Eur Respir J
1991, 4, 1044–1052

Domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD: mechanisms underlying changes in arterial blood gas tensions

M.W. Elliott*, D.A. Mulvey**, J. Moxham***, M. Green**, M.A. Branthwaite*

Domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD: mechanisms underlying changes in arterial blood gas tensions. M.W. Elliott, D.A. Mulvey, J. Moxham, M. Green, M.A. Branthwaite.

ABSTRACT: The improvement in arterial blood gas tensions following assisted ventilation in chronic obstructive pulmonary disease (COPD) has usually been attributed to the relief of incipient or established respiratory muscle fatigue. The contribution of changes in the load placed upon and the drive to the respiratory muscle pump have not been evaluated. We have investigated the contribution of changes in respiratory muscle strength, the ventilatory response to CO_2 and ventilatory function to changes in arterial blood gas tensions in eight patients with severe COPD completing six months domiciliary nasal intermittent positive pressure ventilation.

Six patients showed a reduction and two an increase in arterial carbon dioxide tension ($Paco_2$), median (range) for eight patients, -0.9 kPa (-1.5 to +0.4) ($p<0.05$) and seven showed an improvement in arterial oxygen tension (Pao_2), +0.7 kPa (-0.4 to +1.7) ($p<0.05$) during daytime spontaneous breathing. The reduction in $Paco_2$ was not related to increased inspiratory muscle strength but was correlated with a decrease in gas trapping (Spearman rank correlation coefficient (r_s) 0.85, $p<0.05$) and in the residual volume (r_s 0.78, $p<0.05$), suggesting reduced small airway obstruction and, therefore, a reduction in load. The change in $Paco_2$ also correlated with the increase in ventilation at an end-tidal CO_2 of 8 kPa during rebreathing (r_s -0.76, $p<0.05$) suggesting improved chemosensitivity to CO_2.

Our data do not support the hypothesis that improvements were due to the relief of muscle fatigue. We suggest that the contribution of changes in load and central drive warrant further investigation.

Eur Respir J., 1991, 4, 1044–1052.

*Dept of Thoracic Medicine, The Royal Brompton and National Heart Hospital, London, UK.

**National Heart and Lung Institute, Dovehouse Street, London, UK.

***Dept of Thoracic Medicine, King's College Hospital and Medical School, London, UK.

Correspondence: M. Elliott, The Royal Brompton and National Heart Hospital, Fulham Road, London SW3 6HP, UK.

Keywords: Domiciliary; obstructive lung diseases; positive pressure respiration.

Received: November 22, 1990; accepted after revision June 13, 1991.

M.W.E. was supported by the Brompton Hospital Clinical Research Committee and the British Lung Foundation.

Intermittent mechanical ventilation, using negative or positive pressure devices, results in improved arterial blood gas tensions during spontaneous ventilation in patients with respiratory failure due to chest wall deformity and neuromuscular disease [1–5]. Similar results have been reported in hospital for patients with chronic obstructive pulmonary disease (COPD) but studies have involved relatively short periods of ventilation, during the day, using negative pressure devices [6–11]. The improvement in arterial blood gas tensions in COPD has usually been attributed to improved respiratory muscle strength secondary to the relief of chronic fatigue [6–10]. However, other factors including changes in respiratory drive and the load placed upon the ventilatory apparatus may also be important.

We have, therefore, evaluated the effect of six months domiciliary nocturnal nasal intermittent positive pressure ventilation (NIPPV) in patients with COPD upon respiratory drive, load and respiratory muscle strength and the possible mechanisms of improved arterial blood gas tensions.

Patients and protocol

The study was approved by the Ethical Committee of the Brompton Hospital and all patients gave informed consent.

Six male and two female patients (table 1) with severe stable COPD, median (range), age 54 yrs (49–64 yrs), forced expiratory volume in one second (FEV_1) 535 ml (290–880 ml), fraction of forced vital capacity expired in one second (FEV_1/FVC) 30% (19–38%) completed six months nightly NIPPV at home. All were hypoxic, arterial oxygen tension (Pao_2) 6.5 kPa (5.6–7.0 kPa) and hypercapnic, arterial carbon dioxide tension ($Paco_2$) 8.0

kPa (6.3–9.9 kPa) at the start of the study. Seven patients were moderately overweight (body mass index >25 kg·m^{-2}), however, none had evidence of obstructive sleep apnoea during full polysomnography. Six of the eight patients were recruited at least six weeks after an exacerbation of their COPD and clinical stability was confirmed by measurement of arterial blood gas tensions, spirometry and weight at the beginning and end of a four week run-in period. Two patients (nos 6 and 8) had a long history of clinical decline despite maximum conventional therapy, including oxygen, and had been referred to this hospital with life-threatening respiratory failure. They were resuscitated using NIPPV in hospital and discharged with markedly improved blood gas tensions. Domiciliary NIPPV was subsequently started because of symptomatic recurrence of respiratory failure at home. When entered into the study, blood gas tensions were better than at their first presentation in respiratory failure.

Table 1. – Patient clinical details

Patient yrs	Age Sex M/F	Height cm	Weight kg	Body mass index kg·m^{-2}
1	55 M	169	83	29
2	58 M	180	89	27
3	50 M	164	70	26
4	53 M	163	70	26
5	64 M	166	55	20
6	51 M	171	79	27
7	62 F	160	63	25
8	49 F	148	72	32
Mean	55	165	72.6	26.5
±SD	±5.6	±9.2	±10.9	±3.4

Patients were acclimatized to NIPPV in hospital using the Bromptonpac ventilator (Pneupac Ltd, Luton, UK), a volume cycled flow generator designed for home use, and commercially available silicone nasal masks (Respironics Inc, Monroeville, PA, USA). All patients were ventilated with air. Ventilator settings were adjusted according to patient comfort and to maximize gas exchange, and arterial blood gas tensions were checked after 30 min use.

The aim of treatment in this study was the control of nocturnal hypoventilation. Effective treatment was confirmed firstly by demonstrating improved arterial blood gas tensions, with the patient awake during NIPPV compared with spontaneous breathing, at the first hospital visit. Pao_2 improved, median (range) +1.65 kPa (+0.1 to +2.5 kPa) and $Paco_2$ fell, -0.8 kPa (0 to -4.3 kPa) in all patients. Secondly, effective overnight ventilation was confirmed by demonstrating improved oxygen saturation +11% (+2% to +23%) and a reduction in transcutaneous CO_2 -2.7 kPa (-1.3 to -5.1) during NIPPV overnight in hospital, after four weeks home use.

Measurements of arterial blood gas tensions, the pattern of breathing during resting ventilation, respiratory muscle strength, load (in terms of ventilatory function) and drive (as assessed by ventilation and occlusion pressure ($P_{0.1}$) during CO_2 rebreathing) were made before the start of treatment and after six months home use. One patient (no. 1) was unable to co-operate with all of the tests.

Methods

Arterial blood gas tensions and ventilatory function

Arterial blood gas tensions were measured on a radial arterial sample drawn during the mid-afternoon, after a 15 min rest, with the patient seated breathing air. Samples were processed by a Corning 178 blood gas analyser (Ciba-Corning Ltd, Halstead, Essex, UK).

Ventilatory function was measured in the hospital clinical laboratory using a constant volume whole body plethysmograph (Pulmostar SMB, Dr Fenyves and Gut, Basle, Switzerland), a Spiroflow Spirometer (P.K. Morgan Ltd, Rainham, Kent, UK) and gas transfer apparatus (Model B, P.K. Morgan Ltd, Rainham, Kent, UK). Alveolar volume (V_A) was measured using a single breath technique involving a 10 s breath hold [12] and an approximation of gas trapping was made by subtracting V_A from total lung capacity (TLC), assuming the same volume of extra-pulmonary gas at the two visits [13].

Tests of respiratory muscle strength

All recordings were made with the patient seated. Oesophageal (Poes) and gastric (Pgas) pressures, reflecting pleural and abdominal pressure, respectively, were measured using balloon-tipped catheters 100 cm in length (P.K. Morgan, Rainham, Kent, UK) positioned in the standard manner [14]. Transdiaphragmatic pressure (Pdi) was obtained by electronic subtraction (Pdi = Pgas-Poes) using Pdi at resting end-expiration as the zero reference level [15]. The catheters were connected to Validyne MP45-1 differential pressure transducers (range ±250 cmH_2O; Validyne Corp., Northridge, CA, USA), calibrated before each study and referenced to atmospheric pressure. Maximal inspiratory (P_{Imax}) and expiratory (P_{Emax}) mouth pressures were measured using a flanged mouthpiece [16]. P_{Imax} was measured at residual volume and P_{Emax} at total lung capacity. After practice manoeuvres the best value from five efforts was taken. Poes, Pgas and Pdi were also measured during a maximal natural sniff through the unoccluded nose and, after training, the best value from ten taken. The best of three measurements of Pdi during a P_{Imax} manoeuvre from residual volume (RV) was also recorded. During all voluntary manoeuvres patients received vigorous verbal encouragement and uncalibrated visual feedback of their respiratory efforts on an oscilloscope. Tidal volume was measured during quiet breathing using an Ohio 840 dry spirometer (Ohio Medical Products, Wisconsin, USA) and dynamic compliance computed from simultaneous measurements of Poes at zero flow. All signals were recorded on paper by a Mingograf 800 inkjet recorder (Siemens-Elema AB, Stockholm, Sweden).

Pattern of breathing during spontaneous ventilation and the ventilatory and $P_{0.1}$ response to CO_2 rebreathing

All studies were performed with the patient seated. The patient breathed on a mouthpiece, with a noseclip, through a low resistance one way valve (Hans Rudolph, Kansas City, MO, USA). Flow was measured with a Fleisch No. 4 pneumotachograph head, situated in the inspiratory limb of the circuit to minimize turbulence and connected to a Mercury CS6 electrospirometer (Mercury Electronics, Glasgow, UK). The electrospirometer integrated flow on a breath-by-breath basis and computed tidal volume. The accuracy of this equipment in measuring 3 *l* of air delivered through the valve box by a calibrating syringe was ±3% over a 0.8–8 $l \cdot s^{-1}$ range of peak flows.

The resistance of the circuit at flow rates of 0.5 and 3 $l \cdot s^{-1}$ was 1.1 and 2.7 $cmH_2O \cdot l^{-1} \cdot s$, respectively, for the inspiratory limb and 1.5 and 2.6 $cmH_2O \cdot l^{-1} \cdot s$, respectively, for the expiratory limb.

A fast reacting pneumatically driven shutter situated in the inspiratory limb was used to occlude airflow and mouth pressure was measured with a Validyne MP45-1 differential pressure transducer (range ±250 cmH_2O, Validyne Corp., Northridge, CA, USA). The shutter was closed during expiration and opened again 200–300 ms after the onset of inspiration. Patients were unable to see the operator activate the shutter and listened to a radio programme through headphones. Questioning at the end of the study confirmed that these measures had been successful in preventing anticipation of shutter occlusions.

The ventilatory response to CO_2 was determined using a modification of the rebreathing method of READ [17]. Patients inhaled from a six litre anaesthesia bag, which had been filled with a concentration of CO_2 approximating to the end-tidal CO_2 ($Etco_2$) and an oxygen content of at least 90%. The rebreathing bag remained flaccid so that the pressure within it was atmospheric. Inhaled O_2 concentration and $Etco_2$ were measured with a Hewlett Packard 78356A gas parameter monitor (Hewlett Packard, Waltham, MA, USA).

Flow, tidal volume, CO_2 and mouth pressure were recorded on paper by a Mingograf 800 ink-jet recorder (Siemens-Elema AB, Sweden) at a paper speed of 5 $cm \cdot s^{-1}$.

Quiet breathing. The patient breathed through the circuit with the three-way taps switched to room air. After a period of acclimatization occlusions were made to inspiration every 30 s during a 4 min recording. The onset of inspiration and expiration were determined from the change in flow at the mouth and inspiratory time (Ti) and total breath duration (Ttot) determined. $P_{0.1}$ was measured as the mouth pressure 100 ms after the onset of inspiration [18]. Rate, duty cycle (Ti/Ttot) and minute ventilation (MV) were calculated from the average of the three breaths preceding each occluded breath.

CO_2 rebreathing. After a short rest the patients again breathed through the circuit with the three-way taps open to room air. At the end of an expiration they were switched to the rebreathing circuit, asked to take four large breaths and then to breath "normally". The shutter was closed every 30 s and each rebreath lasted 4 min. Three rebreaths were performed and patients rested for at least 15 min between each. The slopes of the ventilatory and $P_{0.1}$ response to CO_2 rebreathing were computed using least squares regression and the values at an $Etco_2$ of 8 kPa measured.

Statistical analysis

Statistical analysis of all data was performed using the "Minitab" (Minitab Inc, State University, PA, USA) and "Unistat III" (Unistat Ltd, PO Box 383, London, UK). Comparison of the results between the two visits was made using a Wilcoxon signed rank test and correlations using Spearman's rank correlation with the level of significance set at <0.05.

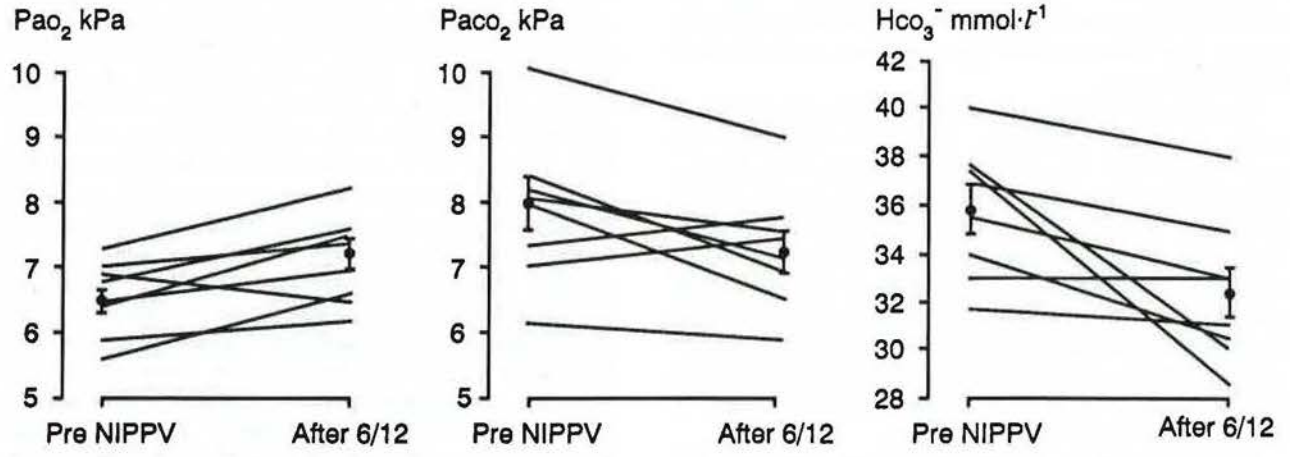

Fig 1. – Arterial blood gas tensions and bicarbonate ion concentration before and after six months nasal intermittent positive pressure ventilation (NIPPV) for each patient. Symbols represent mean±standard errors for all patients. Pao_2 and $Paco_2$: arterial oxygen and carbon dioxide tension, respectively; HCO_3^-: bicarbonate ions.

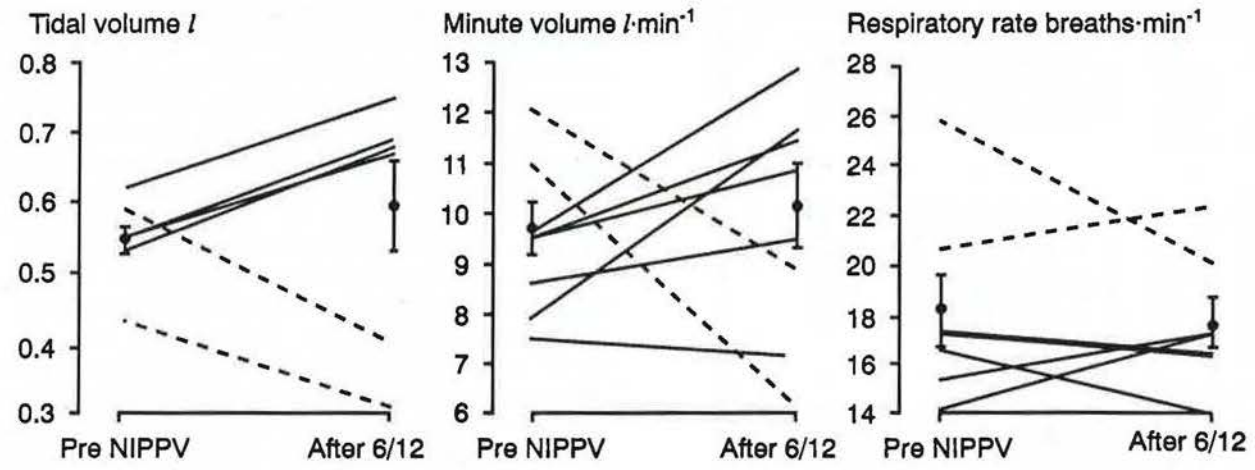

Fig. 2. – Pattern of breathing before and after six months NIPPV. Broken lines represent patients (no. 7 and 8) in whom $Paco_2$ during spontaneous breathing increased. Symbols represent mean±standard errors for all patients. For abbreviations see legend to figure 1.

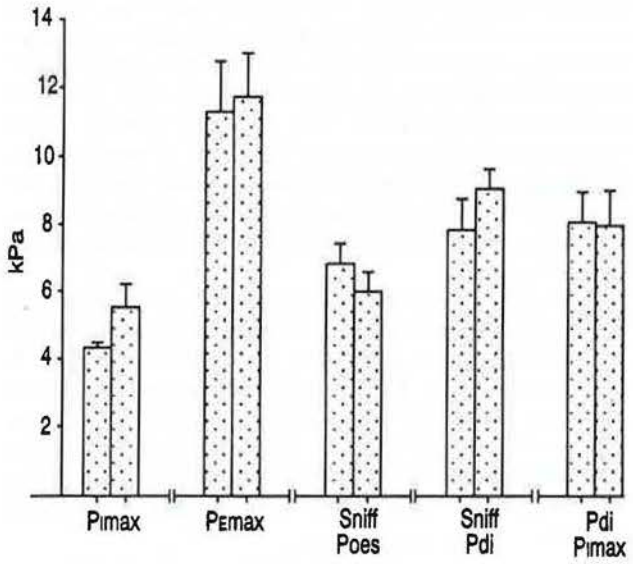

Fig. 3. – Indices of respiratory muscle strength before and after six months nasal intermittent positive pressure ventilation (NIPPV). Results are expressed in kPa as mean±standard error. Pimax: maximal inspiratory pressure; PEmax: maximal expiratory pressure; Poes: oesophageal pressure; Pdi: diaphragmatic pressure.

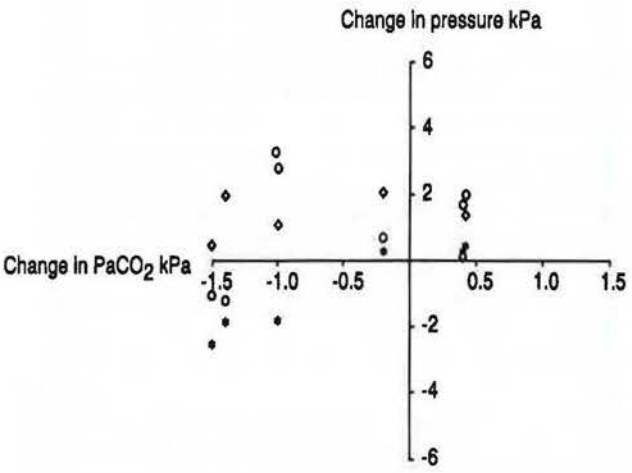

Fig. 4. – The relationship between the change in $Paco_2$ and changes in inspiratory muscle strength following six months NIPPV. Each point represents that measure of muscle strength for one patient plotted against the change in $Paco_2$ for that patient. o: Pimax; * : sniff poes; ◊: sniff Pdi. For abbreviations see legends to figures 1 and 3.

Results

The patients used the ventilator at home for between six and ten hours each night and, after six months, six patients showed a reduction and two an increase in $Paco_2$, median (range) for eight patients, -0.9 kPa (-1.5 to +0.4 kPa), $p<0.05$, and seven an improvement in Pao_2, median (range) for eight patients, +0.7 kPa (-0.4 to +1.7 kPa), $p<0.05$, during the day. Bicarbonate ion concentration fell in seven patients -2.25 mmols·l^{-1} (0 to -8.0 mmols·l^{-1}), $p<0.05$ (fig. 1).

Figure 2 shows the pattern of breathing at the start of the study and the change after six months. Initially all patients had the breathing pattern characteristic of hypercapnic COPD patients [19–23] with normal or slightly elevated minute ventilation, a rapid respiratory rate and breaths of small tidal volume. After NIPPV there were no statistically significant differences in these variables other than an increase in the duty cycle (TI/Ttot) from median 0.39 (0.31–0.40) to 0.41 (0.37–0.42). The patients in whom $Paco_2$ fell showed an increase in MV and VT, whereas those in whom it rose showed a decrease in both of these variables. There was no consistent change in respiratory rate. The two patients (nos 7 and 8) who did not show a reduction in $Paco_2$ had a higher pretreatment minute ventilation and a faster respiratory rate than the other patients.

Table 2. – Load: lung function data at the start of the study and the change after six months nasal intermittent positive pressure ventilation (NIPPV), in brackets

No.	FEV_1 $l \cdot s^{-1}$	FVC ml	TLC ml	RV ml	V_A ml	Kco mmols·min·kPa·l	Trap ml	Cdyn $ml \cdot cmH_2O^{-1}$
2	560 (+150)	2190 (+630)	7300 (+270)	4950 (-380)	4200 (+410)	0.87 (-0.03)	3100 (-140)	* (*)
3	570 (-70)	1770 (-340)	5020 (+260)	3120 (+390)	3060 (+390)	1.18 (-0.28)	1960 (-130)	54 (+10)
4	440 (+200)	1600 (+580)	5660 (0)	3760 (-300)	2990 (+200)	1.44 (-0.08)	2670 (-220)	40 (+2)
5	610 (+40)	2050 (+540)	7270 (-610)	4520 (-280)	5020 (-270)	0.57 (-0.04)	2250 (-340)	36 (+20)
6	510 (+90)	2650 (+140)	7340 (-320)	4640 (-260)	4540 (-50)	1.11 (-0.04)	2800 (-270)	35 (+5)
7	290 (+60)	970 (-30)	4170 (+410)	2970 (+440)	2060 (+250)	1.57 (-0.10)	2110 (+160)	36 (-4)
8	480 (+80)	1360 (+330)	4130 (+50)	2430 (+10)	2890 (-60)	1.27 (-0.30)	1240 (+110)	31 (-2)
Mean	595 (+78)	1897 (+264)	5819 (+9)	3673 (-54)	3537 (+127)	1.14 (-0.12)	2304 (-118)	39 (+5)
±SD	±245 (±85)	±571 (±361)	±1271 (±362)	±850 (±343)	±1062 (±257)	±0.12 (±0.12)	±620 (±188)	±8 (±9)
p	NS	NS	NS	NS	NS	0.02	NS	NS

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; V_A: alveolar volume; Kco: carbon monoxide transfer coefficient; trap: trapped gas (TLC-V_A); Cdyn: dynamic compliance during tidal breathing.

Figure 3 shows indices of respiratory muscle strength before and after six months NIPPV and figure 4 the relationship between these changes and those in $Paco_2$. Pre-NIPPV all patients had a Pimax, sniff Poes and four patients a sniff Pdi and Pdi during a Pimax manoeuvre below the normal range. The only consistent finding after six months NIPPV was an increase in sniff Pdi (median +1.25 kPa, range +0.1 to +2.1), p=0.04, primarily as a consequence of an increase in sniff Pgas (median +2.33 kPa, range -0.15 to +3.9), p=0.059. However, three patients showed a reduction in Pdi during a Pimax manoeuvre (median +0.03 kPa, -3.75 to +3.9), p=1.0. Pimax increased in five patients (median +1.65 kPa, -1.15 to +3.25 kPa), p=0.15, Pemax in four patients (median +0.5 kPa, -4.7 to +4.75), p=0.46, and sniff Poes in three patients (median -0.75 kPa, -2.5 to 0.5), p=0.4. There was no relationship between the improvement in $Paco_2$ and increased inspiratory muscle strength (fig. 4).

Table 2 shows baseline ventilatory function and the change after six months. All patients had severe airflow limitation with hyperinflation and gas trapping. Ventilatory function tended to improve with NIPPV, with six patients showing an improvement in FEV_1 and five an improvement in FVC. The change in daytime $Paco_2$ was related to the change in the amount of gas trapping (Spearmans correlation coefficient (r_s) 0.85, $p<0.05$) and in the RV (r_s 0.78, $p<0.05$) (fig. 5). In all patients there was a fall in carbon monoxide transfer coefficient (Kco) over six months.

Pretreatment central respiratory drive, as measured by $P_{0.1}$ was high during quiet respiration and following NIPPV four patients showed an increase and three a decrease (table 3). Four patients showed an increase in the slope of the ventilatory response to CO_2 and five an increase in the $P_{0.1}$ response. The change in daytime $Paco_2$ correlated with the increase in ventilation (r_s -0.76, $p<0.05$) at an $Etco_2$ of 8 kPa during rebreathing (fig. 6).

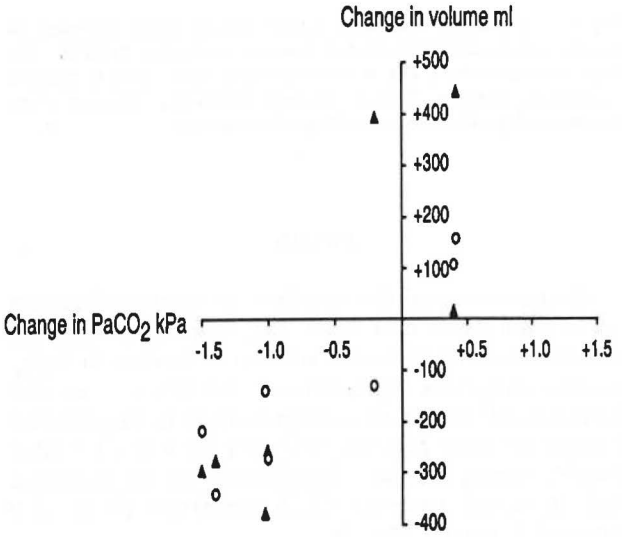

Fig. 5. – The relationship between the change in $Paco_2$ and changes in residual volume and gas trapping. o: trapped gas; ▲ : residual volume; $Paco_2$: arterial carbon dioxide tension.

Table 3. – Drive: minute ventilation (MV) and $P_{0.1}$ during quiet respiration and during CO_2 rebreathing at the start of the study with the change after six months nasal intermittent positive pressure ventilation (NIPPV) in brackets

	Ventilation			$P_{0.1}$		
No.	MV $l \cdot min^{-1}$	Slope $l \cdot min^{-1} \cdot kPa$	MV at 8 kPa $l \cdot min^{-1}$	$P_{0.1}$ cmH_2O	Slope $cmH_2O \cdot kPa^{-1}$	$P_{0.1}$ at 8 kPa cmH_2O
2	9.60 (+3.33)	0.73 (+0.67)	11.4 (+3.1)	2.4 (+1.4)	-0.16 (+0.63)	2.9 (+1.3)
3	7.90 (+3.79)	3.40 (-0.70)	12.0 (+5.1)	0.9 (+3.4)	2.40 (+1.70)	3.5 (+7.5)
4	9.51 (+1.41)	1.20 (+0.60)	8.9 (+6.3)	5.5 (+2.0)	2.60 (-0.80)	2.5 (+6.1)
5	9.54 (+1.98)	1.80 (+0.70)	8.2 (+4.9)	3.9 (+0.5)	2.40 (+0.90)	1.6 (+3.1)
6	8.60 (+0.90)	1.20 (+0.00)	9.4 (+2.6)	4.2 (-2.3)	2.20 (-1.10)	-1.5 (+3.8)
7	10.89 (-4.74)	0.80 (+1.10)	12.9 (-4.9)	3.7 (-1.9)	1.70 (+0.10)	2.3 (-1.1)
8	12.13 (-3.21)	2.30 (-0.20)	12.8 (+0.4)	4.8 (-1.7)	2.70 (+1.50)	4.3 (-0.1)
Mean	10.29 (+0.50)	1.63 (+0.31)	10.8 (+2.5)	3.3 (+0.2)	1.98 (+0.42)	2.5 (+2.9)
±SD	±1.78 (±3.24)	±0.96 (±0.63)	±1.9 (±3.8)	±1.4 (±2.2)	±0.10 (±1.08)	±1.6 (±3.2)
p	NS	NS	NS	NS	NS	NS

MV and $P_{0.1}$ at 8 kPa = the value of minute ventilation and occlusion pressure predicted from the regression equation at an end-tidal ($Etco_2$) of 8 kPa.

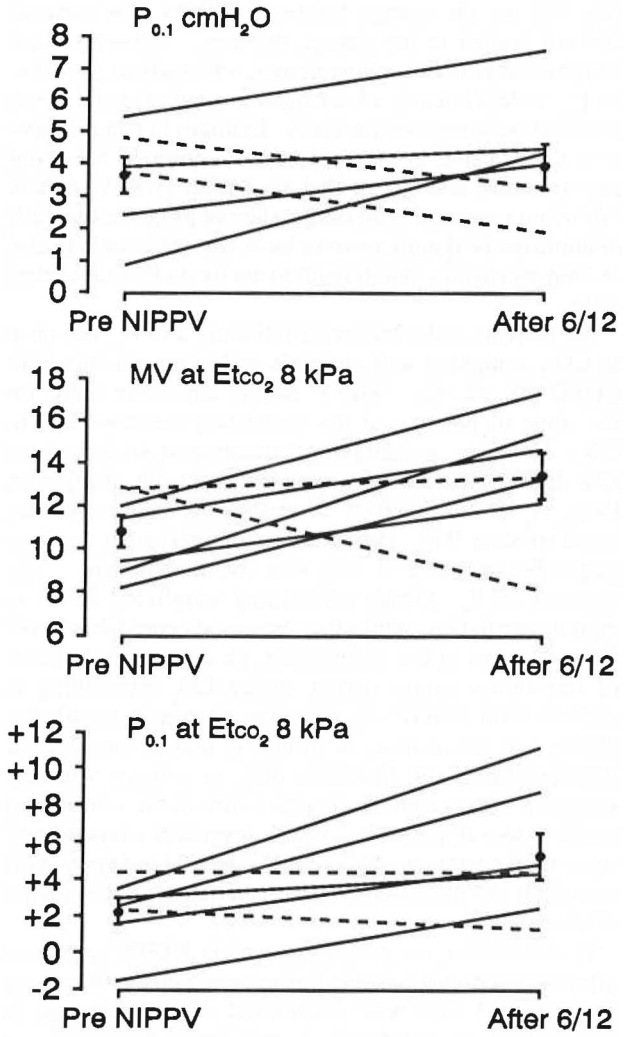

Fig. 6. – Occlusion pressure ($P_{0.1}$) during resting breathing and minute ventilation (MV) and $P_{0.1}$ before and after six months. Broken lines represent patients (no. 7 and 8) in whom $Paco_2$ during spontaneous breathing, increased. Symbols represent mean±standard errors for all patients. $Etco_2$: end-tidal CO_2; $Paco_2$: arterial CO_2 tension.

Discussion

The use of NIPPV is well-established in patients with extrapulmonary restrictive disorders but its place in the management of patients with COPD has not yet been determined. The aim of this study was to investigate possible mechanisms of the improvement in arterial blood gas tensions following NIPPV, since the correct use of the technique in COPD can only be established when its physiological effects are understood. Overall the changes in arterial blood gas tensions were small and cannot be taken as evidence that NIPPV should be used routinely in patients with COPD.

Previous studies of assisted ventilation in patients with COPD have shown a reduction in daytime $Paco_2$, in association with improved inspiratory muscle strength following periods of treatment ranging from a few hours to several days [6–10]. These improvements have been cited as evidence that the benefit from assisted ventilation is a consequence of the relief of respiratory muscle fatigue. We could not confirm this hypothesis since, although the changes in blood gas tensions in our study are similar to previously reported data, respiratory muscle strength, as measured by the described indices, did not increase. Where increases did occur in individual patients they were unrelated to changes in gas tensions; patients no. 4–6 had decreased Pimax and/or sniff Poes but improved gas tensions, whereas patients no. 7 and 8 had improved strength and worse gas tensions.

There was a statistically significant increase in the group result for sniff Pdi after NIPPV. This was principally due to large changes in 4 out of 6 patients and was a consequence of increased sniff Pgas with sniff Poes being unchanged or less. However, the increase in sniff Pdi was not paralleled by increases in Pdi Pimax and in patients no. 3 and 5 these indices of diaphragm strength changed in opposite directions following NIPPV. This suggests that increases in sniff Pdi did not necessarily

reflect improved diaphragmatic strength but may result from a difference in the pattern of muscle group activation during the two manoeuvres on the two test days.

Changes in respiratory muscle strength, may be poor indicators of respiratory muscle fatigue since the tests, used in this and other studies, are volitional and depend upon patient co-operation. It is possible that a symptomatically improved patient may perform the tests with more committment giving the impression of a causal relationship between improved respiratory muscle strength and changes in gas tensions. Secondly, pressure changes are only an indirect measure of the tension generated in the muscles and may be affected by changes in chest wall or diaphragm configuration independently of intrinsic changes in muscle function. We did not formally document "respiratory muscle rest" since the primary aim of this study was the control of nocturnal hypoventilation. NIPPV can be used to reduce respiratory muscle activity during the day in patients with COPD, who have been acclimatized to the technique [24] but this may not pertain during sleep. If inspiratory muscle activity was not reduced in our patients [25] this would be further evidence against the hypothesis that the improved arterial blood gas tensions were primarily a consequence of the relief of respiratory muscle fatigue.

A rapid shallow pattern of breathing has been postulated to indicate, amongst other possibilities, the presence of muscle fatigue [26–28] and ROCHESTER [29] has hypothesized that the relief of incipient rather than actual chronic respiratory muscle fatigue may be important. All of our patients had a rapid shallow pattern of breathing and in those where $Paco_2$ fell following NIPPV this was associated with an increase in minute ventilation, as a consequence of an increase in VT. The opposite was true in the two patients whose $Paco_2$ rose. This might, therefore, be taken to imply resolution of respiratory muscle fatigue. However, experimental evidence that this pattern of breathing is seen with fatigued respiratory muscles has usually followed inspiratory resistive loading (IRL) and has been implied rather than proven. Indeed, ADAMS *et al.* [30] found no evidence of diaphragmatic fatigue, as measured by phrenic stimulation, in dogs subjected to a severe IRL, who developed hypercapnia and rapid shallow breathing. Under conditions of increased load, such as in COPD or during a failed weaning trial [31], patients adopt this pattern of breathing since it is beneficial to the inspiratory muscles in terms of energy expenditure but is detrimental to alveolar ventilation [32]. In other words the central nervous system alters the pattern of breathing in response to an increase in load to prevent fatigue rather than in response to it.

Our patients showed some evidence of a change in the load upon the respiratory system. FEV_1 improved and in the five patients in whom $Paco_2$ fell there was a reduction in the amount of gas trapping, suggesting reduced small airway obstruction [33], and in four a small increase in the dynamic compliance. These changes are likely to be a true effect of NIPPV since bronchodilator therapy had been maximized and clinical stability confirmed before recruitment. There were no changes in therapy other than a reduction in diuretic dosage and decreased requirements for beta-agonists in two patients.

The reasons why ventilatory function and mechanics should improve following NIPPV are not clear. Pulmonary oedema causes tachypnoea [34, 35] and small airway narrowing [36] and has been postulated as a possible mediator of the breathing pattern seen following IRL [30]. Pulmonary venous congestion decreases lung compliance and may contribute to airway narrowing. Positive pressure ventilation is an effective treatment for pulmonary oedema and vigorous diuretic therapy has been shown to achieve improved daytime blood gas tensions in patients with cor pulmonale [37]. All of our patients had previous or present peripheral oedema and the improvement in the pattern of breathing, ventilatory function and mechanics may reflect a reduction in lung water following NIPPV.

Central drive as measured by $P_{0.1}$ was high during quiet breathing pretreatment, as described previously in COPD [20, 38], but the change following NIPPV was variable and not related to the change in $Paco_2$. However, lung volume and pulmonary compliance, which affect the value of $P_{0.1}$ independently of changes in central drive, were different between the two visits. Changes in central drive may be reflected in changes in the pattern of breathing and a similar change, to that seen after NIPPV, occurs following treatment with drugs, such as progesterone [39] or almitrine [40] not known to have any effect on muscles or lung mechanics and thought to act by increasing central drive.

All patients had a reduced ventilatory and $P_{0.1}$ response to CO_2, compared with normals and other patients with COPD [38, 41, 42]. NIPPV had no consistent effect on the slope or position of the ventilatory response line to CO_2. However, a change in ventilation at an $Etco_2$ of 8 kPa during rebreathing was correlated with changes in $Paco_2$ (r_s -0.76, $p<0.05$). A change in lung mechanics could explain this. However, an improvement in slope might be expected if this was the mechanism. The changes in $P_{0.1}$ during rebreathing paralleled those in minute ventilation, suggesting increased central drive, but $P_{0.1}$, measured at the mouth, may be an unreliable index of respiratory centre output during CO_2 rebreathing in patients with COPD [43, 44]. The change in ventilation during CO_2 rebreathing is similar to that in the study of BERTHON-JONES and SULLIVAN [45], in patients with obstructive sleep apnoea treated with nasal continuous positive airway pressure. It may represent adaptation of the central chemoreceptors to the reduction in hypercapnia overnight or alternatively reflect changes in the quality of sleep [46].

In conclusion, six months overnight NIPPV improved arterial blood gas tensions during spontaneous breathing by day and this was associated with a change in the pattern of breathing to one more favourable to alveolar ventilation. No single factor is responsible for this change and in particular we could find no convincing evidence that the improvement was the result of increased respiratory muscle strength consequent upon the relief of

muscle fatigue. Our data suggest that the effect of NIPPV upon changes in load and central drive warrant further investigation.

Acknowledgements: Purchase of the ventilators was funded by the Department of Health. The authors thank J.A. Wedzicha and M.P. Carroll for allowing the study of patients under their care.

References

1. Hoeppner VH, Cockcroft DW, Dosman JA, Cotton DJ. – Night-time ventilation improves respiratory failure in secondary kyphoscoliosis. *Am Rev Respir Dis*, 1984, 129, 240–243.
2. Goldstein RS, Moloyiu N, Skrastins R, Long S, De Rosie J, Contreras M, Popkin J, Rutherford R, Philipson EA. – Reversal of sleep-induced hypoventilation and chronic respiratory failure by nocturnal negative pressure ventilation in patients with restrictive ventilatory impairment. *Am Rev Respir Dis*, 1987, 135, 1049–1055.
3. Ellis ER, Bye PTB, Bruderer JW, Sullivan CE. – Treatment of respiratory failure during sleep in patients with neuromuscular disease. *Am Rev Respir Dis*, 1987, 135, 148–152.
4. Carroll N, Branthwaite MA. – Control of nocturnal hypoventilation by nasal intermittent positive pressure ventilation. *Thorax*, 1988, 43, 349–353.
5. Heckmatt JZ, Loh L, Dubowitz V. – Night-time ventilation in neuromuscular disease. *Lancet*, 1990, 335, 579–582.
6. Gutierrez M, Beroiza T, Contreras G, Diaz O, Cruz E, Moreno R, Lisboa C. – Weekly cuirass ventilation improves blood gases and inspiratory muscle strength in patients with chronic airflow limitation and hypercarbia. *Am Rev Respir Dis*, 1988, 138, 617–623.
7. Cropp A, Dimarco AF. – Effects of intermittent negative pressure ventilation on respiratory muscle function in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis*, 1987, 135, 1056–1061.
8. Celli B, Lee H, Criner G, Bermudez M, Rassulo J, Gilmartin M, Miller G, Make B. – Controlled trial of external negative pressure ventilation in patients with severe chronic airflow limitation. *Am Rev Respir Dis*, 1989, 140, 1251–1256.
9. Ambrosino N, Montagna T, Nava S, Negri A, Brega S, Fracchia C, Zocchi L, Rampulla C. – Short-term effect of intermittent negative pressure ventilation in COPD patients with respiratory failure. *Eur Respir J*, 1990, 3, 502–508.
10. Scano G, Gigliotti F, Duranti R, Spinelli A, Gorini M, Schiavina M. – Changes in ventilatory muscle function with negative pressure ventilation in COPD. *Chest*, 1990, 97, 322–327.
11. Corrado A, Bruscoli G, De Paola E, Ciardi-Dupre GF, Baccini A, Taddel M. – Respiratory muscle insufficiency in acute respiratory failure of subjects with severe COPD: treatment with intermittent negative pressure ventilation. *Eur Respir J*, 1990, 3, 644–648.
12. Van Ganse W, Comhaire F, Van Der Straeten M. – Alveolar volume and transfer factor determined by single breath dilution of a test gas at various apnoea times. *Scand J Respir Dis*, 1970, 51, 82–92.
13. Denison DM, Pierce RJ, Waller JF. – How big are the lungs? *Br J Dis Chest*, 1981, 75, 371–385.
14. Milic-Emili J, Mead J, Turner JM, Glauser EM. – Improved technique for estimating pleural pressures from esophageal balloons. *J Appl Physiol*, 1964, 19, 207–211.
15. Agostoni E, Rahn H. – Abdominal and thoracic pressures at different lung volumes. *J Appl Physiol*, 1960, 15, 1087–1092.
16. Koulouris N, Mulvey D, Laroche CM, Green M, Moxham J. – Comparison of two different mouthpieces for the measurement of Pimax and Pemax in normal and weak subjects. *Eur Respir J*, 1988, 1, 863–867.
17. Read DMC. – A clinical method for assessing the ventilatory response to carbon dioxide. *Australas Ann Med*, 1967, 16, 20–32.
18. Whitelaw WA, Derenne JP, Milic-Emili J. – Occlusion pressure as a measure of respiratory centre output in conscious man. *Respir Physiol*, 1975, 23, 181–199.
19. Gilbert R, Keighley J, Auchinloss JH. – Mechanisms of chronic carbon dioxide retention in patients with obstructive pulmonary disease. *Am J Med*, 1965, 38, 217–225.
20. Sorli J, Grassino A, Lorange G, Milic-Emili J. – Control of breathing in patients with chronic obstructive lung disease. *Clin Sci Molec Med*, 1978, 54, 295–304.
21. Skatrud JB, Dempsey JA, Bhansall P, Irvin C. – Determinants of chronic carbon dioxide retention and its correction in humans. *J Clin Invest*, 1980, 65, 813–821.
22. Javaheri S, Blum J, Kazemi H. – Pattern of breathing and carbon dioxide retention in chronic obstructive lung disease. *Am J Med*, 1981, 71, 228–234.
23. Parot S, Miara B, Milic-Emili J, Gautier H. – Hypoxaemia, hypercapnia, and breathing pattern in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*, 1982, 126, 882–886.
24. Carrey Z, Gottfried SB, Levy RD. – Ventilatory muscle support in respiratory failure with nasal positive pressure ventilation. *Chest*, 1990, 97, 150–158.
25. Rodenstein DO, Stanescu DC, Cuttita G, Liistro G, Veriter C. – Ventilatory and diaphragmatic EMG responses to negative pressure ventilation in airflow obstruction. *J Appl Physiol*, 1988, 65(4), 1621–1626.
26. Cohen CA, Zagelbaum G, Gross D, Roussos C, Macklem P. – Clinical manifestations of inspiratory muscle fatigue. *Am J Med*, 1982, 73, 308–316.
27. Gallagher CG, Im Hof V, Younes M. – Effect of inspiratory muscle fatigue on breathing pattern. *J Appl Physiol*, 1985, 59(4), 1152–1158.
28. Roussos C. – Ventilatory muscle fatigue governs breathing frequency. *Bull Eur Physiopathol Respir*, 1984, 20, 445–451.
29. Rochester DF. – Does respiratory muscle rest relieve fatigue or incipient fatigue? *Am Rev Respir Dis*, 1988, 138, 516–517.
30. Adams JM, Farkas GA, Rochester DF. – Vagal afferents, diaphragm fatigue and inspiratory resistance in anesthetised dogs. *J Appl Physiol*, 1988, 64(6), 2279–2286.
31. Tobin MJ, Perez W, Guenther SM, Semmes BJ, Mador MJ, Allen SJ, Lodato RF, Dantzker DR. – The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. *Am Rev Respir Dis*, 1986, 134, 1111–1118.
32. Moxham J. – Respiratory muscle fatigue: mechanisms, evaluation and therapy. *Br J Anaesth*, 1990, 65, 43–53.
33. Chrystyn H, Mulley BA, Peake MD. – Dose response to oral theophylline in severe chronic obstructive airways disease. *Br Med J*, 1988, 297, 1506–1510.
34. Paintal AS. – Mechanism of stimulation of type J pulmonary receptors. *J Physiol*, 1969, 203, 511–532.
35. Widdicombe JG. – The activity of pulmonary stretch receptors during bronchoconstriction, pulmonary oedema, atelectasis and breathing against a resistance. *J Physiol*, 1961, 159, 436–450.

36. Cosby RS, Stowell EC, Hartwig WR, Mayo M. – Pulmonary function in left ventricular failure including cardiac asthma. *Circulation*, 1957, 15, 492–501.
37. Noble MIM, Trenchard D, Guz A. – The value of diuretics in respiratory failure. *Lancet*, 1966, July 30th, 257–260.
38. Scano G, Gigliotti F, Spinelli A, Van Meerhaeghe A, Sergysels R. – Breathing pattern and neuromuscular drive during CO_2 rebreathing in normal man and in patients with COPD. *Respiration*, 1986, 50, 73–82.
39. Cullen JH, Brum VC, Reidt WU. – The respiratory effects of progesterone in severe pulmonary emphysema. *Am J Med*, 1959, 27, 551–557.
40. Stradling JR, Nicholl CG, Cover D, Davies EE, Hughes JMB, Pride NB. – The effects of oral almitrine on pattern of breathing and gas exchange in patients with chronic obstructive pulmonary disease. *Clin Sci*, 1984, 66, 435–442.
41. Gribben HR, Gardiner IT, Heinz III GJ, Gibson GJ, Pride NB. – Role of impaired inspiratory muscle function in limiting the ventilatory response to carbon dioxide in chronic airflow obstruction. *Clin Sci*, 1983, 64, 487–495.
42. Molho M, Faibis A, Lusky A, Shiner RJ, Ram A. – Ventilatory response and pattern of breathing during hypercapnia. *Bull Eur Physiopathol Respir*, 1986, 22, 21–26.
43. Marazzini L, Cavestri R, Gori D, Gatti L, Longhini E. – Difference between mouth and esophageal occlusion pressure during CO_2 rebreathing in chronic obstructive pulmonary disease. *Am Rev Respir Dis*, 1978, 118, 1027–1033.
44. Murciano D, Aubier M, Bussi S, Derenne JP, Pariente R, Milic-Emili J. – Comparison of esophageal, tracheal and mouth occlusion pressure in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis*, 1982, 126, 837–841.
45. Berthon-Jones M, Sullivan CE. – Time course of change in ventilatory response to CO_2 with long-term CPAP therapy for obstructive sleep apnea. *Am Rev Respir Dis*, 1987, 135, 144–147.
46. White DP, Douglas NJ, Pickett CK, Zwillich CW, Weil JV. – Sleep deprivation and the control of ventilation. *Am Rev Respir Dis*, 1983, 128, 984–986.

Ventilation sous pression positive intermittente nasale, la nuit, au domicile, dans les BPCO: mécanismes responsables des modifications des tensions gazeuses dans le sang artériel.
M.W. Elliot, D.A. Mulvey, J. Moxham, M. Green, M.A. Branthwaite.

RÉSUMÉ: L'amélioration des tensions des gaz du sang artériel après ventilation assistée dans les BPCO a habituellement été attribuée au soulagement d'une fatigue débutante ou établie des muscles respiratoires. La contribution des modifications de la charge imposée et celle de la stimulation de la pompe des muscles respiratoires n'ont pas été évaluées. Nous avons investigué la contribution de modifications de la force des muscles respiratoires, de la réponse ventilation au CO_2, et de la fonction ventilatoire, aux modifications des tensions des gaz artériels, chez huit patients atteints de BPCO sévère, ayant complété six mois de ventilation nasale sous pression positive intermittente à leur domicile.

Au cours de la respiration spontanée pendant le jour, l'on a observé chez six patients une réduction, et chez deux une augmentation, de $Paco_2$: valeur médiane (extrêmes) pour huit patients, -0.9 kPa (-1.5 à +0.4) ($p<0.05$) et chez sept une amélioration de la Pao_2: valeur médiane (extrêmes), + 0.7 kPa (-0.4 à + 1.7) ($p<0.05$). La réduction de la $Paco_2$ est sans relation avec une augmentation de la force des muscles inspiratoires, mais est en corrélation avec une diminution du trappage des gaz (coefficient de corrélation rank Spearman (r_s) 0.85, $p<0.05$) et avec une diminution du volume résiduel (r_s 0.78, $p<0.05$), ce qui suggère une diminution de l'obstruction des petites voies aériennes et dès lors une diminution de la charge. Les modifications de $Paco_2$ sont également en corrélation avec l'augmentation de ventilation sous un CO_2 en fin de volume courant de 8 kPa au cours du rebreathing (r_s -0.76, $p<0.05$), ce qui suggère une amélioration de la chimiosensibilité au CO_2.

Nos observations ne confirment pas l'hypothèse selon laquelle les améliorations seraient dues au soulagement de la fatigue musculaire. Nous suggérons que la contribution des modifications de la charge et du stimulus central mérite des investigations complémentaires.
Eur Respir J., 1991, 4, 1044–1052.