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Mechanisms underlying effects of nocturnal ventilation on daytime blood gases in neuromuscular diseases

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ABSTRACT: The hypothesis that, in neuromuscular and chest wall diseases, improvement in central respiratory drive explains the effects of night-time ventilation on diurnal gas exchanges was tested.

The effects at 6 months, 1, 2 and 3 yrs of intermittent positive pressure ventilation (IPPV) on arterial blood gas tension, pulmonary function, muscle strength, sleep parameters, respiratory parameters during sleep and ventilatory response to CO_2 were evaluated in 16 consecutive patients with neuromuscular or chest wall disorders.

As compared with baseline, after IPPV daytime arterial oxygen tension (P_{a,O_2}) increased (+2.3 kPa at peak effect) and arterial carbon dioxide tension (P_{a,CO_2}) and total bicarbonate decreased (-1.8 kPa and -5 mmol·L^{-1}, respectively) significantly; vital capacity, total lung capacity, maximal inspiratory and expiratory pressures and alveolar-arterial oxygen gradient did not change; the apnoea–hypopnoea index and the time spent with an arterial oxygen saturation (S_{a,O_2}) value <90% decreased (-24 and -101 min, respectively), sleep efficiency and mean S_{a,O_2} increased (+16% and +5%, respectively); and ventilatory response to CO_2 increased (+4.56 L·min^{-1}·kPa^{-1}) significantly. The reduction in P_{a,CO_2} observed after IPPV correlated solely with the increase in the slope of ventilatory response to the CO_2 curve (r=-0.68, p=0.008).

In neuromuscular or chest wall diseases, improvement of daytime hypoventilation with nocturnal intermittent positive pressure ventilation may represent an adaptation of the central chemoreceptors to the reduction of profound hypercapnia during sleep or reflect change in the quality of sleep.

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Nocturnal intermittent positive pressure ventilation (IPPV) results in improved chronic hypoventilation during daytime spontaneous ventilation in patients with neuromuscular or chest-wall diseases [1–6] and chronic obstructive pulmonary disease (COPD) [7]. In COPD, this improvement has usually been attributed to improved respiratory muscle strength [8–11] (see however, ELLIOTT *et al.* [12]), rather than to an increase in ventilatory response to CO_2 [12]. Because numerous studies [1, 6, 13] provided evidence that in neuromuscular diseases nocturnal IPPV did not affect respiratory muscle strength, it appears that mechanisms for the improvement of diurnal arterial blood gases with nocturnal IPPV are different in these patients than in COPD patients. Therefore, an improvement in lung mechanics with IPPV in neuromuscular or chest wall diseases could account for an improvement in arterial blood gases. However, although slight increases in lung volumes have been reported [1, 14], it seems more likely that night-time IPPV has no significant effect on lung compliance [6, 15]. The last possible mechanism may be an improvement in central respiratory drive. The explanation could be a reduction of an exposure of the central chemoreceptors to profound hypercapnia during sleep and a possible relief of sleep deprivation with nocturnal IPPV, which both would increase the carbon dioxide sensitivity.

Therefore, to understand the mechanisms by which hypercapnia is improved by IPPV in neuromuscular or chest wall disorders, the effect of long-term night-time IPPV was evaluated on arterial blood gas tension, pulmonary function, muscle strength, sleep parameters, respiratory parameters during sleep and ventilatory response to CO_2 in patients with neuromuscular or chest wall disorders.

Methods

Study population

Adult patients were eligible, after verbal informed consent was obtained, if they had neuromuscular and/or chest wall-related stable chronic alveolar hypoventilation and required nocturnal IPPV through tracheostomy or nasal mask. Exclusion criteria included no ventilator-free time, rapidly progressive disease (*i.e.* Duchenne muscular dystrophy or amyotrophic lateral sclerosis), and chronic obstructive lung disease.

Pulmonary function tests

Patients were always studied in the morning, in the sitting position and breathing room air. Pulmonary function

tests were obtained after a 2-week period of stability. Forced spirometry (PK Morgan; Gillingham, Kent, UK) was measured according to the American Thoracic Society recommendations [16], lung volumes by the helium dilution technique (PK Morgan), and maximal inspiratory (MIP) and expiratory (MEP) pressures following the method of BLACK and HYATT [17]. Blood gases were obtained from an arterial sample while the patient was at rest in the sitting position and breathing room air (ABL 330; Radiometer; Copenhagen, Denmark). The alveolar–arterial pressure difference for oxygen ($P_{A\text{-}a,O_2}$) was calculated according to the standard formula, assuming a respiratory quotient value of 0.8.

Ventilatory responses to carbon dioxide

Patients were always studied in the morning and had been in the fasting state for at least 12 h. The ventilatory response to hypercapnia was determined by a modified method described by ADLER [18] based on the original concept of Read [19]. The initial breathing gas mixture was 5% CO_2 in oxygen. Subjects remained in the sitting position and breathed room air through the mouthpiece for almost 5 min to achieve a steady state for end tidal carbon dioxide tension (P_{ET,CO_2}). Thereafter patients began rebreathing for 4 min. The CO_2 fractions (F_{CO_2}) in respiratory air (Infrared analyser; Gould, Ballainvilliers, France) were measured in the breathing tube, close to the lips. The variables determined breath-by-breath during the rebreathing period were total respiratory duration (t_{tot}), tidal volume (V_T), and CO_2 fraction (F_{ET,CO_2}) as the end-tidal value. From these values, the following were calculated breath-by-breath: respiratory frequency, ($f_R=1/t_{tot}$), total minute ventilation ($V'_E=f_R \times V_T$). Records were analysed by plotting V'_E against P_{ET,CO_2}. The resulting plots were linear and therefore were analysed by fitting the data to the following equation:

$$V'_E = S(P_{ET,CO_2}-\beta)$$

where S is the slope of V'_E *versus* P_{ET,CO_2} and β the intercept on the P_{ET,CO_2} axis when $V'_E=0$. In each patient the mean slope of V'_E *versus* P_{ET,CO_2} and the mean V'_E corresponding to a P_{ET,CO_2} at 8 kPa, from three consecutive CO_2 response curves (at 30-min intervals) were obtained.

Sleep studies

The polysomnographic recording included electroencephalography (EEG) (C4-A1 and C3-A2 derivations), electrooculography, chin electromyography, electrocardiography (ECG), oronasal flow by thermistors, thoracic and abdominal movements by noncalibrated inductive plethysmography (Respitrace; Ardsley, NY, USA), and arterial oxygen saturation (S_{a,O_2}) by finger pulse-oximetry (Biox Ohmeda 3700; Columbia, MD, USA). Sleep and sleep stages were scored according to the criteria of RECHTSCHAFFEN and KALES [20]. Apnoea was defined by the absence of airflow both at the nose and mouth for at least 10 s. Hypopnoea was defined by the reduction in airflow (for at least 10 s), of at least 50% of baseline, associated with a decrease in S_{a,O_2} of >4% of the preceding baseline [21]. Apnoea were considered obstructive when thoracic or abdominal movements were present, and central when these movements were absent. From raw data, the respiratory disturbance index (RDI) defined as the ratio of number of apnoeas plus hypopnoea/total sleep time (TST) in hours, and the sleep efficiency (SE) defined as the ratio TST×100/(total sleep period) were calculated.

Intermittent positive pressure ventilation implementation

All patients were ventilated using a volume-cycled portable ventilator (Monnal D, CFPO, Meudon la Foret, France or Eole 2A, SAIME Electronique, Savigny le Temple, France). Ten patients were treated by nasal IPPV with a home-made or manufactured (Respironics, Murrysville, PA, USA or ResMed Ventilator Mask System, Abington, UK) nasal masks, in two and eight cases, respectively. The remaining patients had to be tracheostomized for severe swallowing dysfunction (one case) or nasal mask-related complications (*i.e.* nasal bridge ulcerations in three cases). In all cases, IPPV was initiated at the hospital during the daytime. All patients were ventilated in the assist/control mode with a respiratory rate adjusted to the patient's spontaneous breathing frequency and an initial V_T adjusted at 10 $mL \cdot kg^{-1}$. Exhaled V_T measurements allowed adaptation of V_T to compensate for leaks in patients with nasal IPPV. None of the patients received oxygen therapy. Patients were discharged from the hospital when arterial carbon dioxide tension (P_{a,CO_2}) (during IPPV) was <6 kPa and adequate oxygenation during night-time was confirmed by oximetry monitoring.

Patient follow-up

All patients were followed-up at the outpatient clinic. The office follow-up included twice yearly reviewing of symptoms and physical signs, and seeking evidence of recurrent symptoms of hypoventilation. Pulmonary function tests, arterial blood gas, ventilatory response to CO_2 tests were obtained at 6 months, 1, 2 and 3 yrs and sleep studies at 1 and 3 yrs after IPPV

Statistical analysis

Results are expressed as mean±SD. For quantitative variables, baseline values were compared with follow-up measurements using analysis of variance (ANOVA) for repeated measures, completed by Bonferroni tests when needed. The relationship between the maximum variation of diurnal P_{a,CO_2} and the maximum variation of the slope of the rebreathing test was assessed by linear regression analysis.

Results

Patient characteristics

Sixteen consecutive patients meeting the criteria for eligibility in the study were followed-up. One myasthenic patient was excluded because of a rapid deterioration of respiratory function and another patient with idiopathic scoliosis was lost during follow-up. The demographic and anthropometric characteristics, diagnosis and home ventilation techniques and duration are shown for the 14 remaining patients in table 1. Six patients had stable idiopathic or postpolio (one case) scoliosis. Seven patients presented with myopathy, *i.e.* myotonic dystrophy (two), maltase acid deficiency (two), Becker muscular dystrophy (one) and unknown myopathy (two). Finally, one patient

Table 1. – Demographic data of 14 patients with neuromuscular or chest wall diseases

Pt No.	Diagnosis	Sex	Age yr	Weight kg	Height cm	Ventilation techniques
1	Myo.	M	59	80	180	Nasal mask
2	Myo.	M	44	90	165	Nasal mask
3	Myo.	M	56	63	170	Tracheostomy
4	Myas.	F	50	62	150	Nasal mask
5	Scol.	M	65	50	150	Tracheostomy
6	Myo.	M	25	65	167	Tracheostomy
7	Scol.	F	61	55	142	Nasal mask
8	Scol.	F	47	46	126	Nasal mask
9	Myo.	M	57	85	169	Nasal mask
10	Myo.	F	54	59	168	Nasal mask
11	Scol.	M	40	43	165	Nasal mask
12	Scol.	M	61	60	165	Nasal mask
13	Scol.	M	49	98	180	Tracheostomy
14	Myo.	M	48	77	180	Nasal mask

Pt: patient; Myo.: myopathy; Myas.: myasthenia; Scol.: scoliosis; M: male; F: female.

Table 3. – Polysomnographic results at baseline and while receiving nocturnal intermittent positive pressure ventilation

	Baseline	1 yr	3 yrs	F	p-value
TST min	294±95	340±90	336±56	1.30	0.28
RDI	27±19	3±7**	2±6	17.9	0.001
S1+S2 %	69±6	62±17	62±13	2.39	0.13
S3+S4 %	11±6	20±7*	20±10	5.36	0.01
REM %	15±6	17±6	20±5	2.75	0.09
SE %	74±10	87±7**	90±8	29.1	0.001
Sa,O_2 <90% min	102±94	13±26**	1±2*	4.78	0.002
Mean Sa,O_2 %	89±3	93±3**	94±2	9.52	0.002
Minimal Sa,O_2 %	68±14	80±14**	88±4	5.96	0.01

TST: total sleep time; RDI: respiratory disturbance index; S1+S2 and S3+S4: percentage of TST spent in sleep stage 1+2 and 3+4, respectively; REM: percentage of TST spent while in rapid eye movement (REM) phase; Sa,O_2 <90%: percentage of TST spent with an arterial oxygen saturation (Sa,O_2) below 90%; SE: sleep efficiency. *: p<0.05; **: p<0.01 (Bonferroni tests)

had diaphragmatic paralysis as a sequaele of myasthenia gravis. All patients had moderate to severe ventilatory restriction, with vital capacity ranging 11–68% predicted (38±17%, mean±SD) and total lung capacity ranging 22–69% pred (46±16, mean±SD) (table 2). They had chronic alveolar hypoventilation with diurnal Pa,CO_2 ranging 6.5–9.9 kPa (7.3±0.9, mean±SD), arterial oxygen tension (Pa,O_2) ranging 6.5–9.7 kPa (8.1±1.1, mean±SD), and [HCO_3^-] ranging 28–36 mmol·L^{-1} (32±2, mean±SD). Finally, patients had reduced MIP from 26 to 64% pred (45±21%, mean±SD), MEP from 17 to 91% pred (51±34%, mean±SD) and static transdiaphragmatic pressures from 0 to 5.3 kPa (1.7±1.9, n=12, mean±SD).

All patients had decreased ventilatory response to CO_2 with a slope ranging 0 (n=2) to 3.4 L·min^{-1}·kPa^{-1} (1.33±0.94, mean±SD) (table 2).

Regarding baseline polysomnographic data (table 3), all patients had major respiratory events during sleep with an RDI ranging 15–85 (27±19, mean±SD), prolonged time of oxygen desaturation below 90% (42–345 min 102±94, mean±SD), decreased mean Sa,O_2 (86–92%, 89±3%, mean ±SD) and minimal Sa,O_2 (49–80%, 67±12%, mean±SD). Apnoeas were of both types and predominantly of the central type (76±10%, mean±SD). The high percentage of TST spent in sleep stages 1 and 2 (59–79%, 68±14%, mean±SD) with a shortening of the duration of sleep stages

Table 2. – Respiratory function before and after nocturnal intermittent positive pressure ventilation in 14 patients with neuromuscular or chest wall diseases

	Baseline	6 months	1 yr	2 yrs	3 yrs	*F*	p-value
VC mL	1457±719	1460±650	1471±781	1457±767	1407±8.05	0.41	0.80
VC % pred	38±17	47±24	43±20	41±20	43±23		
RV mL	1227±437	1165±387	1180±290	1170±236	1154±277	0.11	0.98
RV % pred	65±19	65±22	65±16	62±11	61±19		
FEV1 mL	1177±594	1131±460	1176±571	1080±568	1092±564	0.71	0.59
FEV1 % pred	38±19	39±16	42±19	39±20	39±20		
TLC mL	2646±1081	2768±1151	2880±1599	2785±1161	2878±1202	1.39	0.26
TLC % pred	46±16	46±17	52±21	50±17	50±18		
FRC mL	1643±750	1498±612	1726±901	1567±508	1634±564	0.64	0.64
FRC % pred	53±20	51±19	56±25	51±13	54±14		
FEV1/FVC %	102±11	100±8	101±8	103±7	91±17	0.71	0.59
MIP kPa	3.6±1.1	3.5±1.2	3.8±1.2	4.1±1.5	4.1±1.6	0.83	0.52
MIP % pred	45±21	48±24	49±21	47±23	50±22		
MEP kPa	5.9±3.0	6.0±3.3	6.1±3.7	6.3±3.4	6.4±3.6	0.34	0.85
MEP % pred	51±34	59±35	56±33	53±35	52±23		
$\Delta V'E/\Delta P_{ET,CO_2}$ L·min·kPa^{-1}	1.33±0.94	2.69±1.30*	2.45±1.18	4.22±1.77	5.89±5.08	6.10	0.006
$V'E$-60 L	9.6±3.1	11.4±2.8*	14.1±3.7	16.4±1.1*	15.7±2.9	4.66	0.017
Pa,O_2 kPa	8.1±1.1	9.4±1.3**	10.2±1.4*	10.4±0.9	9.8±1.4	12.9	0.001
Pa,CO_2 kPa	7.3±0.9	6.1±0.4**	5.7±0.6**	5.5±0.7	5.5±0.1	14.9	0.001
$P_{A\text{-}a,O_2}$ kPa	2.4±1.2	2.6±1.4	2.3±1.7	2.4±1.0	2.9±2.5	0.40	0.87
[HCO_3^-] mmol·L^{-1}	32±2	28±1**	27±2	27±2	27±3	10.5	0.001

Values are presented as mean±SD. VC: vital capacity; RV: residual volume; FEV1: forced expiratory volume in one second; FRC: functional residual capacity; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; Pa,O_2: arterial oxygen tension; Pa,CO_2: arterial carbon dioxide tension; FEV1/FVC: ratio between FEV1 and the forced vital capacity (FVC); TLC: total lung capacity; $\Delta V'E/\Delta P_{ET,CO_2}$: is the slope of minute ventilation ($V'E$) *versus* end tidal carbon dioxide tension (P_{ET,CO_2}); $V'E$-60: $V'E$ value at a P_{ET,CO_2}=8 kPa (60 mmHg). *: p<0.05; and **: p<0.01 (Bonferroni tests).

3 and 4 (6–16%, 11±6%, mean±SD) and of rapid eye movement (REM) sleep (10–27%, 15±6%, mean±SD), demonstrated that sleep architecture was disrupted in this population [22]. Similarly sleep efficiency was reduced and ranged 50–83% (74±10%, mean±SD).

Effects of nocturnal IPPV

Patients reported a mean use of IPPV of 8±3 h (ranging 5–12 h) per night. No major complications related to nasal mask or tracheostomy were observed.

As shown in table 2 (see also fig. 1), after nocturnal IPPV, as compared with baseline, pulmonary volumes, respiratory muscle function and $P_{A\text{-}a,O_2}$ remained relatively unchanged. By contrast, P_{a,CO_2} and $[HCO_3^-]$ significantly decreased (at peak effect, -23% and -18%, respectively) and P_{a,O_2} increased (at peak effect, +28%). Similarly, as compared with baseline, after nocturnal IPPV, the ventilatory response to CO_2 was improved, $\Delta V'_E/\Delta P_{ET,CO_2}$ increasing by +340% (at peak effect).

As shown in table 3, as compared with baseline, after nocturnal IPPV, respiratory events during sleep were significantly reduced with, at peak effect, a decrease of -92% for the RDI, and -94% for the amount of time spent with an S_{a,O_2} below 90% and an increase of +6% for mean S_{a,O_2}. Simultaneously, nocturnal IPPV was associated with an improvement of sleep architecture as witnessed by the reduction of stages 1 and 2 duration (at peak effect, -10%) and by the increase in the time spent in stages 3 and 4 (at peak effect, +84%) and in sleep efficiency (at peak effect, +21%).

The reduction of diurnal P_{a,CO_2} correlated with the increase of $\Delta V'_E/\Delta P_{ET,CO_2}$ (r=-0.68, p=0.008) (fig. 2). By contrast, the reduction of diurnal P_{a,CO_2} did not correlate with the changes in MIP (fig. 3).

Discussion

This study was aimed at evaluating the potential mechanisms for diurnal P_{a,CO_2} improvement in neuromuscular patients receiving long-term nocturnal IPPV. As previously described, IPPV was easy to implement and was associated with a substantial improvement in alveolar hypoventilation during both night and daytime [1–6]. Furthermore, this study shows, in keeping with previous reports [6, 23] that in stable patients nocturnal IPPV effects may be prolonged after a very long period of ventilation.

The respiratory pump mechanics remained stable in each patient throughout the study follow-up. This observation confirms that the patients enrolled in this study have very slowly progressive disease. Thus, it seems very unlikely that the improvement in daytime arterial blood gases were related to improved lung mechanics. This result is in line with previous studies [2, 6, 24].

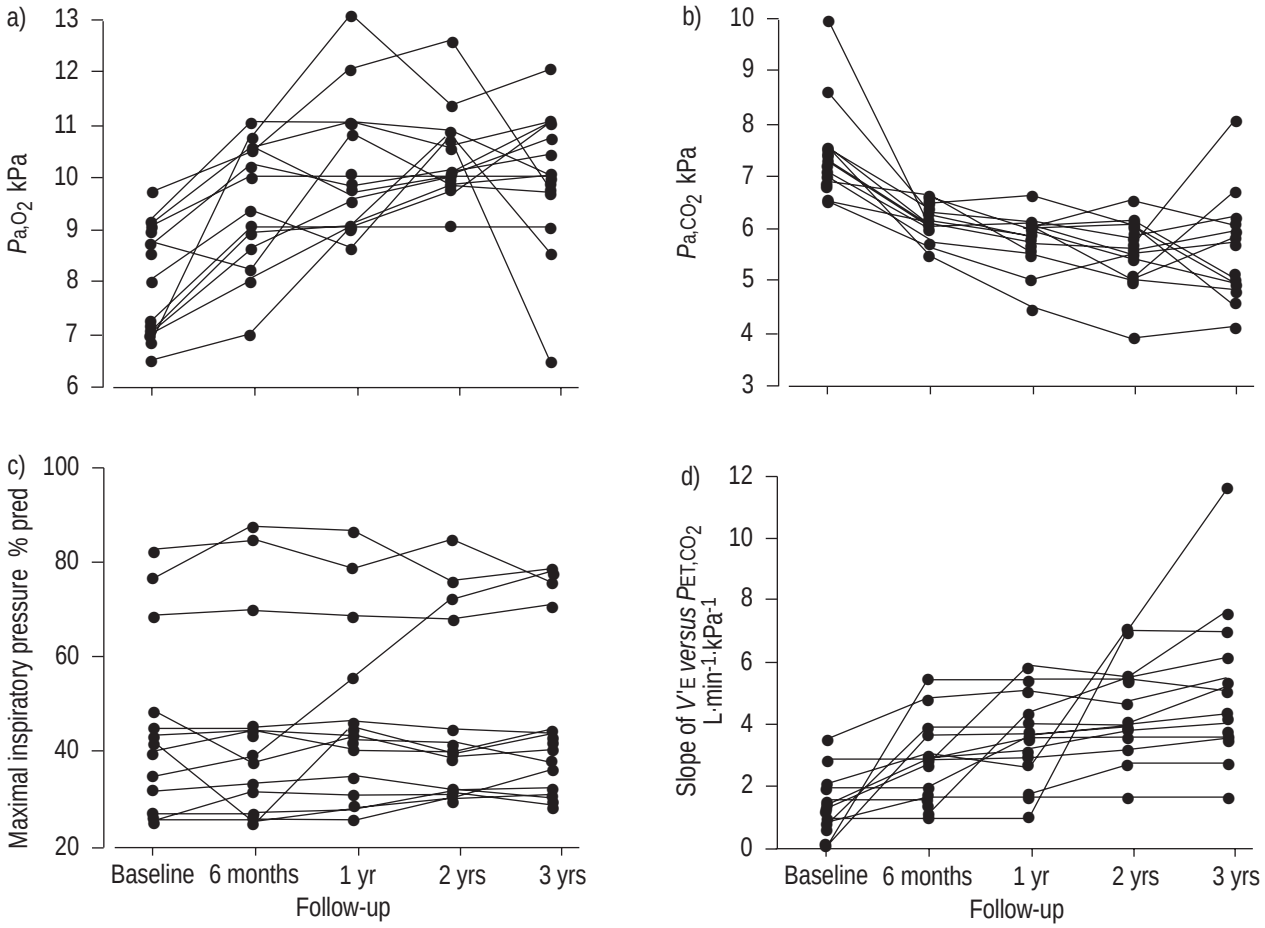

Fig. 1. – The variations of arterial oxygen tension (P_{a,O_2}; a), arterial carbon dioxide tension (P_{a,CO_2}; b), maximal inspiratory pressure (c) and slope of minute ventilation (V'_E) *versus* end tidal carbon dioxide tension (P_{ET,CO_2}; d) are given for each of the 14 patients.

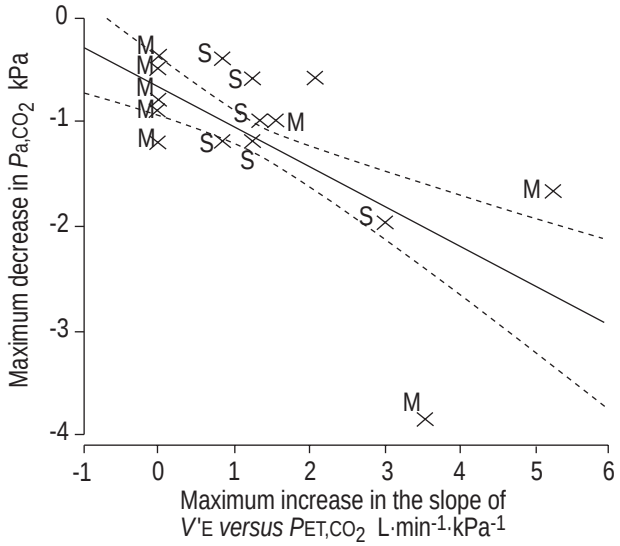

Fig. 2. – The maximum decrease in arterial carbon dioxide tension (P_{a,CO_2}) was significantly related to the maximum increase of the slope of minute ventilation (V'_E) *versus* end tidal carbon dioxide tension (P_{ET,CO_2}) (n=14, r=0.68 and p=0.008). The dependence between the two variables appeared similar in patients with myopathy (M; n=8) and in those with scoliosis (S; n=6). The regression line (——) with the 95% confidence interval (- - -) are given. (For further explanation see text.)

In chronic neuromuscular disorders, maximal static inspiratory and expiratory mouth pressure measurement is conventionally used to assess respiratory muscle strength [25, 26]. However, these tests require patient's volition and may be less accurate than transdiaphragmatic pressure measurement during electric or magnetic phrenic nerve stimulation. No significant change in maximal static mouth pressures were noted throughout the study period, as previously observed in neuromuscular diseases [6, 19] and contrary to COPD patients [8–11]. Although we did not use nonvolitional tests, it seems very unlikely that the improvement in daytime arterial blood gases is related to an improved respiratory muscle strength.

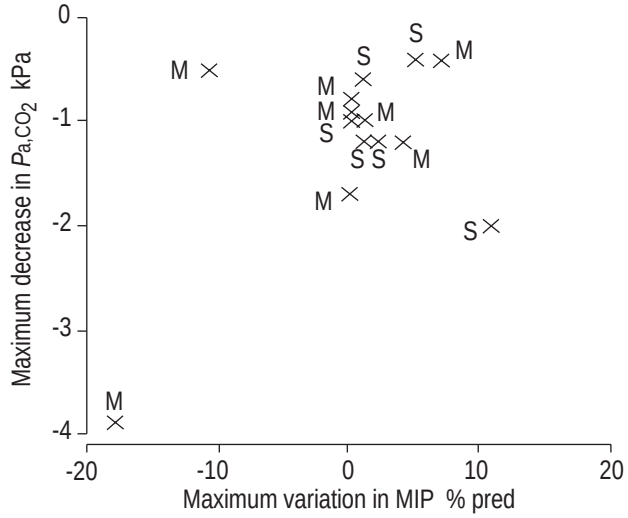

Fig. 3. – The maximum decrease in arterial carbon dioxide tension (P_{a,CO_2}) was not related to the maximum variation of maximal inspiratory pressure (MIP) in the whole population (n=14), in patients with myopathy (M; n=8) and in those with scoliosis (S; n=6). (For further explanation see text.)

In this study, the patients had a substantial increase in mismatching of ventilation to perfusion in the lung, as depicted by the high $P_{A\text{-}a,O_2}$ values. These values are very close to those previously reported in neuromuscular patients [6, 15]. Although a slight decrease in the $P_{A\text{-}a,O_2}$ was observed after IPPV, the difference with baseline values failed to reach a level of statistical significance. Thus, as previously suggested [6], in chronic neuromuscular patients receiving nocturnal IPPV, the improvements in daytime arterial blood gases were probably not related to a reduction in ventilation–perfusion mismatching.

Numerous studies demonstrated that the ventilatory response to CO_2 is blunted in neuromuscular and thoracic cage disorders [15, 27–29]. Our data corroborate the findings from these studies and demonstrate that night-time IPPV improves the ventilatory response to CO_2. Moreover, the changes in slope of ventilatory response to CO_2 were found to be correlated with the changes in daytime P_{a,CO_2}. In theory, the improvement in ventilatory response to CO_2 may be related to improved respiratory muscle strength, improved lung compliance or improved respiratory drive. In practice, in this study, no change in respiratory muscle strength or in pulmonary compliance could be observed, thus it seems likely that improved respiratory drive was accounted for by the observed increase in ventilatory response to CO_2. Although the inspiratory occlusion pressure after 0.1 s was not recorded in this study, it is suggested that the improvement of daytime hypoventilation was due to the improvement in central respiratory drive.

The change in ventilatory response to CO_2 rebreathing has also been observed in patients with obstructive sleep apnoea treated with nasal continuous positive airway pressure or after tracheostomy [30–32]. It is generally admitted that this improvement represents adaptation of the central chemoreceptors to the reduction of hypercapnia overnight or alternatively reflects changes in the quality of sleep, since sleep deprivation results in a significant deterioration of hypercapnic ventilatory responses [33, 34]. Interestingly, important sleep-disordered breathing and sleep disruption were observed in this population, which met the criteria of severe obstructive and/or central sleep apnoea [35] and which were reversed by IPPV. Therefore, it was assumed that, as in severe sleep apnoea syndrome, sleep-disordered breathing observed in this population is a potentially critical component in the decrease of the central respiratory drive and therefore in the pathogenesis of daytime arterial hypercapnia. In addition, this hypothesis explained why the pathogenesis of daytime arterial hypercapnia is different in our population and in COPD patients. It has been demonstrated that sleep abnormalities with several arousals and long periods of wakefulness are generally present in patients with severe COPD [36]. However, these phenomenon and therefore the beneficial effects of positive pressure ventilation are generally less important [37] than were observed in this population.

In conclusion, prolonged nocturnal intermittent positive pressure ventilation results in improved chronic hypoventilation during daytime spontaneous ventilation in patients with neuromuscular or chest wall diseases. These data do not support the hypothesis that this improvement was due to a relief of muscle fatigue or to an improvement in lung mechanics. However, because the increase in daytime arterial carbon dioxide tension is correlated with an increase of ventilatory response to carbon dioxide rebreathing and

is associated with an improvement of severe sleep-disordered breathing, this supports the fact that hypercapnia in neuromuscular or chest-wall diseases is due to a decrease in central respiratory drive, and that improvement of daytime hypoventilation with nocturnal intermittent positive pressure ventilation may represent adaptation of the central chemoreceptors to the reduction of profound hypercapnia during sleep and/or reflect change in quality of sleep.

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