Table II. *Motives for launching home mechanical ventilation electively in 268 patients*

Motive	Average	Post-polio	ALS	DMD	DM	SMA	Other
Sleepiness	56	68	45	54	68	30	56
ABG daytime	38	59	8	26	46	17	54
Dyspnoea	37	44	55	9	31	17	34
Cough insuff.	27	13	31	31	23	70*	24
Headache	21	28	12	34	23	4	20
Sleeping disorder	21	21	35	6	32	4	16
ABG night	18	18	7	43	18	13	18
Apnoeas	11	15	5	11	9	9	14
General	11	5	23	11	9	26	0
Oedema	6	13	0	3	9	4	4

Numbers in the columns show the percentage distribution for each motive in the different patient groups.
*$p < 0.01$.
ALS = amyotrophic lateral sclerosis; DMD = Duchenne muscular dystrophy; DM = dystrophia myotonica; SMA = spinal muscular atrophy; Sleepiness = daytime sleepiness, ABG daytime = daytime blood gas analysis; Cough insuff = cough insufficiency; ABG night = nocturnal blood gas assessment; General = general physical deterioration.

more significant problem. Therefore, we annually send out individualized reports to each clinic with a request for completion of data if necessary. It is estimated that the register covers at least 95% of the target population.

We acknowledge that most motives (including daytime sleepiness and sleeping disturbances) are entirely subjective data provided by the clinicians. The only motive that is validated is abnormal daytime blood gases; in patients where this motive was reported, objective data confirmed worse values of the motive. The pre-defined list of motives was elaborated during several meetings with clinical experts in the field, we therefore believe that it reflects common clinical practice. We acknowledge, however, that the term "daytime sleepiness" is one possible translation of the Swedish expression *dagtrötthet*, used in the register forms. Other possible translations are daytime fatigue and daytime tiredness.

The most common motive was daytime sleepiness, and comparable symptoms have previously been stated as important indicators for the possible need of HMV: fatigue (2), reduced alertness (7) and excessive daytime sleepiness (8). Others (9) found sleepiness in 18–20% of the patients, while dyspnoea and headache were seen in the majority of the patients. In another study, headache was more specific than tiredness for hypoventilation (10). Recently, the severity of nocturnal respiratory dysfunction has been posited not to directly reflect the extent of sleep impairment in patients with chronic neuromuscular diseases (11). In this study of Weinberg et al. the conclusion was based on findings from polysomnography, however, they did not include symptoms and clinical findings in their analysis.

Daytime sleepiness and headache in patients with respiratory insufficiency is sometimes believed to be a consequence of hypercapnia. This study does not support those assumptions since the CO_2 levels were similar in the patients with and without daytime sleepiness and headache, and this is a novel finding. Extreme hypercapnia may be compatible with being awake (7) and it is a general clinical experience that in mild to moderate hypercapnia, it is the duration of the CO_2 retention rather than the absolute level of arterial PCO_2 that determines the impact on the alertness. However, these patients, at least periodically during sleep, are more hypercapnic than during the daytime (12), and intermittent CO_2 peaks may be associated with disturbed sleep and this may explain headache especially after the patients' awakening. In our study nocturnal hypercapnia may be the cause of the elevated base excess in patients with daytime sleepiness as motive (Table IV). Furthermore, chronic muscle or joint pain may disturb sleep and thereby cause daytime sleepiness.

Table III. *Blood gas data and vital capacity in percent of the predicted value in the different diagnostic groups of the 268 elective patients. Mean values (SD)*

	Post-polio $n = 78$	ALS $n = 60$	DMD $n = 35$	DM $n = 22$	SMA $n = 23$	Other $n = 50$
PaO_2 (kPa)	8.4 (1.4)*	9.5 (1.7)	9.6 (2.3)	8.3 (1.7)*	9.2 (2.5)	8.9 (1.9)
	86%	44%	79%	76%	50%	78%
$PaCO_2$ (kPa)	7.2 (2.5)	6.7 (1.1)	7.4 (2.3)	6.9 (1.3)	7.2 (2.5)	7.3 (1.4)
	86%	46%	79%	76%	50%	80%
BE (mmol/l)	5.6 (2.6)	4.9 (3.8)	5.7 (5.2)	4.0 (3.1)	3.1 (5.6)*	6.6 (2.9)
	71%	38%	60%	62%	33%	73%
VC% of prediction	40 (13)	43 (14)	26 (13)*	35 (10)	44 (31)	38 (15)
	68%	65%	75%	62%	38%	65%

The percentage under each figure indicates the proportion of patients in the diagnostic groups from which we have valid blood gas and vital capacity (VC) data. * indicates statistically significant difference ($p < 0.05$) for the specific group compared with the other groups combined. ALS = amyotrophic lateral sclerosis; DMD = Duchenne muscular dystrophy; DM = dystrophia myotonica; SMA = spinal muscular atrophy.

Table IV. *Blood gas data and vital capacity in percent of the predicted value in the 268 elective patients prior to commencing home mechanical ventilation. Data are shown for the five most common motives.*

	Sleepiness		ABG daytime		Dyspnoea		Cough insufficiency		Headache	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
PaO_2 (kPa)	8.9 (1.9)	9.1 (1.8)	8.3 (1.7)*	9.6 (1.8)	8.4 (1.7)*	9.3 (1.9)	9.6 (2.1)*	8.8 (1.8)	9.3 (1.9)	8.8 (1.9)
$PaCO_2$ (kPa)	7.1 (1.3)	6.8 (1.3)	7.6 (1.3)*	6.4 (1.1)	7.2 (1.5)	6.8 (1.2)	6.5 (1.3)*	7.1 (1.3)	6.9 (1.1)	7.0 (1.4)
BE (mmol/l)	5.7 (3.1)*	4.6 (3.3)	6.8 (2.8)*	3.8 (2.8)	6.0 (3.2)*	4.8 (3.1)	4.1 (3.2)*	5.6 (3.1)	5.3 (3.3)	5.2 (3.2)
VC% of pred	39 (15)	38 (14)	37 (13)	40 (16)	43 (15)*	35 (14)	38 (15)	39 (15)	37 (14)	39 (15)

In the patients where the motives were used for prescribing HMV the data are displayed in the "yes" column; in the patients where the motive was not used, the data are displayed in the "no" column. Mean values (SD).
*Statistical significant ($p < 0.05$) difference between the "yes" and "no" groups.
Sleepiness = daytime sleepiness, ABG daytime = daytime blood gas analysis.

It has been hypothesized that patients with muscular weakness may solve the conflict between sleep and respiration with a compromise of relatively preserved blood gases but impaired sleep quality causing daytime sleepiness (13). A high frequency of sleeping complaints in patients with chronic alveolar hypoventilation is reported by Dellborg et al. (14). Resolution of these symptoms may occur after therapy with home mechanical ventilation (15).

It could also be claimed that daytime sleepiness is a consequence of central sleep-wakefulness disturbances due to the underlying neurological disease, especially in dystrophia myotonica (16). We believe this is a less likely explanation in the other patients, since we found an equally high prevalence of daytime sleepiness in non-neurological HMV-patients (unpublished data from our register).

We unexpectedly found worse blood gases and better VC in patients with the clinical motive dyspnoea. This finding is difficult to interpret since the register does not differentiate between dyspnoea at rest or exercise or orthopnoea.

A European consensus conference in 1993 (17) suggested that any $PaCO_2 > 6$ kPa or abnormal nocturnal oxygen desaturation was a sufficient indication for HMV in Duchenne patients. It is obvious that Swedish clinicians have a more conservative approach for Duchenne patients as well as for other groups. The $PaCO_2$ levels are quite similar, approximately 7 kPa, among the groups. This level of $PaCO_2$ thus seems to be a major threshold when the time for starting HMV is decided. We wish to point out that oxygenation is only moderately impaired, all groups showed PaO_2 levels well above 8.0 kPa. Consequently they did not fulfil the criteria for hypoxic respiratory failure, not even for the most hypoxic groups post-polio and DM. As to the hypoxia *per se*, especially in the DM group, we have no explanation for this, which cannot be explained by age or known cardio-pulmonary disorders. Our finding is in accordance with one previous study (8) where the baseline PaO_2 level in DM patients was even lower (7.1 kPa) than in our study. In the literature, there seems to be no explanation for this phenomenon.

In this patient material 76% started HMV electively, but for the SMA patients this fraction was 96%. The likely reason for this is that the SMA group consists of the youngest patients (median age 12 years), who generally are watched over quite intensely by their family and the health sector. Furthermore, in these children the BE were significantly lower than in the other groups, which might indicate a more sufficient nocturnal ventilation in the SMA group suggesting an earlier recognition of their respiratory problem.

We wish to point out that the ALS group fits well into the general pattern, with respect to acute vs elective launching of HMV, as well as to motives and physiological data. We call attention to this since there is a special focus on patients with ALS regarding not only the rapid aggravation in the disease but the ethical aspects on HMV, especially invasive ventilation, as well.

Apart from the Duchenne group the mean VC was approximately 40% of the predicted value for all groups. This is well in accordance with the general recommendations from a recent consensus group (2) considering HMV in patients with VC < 50% of predicted and more specifically with the conclusion in a large ALS study (18). More severe reductions in VC in patients with DMD before starting HMV has earlier been shown (19, 20), and in the latter study a group of patients with DMD, who were not considered as immediate candidates for HMV, had a VC of 35% of the predicted value. It thus seems as if the patients with DMD can tolerate a much lower VC before they need HMV; a feature that is not always recognized in recommendations concerning HMV in neurological diseases (1, 2). Interestingly, in one study early "prophylactic" ventilation in patients with DMD resulted in worse prognosis, and the authors concluded that NIV should not be started in patients with DMD whose VC is over 20% of the predicted value unless mechanical ventilation becomes imperative (21). Though the Raphael study had some methodological limitations, it is well in line with the VC findings in our study.

We conclude that daytime sleepiness was the most common clinical symptom motivating home mechanical ventilation in hypercapnic patients with NMD. This study does not support, however, that headache and daytime sleepiness are unambiguous consequences of daytime hypercapnia.

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