Physiological changes during low- and high-intensity noninvasive ventilation

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ABSTRACT: **In a physiological randomised cross-over study performed in stable hypercapnic chronic obstructive disease patients, we assessed the short-term effects of two settings of noninvasive ventilation.**

One setting was aimed at maximally reducing arterial carbon dioxide tension (P_{a,CO_2}) (high-intensity (Hi) noninvasive positive pressure ventilation (NPPV)): mean$\pm$SD 27.6$\pm$2.1 cmH$_2$O of inspiratory positive airway pressure, 4$\pm$0 cmH$_2$O of expiratory positive airway pressure and respiratory rate of 22 breaths·min^{-1}. The other was performed according to the usual parameters used in earlier studies (low-intensity (Li)-NPPV): 17.7$\pm$1.6 cmH$_2$O of inspiratory positive airway pressure, 4$\pm$0 cmH$_2$O of expiratory positive airway pressure and respiratory rate of 12 breaths·min^{-1}.

Both modes of ventilation significantly improved gas exchange compared with spontaneous breathing (SB), but to a greater extent using Hi-NPPV (P_{a,CO_2} 59.3$\pm$7.5, 55.2$\pm$6.9 and 49.4$\pm$7.8 mmHg for SB, Li-NPPV and Hi-NPPV, respectively). Similarly, Hi-NPPV induced a greater reduction in the pressure–time product of the diaphragm per minute from 323$\pm$149 cmH$_2$O·s·min^{-1} during SB to 132$\pm$139 cmH$_2$O·s·min^{-1} during Li-NPPV and 40$\pm$69 cmH$_2$O·s·min^{-1} during Hi-NPPV, while in nine out of 15 patients, it completely abolished SB activity. Hi-NPPV also induced a marked reduction in cardiac output (CO) measured noninvasively with a Finometer PRO (Finapres Medical Systems BV, Amsterdam, the Netherlands) compared with Li-NPPV.

We conclude that while Hi-NPPV is more effective than Li-NPPV in improving gas exchange and in reducing inspiratory effort, it induces a marked reduction in CO, which needs to be considered when Hi-NPPV is applied to patients with pre-existing cardiac disease.

KEYWORDS: Chronic obstructive pulmonary disease, noninvasive ventilation, respiratory mechanics

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A recent systematic review on the use of long-term noninvasive ventilation (NIV) in stable hypercapnic chronic obstructive pulmonary disease (COPD) patients was inconclusive as, despite improvement in lung hyperinflation, gas exchange and diaphragmatic effort, no major long-term clinical advantages were observed in randomised controlled trials [1, 2].

Inconsistency in the effectiveness of NIV on the assessed outcomes may be due, among other variables, to the levels of the applied inspiratory and expiratory pressure [3]. It has been suggested that the ''appropriate'' NIV setting to reduce the work of breathing by at least 40% including the portion due to the presence of intrinsic positive end-expiratory pressure (PEEPi) [4] is achieved clinically on the basis of the patient's tolerance and improvement in arterial blood gases. The mean inspiratory pressure applied in that physiological

study [3] was ~15 cmH$_2$O, which is very close to the average values employed in most of the randomised long-term trials [3, 4].

Higher inspiratory pressures (28 cmH$_2$O) and respiratory rates (20 breaths·min^{-1}) were recently adopted to ventilate chronic hypercapnic COPD patients in order to achieve maximal arterial carbon dioxide tension (P_{a,CO_2}) reduction. This type of approach, called high-intensity (Hi) non-invasive positive pressure ventilation (NPPV), has been shown to improve spontaneous diurnal blood gases more than the traditional lower pressures approach (low-intensity (Li)-NPPV). A long-term randomised study will be necessary to determine the effect of Hi-NPPV on long-term survival [5–7].

No data are available, however, to assess physiological effects of this atypical setting on diaphragmatic activity and worsening of dynamic

hyperinflation or auto-PEEP. Moreover, through an increase in intrathoracic pressure, Hi-NPPV could reduce cardiac output (CO) [8, 9].

In this randomised cross-over study, we investigated the acute physiological changes of Hi-NPPV *versus* Li-NPPV in order to clarify the possible detrimental effects of this new ventilatory strategy.

MATERIALS AND METHODS

We studied 15 patients who were admitted to the Dept of Respiratory Rehabilitation, Fondazione Salvatore Maugeri, Pavia, Italy for management of chronic hypercapnic respiratory failure due to COPD. At the time of the study, all patients were in a phase of clinical and haemodynamic stability. The patients' characteristics, including pulmonary function tests and arterial blood gases at the time of the study, are shown in table 1. Enrolment criteria were the presence of chronic hypercapnic respiratory failure (*i.e.* pH $\geqslant$7.35 and P_{a,CO_2} $\geqslant$50 mmHg), while exclusion criteria were the presence of cancer, neuromuscular disease or an ejection fraction (EF) recorded during an echocardiography study of <40% (the mean$\pm$SD in enrolled patients was 58.9$\pm$11%). The study was approved by the local ethics committee and written informed consent was obtained from all patients.

Protocol

The ventilator therapy was stopped at least 1 h before the beginning of each trial. The patients were studied in a semirecumbent position while inspiring additional oxygen. At the beginning of the trial, the patients were asked to breath for a few minutes without any ventilatory assistance (baseline recordings). The physiological data were recorded during two randomised trials, each with different ventilatory settings over 30 min, separated by a return to spontaneous breathing (SB)

for 10 min. The randomisation of the trials was obtained using an *ad hoc* computer program in order to evenly distribute the sequence. The patients were ventilated with a respirator with a dedicated NIV platform (HARMONY (Philips, Amsterdam, the Netherlands), Vivo 50 (Breas, Mölnlycke, Sweden) and V60 (Philips)) and with a full-face mask tailored to each patient's facial features. Great care was taken by the respiratory therapists in charge of NIV, who were blinded to the protocol, to avoid any possible air leaks. Adjustment of the mask was checked at the beginning of each trial. The inspired fraction of oxygen during the different ventilatory settings was estimated according to THYS *et al.* [10].

Li-NPPV

All the patients had stable hypercapnic COPD and were admitted to our unit for a possible home ventilation programme. They were, therefore, familiarised with NIV in the preceding few days, using our usual clinical protocol [3] aimed at reducing P_{a,CO_2} by >10% while on ventilation (P_{a,CO_2} at hospital admission during SB 62.3$\pm$8.2 mmHg and 56.3$\pm$7.5 mmHg during the NIV adaptation trial), achieving an expired tidal volume (V_T) of 6–8 mL·kg^{-1} and a reduction of transdiaphragmatic pressure (P_{di}) to 50% of baseline during the measurement of respiratory mechanics. These settings were chosen by the attending clinician, who was unaware of the aim of the study. The mean$\pm$SD inspiratory support was 17.7$\pm$1.6 cmH$_2$O (range 15–20 cmH$_2$O) with an external continuous positive airway pressure of 4 cmH$_2$O and a back-up rate of 12 breaths·min^{-1}.

Hi-NPPV

With Hi-NPPV, we aimed to reach the maximum tolerated inspiratory pressure (at least 50% greater than Li-NPPV) by increasing pressures stepwise by 0.5 cmH$_2$O. This allowed us

TABLE 1	Patients' characteristics including pulmonary function tests and arterial blood gases								
Patient	Age yrs	Sex	BMI kg·m^{-2}	pH	P_{CO_2} mmHg	P_{O_2} mmHg	FEV$_1$ L (% pred)	FVC L (% pred)	FEV$_1$/FVC %
1	80	M	20.6	7.45	50.10	69.80	0.52 (23)	1.07 (35)	49
2	76	M	21.8	7.35	69.80	58.90	0.43 (20)	1.99 (70)	22
3	54	M	23.7	7.41	51.00	61.00	NA	NA	NA
4	66	M	22.1	7.36	57.30	62.40	0.64 (22)	2.84 (76)	23
5	77	M	33.7	7.39	50.40	59.20	0.89 (46)	1.65 (64)	54
6	64	M	16.6	7.36	56.80	68.80	0.47 (20)	2.34 (80)	20
7	78	M	22.0	7.37	56.50	80.60	0.51 (22)	1.52 (48)	34
8	71	M	25.8	7.41	57.90	58.70	0.52 (20)	1.85 (54)	28
9	60	M	29.4	7.35	59.10	74.70	0.59 (18)	2.18 (53)	59
10	71	F	33.2	7.36	65.00	63.80	NA	NA	NA
11	69	M	30.2	7.35	62.80	67.50	0.48 (15)	1.96 (46)	24
12	81	M	24.5	7.41	54.20	71.90	0.63 (29)	1.17 (40)	54
13	76	M	24.5	7.35	77.30	67.10	0.65 (23)	1.47 (39)	44
14	76	M	13.1	7.43	64.30	79.00	0.49 (17)	1.7 (45)	29
15	78	M	26.1	7.35	56.90	73.00	0.89 (32)	1.83 (49)	49
Mean$\pm$SD	71.8$\pm$7.8		24.5$\pm$5.7	7.38$\pm$0.03	59.3$\pm$7.5	67.8$\pm$7.1	0.61$\pm$0.15 (23.6$\pm$8.11)	1.68$\pm$0.56 (53.8$\pm$14.5)	44.7$\pm$23.13

BMI: body mass index; P_{CO_2}: carbon dioxide tension; P_{O_2}: oxygen tension; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; M: male; F: female; NA: not available.

to reach mean inspiratory pressure values very close to those of WINDISCH and co-workers [5, 6] (27.6 ± 2.1 cmH$_2$O used in our study *versus* ~28 cmH$_2$O used in previous studies), aiming to maximally decrease P_{a,CO_2} by stepwise increases in inspiratory pressure [5–7]. As with Li-NPPV, the external PEEP level was fixed at 4 cmH$_2$O and respiratory rate was set to match the SB rate, usually 20–22 breaths·min^{-1}.

Measurements

Arterial blood gases were obtained from a radial artery during SB and at the end of each ventilatory trial. Flow at the airway opening was measured with a heated pneumotachograph (Model 3700; Hans Rudolph, Shawnee, KS, USA) and a differential pressure transducer (± 300 cmH$_2$O; Honeywell, Freeport, IL, USA) placed between the mask and the Y-piece of the ventilator. V_T was obtained by integration of the flow. Breathing pattern was measured from the flow signal. Expired V_T was used for data analysis. We also measured the difference between expired and inspired V_T to quantify the amount of air leakage.

Airway pressure (± 300 cmH$_2$O; Honeywell) was measured from a side port between the pneumotachograph and the face mask.

Oesophageal and gastric pressures (± 300 cmH$_2$O; Honeywell) were measured with an oesophageal balloon positioned at the lower third of the oesophagus, filled with 0.5 mL air and a gastric balloon filled with 1 mL air. The proper position of the balloon was verified using the occlusion test. P_{di} was calculated as the difference between gastric and oesophageal pressure.

Pressure–time integrals of the diaphragm (PTP$_{di}$) were calculated per breath (pressure–time product of the diaphragm per breath (PTP$_{di/breath}$)) and per minute (pressure–time product of the diaphragm per minute (PTP$_{di/min}$)). Dynamic PEEPi (PEEP$_{i,dyn}$) was obtained from the P_{di} signal, as the value of P_{di} at the moment of zero flow [11, 12]. Ineffective efforts (IEs) were analysed from the P_{di} traces and expressed as percentage of total breaths measured.

We also measured cardiovascular parameters using a non-invasive device (Finometer PRO; Finapres Medical Systems BV, Amsterdam, the Netherlands) [13]. In this group of patients with normal cardiac performance, this method has a good reliability, with 15% error relative to invasively obtained values [14] and only 8% error relative to changes [15] in CO measured by thermodilution.

The Finometer PRO finger cuff was placed on the middle finger and the arm cuff was placed on the same-side upper arm of the patient. The measured and calculated cardiovascular parameters were systolic arterial pressure (SAP), diastolic arterial pressure, mean arterial pressure (MAP), heart rate, stroke volume (SV) and CO.

Dyspnoea was assessed using the Borg scale, with a range of 0–10, at baseline and during the two ventilator trials. For each condition tested, patients placed a finger on the number that best represented the question ''how does your breathing feel during this trial of ventilation?'' Data obtained in the final 3 min of recording were considered for analysis.

Statistical analysis

All signals were collected using a personal computer equipped with an analogue/digital board and stored at a sampling rate of 100 Hz. Data are presented as mean$\pm$SD. Comparisons for each sequence and each continuous variable were performed using ANOVA for repeated measures with the Newman–Keuls *post hoc* test. The protection test for carry-over effects was also performed [16, 17]. Outcome measures were tested for normality with the Kolmogorov–Smirnov test, and when normality was not achieved, we used the Friedman test. Statistical analysis was performed with Prism (GraphPad, La Jolla, CA, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium). All tests were two-sided. A p-value <0.05 was considered statistically significant.

RESULTS

All patients tolerated the experimental procedures well and completed the study. Eight out of 15 patients were randomised to receive Li-NPPV as the first intervention.

Breathing pattern

As shown in table 2, compared with baseline conditions, both Hi-NPPV and Li-NPPV significantly increased expired V_T and minute ventilation (V'_E), but these changes were statistically higher with Hi-NPPV. The amount of air-leaks was significantly lower with Li-NPPV. The mean inspiratory flow was also higher with Hi-NPPV and the duty cycle lower, whereas no statistical difference was observed in breathing frequency.

Respiratory mechanics

Mean values of respiratory mechanics are presented in table 3. Tidal P_{di}, PTP$_{di/breath}$ and PTP$_{di/min}$ were significantly reduced compared with SB, but the decrease in all these parameters was significantly greater using Hi-NPPV *versus* Li-NPPV. Indeed, in nine out of 15 patients, the P_{di} trace was flat and the pleural pressure (P_{pl}) even became positive during Hi-NPPV, suggesting a ''true'' controlled ventilation (fig. 1). For this reason, data on PEEP$_{i,dyn}$ are not presented. Only two out of the six patients with a measurable P_{di} had IEs, both during Li-NPPV (8.0 ± 5.5% of the total breaths) and Hi-NPPV (1.2 ± 2.8%). Lung resistance was also significantly decreased during mechanical ventilation, but no difference was found between the two ventilator settings.

Arterial blood gases

The mean values of blood gas parameters are presented in table 4. Despite different ventilatory settings, pH and P_{a,CO_2} improved significantly *versus* baseline conditions, the changes being significantly less pronounced using Li-NPPV than Hi-NPPV.

Dyspnoea score

No statistical differences were observed between the two modes of ventilation, but both resulted in a statistical reduction *versus* baseline (Borg score 6.93 ± 1.1 in SB *versus* 3.13 ± 1.64 in Li-NPPV (p<0.001) and 4.67 ± 1.04 in Hi-NPPV (p<0.01)).

Cardiovascular parameters and oxygen transport

The mean values of the main cardiovascular parameters and oxygen transport are presented in table 5. Mechanical ventilation induced a significant decrease in SAP, but without any

TABLE 2	Breathing pattern					
Parameter	**SB**	**Li-NPPV**	**Hi-NPPV**	**p-value**		
				SB versus Li-NPPV	**SB versus Hi-NPPV**	**Li-NPPV versus Hi-NPPV**
f_R breaths·min^{-1}	24.8 ± 8.4	21.3 ± 6.3	22.9 ± 3.3	NS	NS	NS
t_I s	1.25 ± 0.3	1.1 ± 0.19	0.74 ± 0.1	NS	<0.05	<0.001
t_E s	1.46 ± 0.75	1.98 ± 0.77	1.93 ± 0.34	NS	NS	NS
t_I/t_{tot}	0.48 ± 0.09	0.37 ± 0.08	0.27 ± 0.05	<0.001	<0.001	<0.001
V_T L	0.4 ± 0.1	0.56 ± 0.11	0.67 ± 0.13	<0.001	<0.001	<0.001
V_T/t_I L·s^{-1}	0.33 ± 0.08	0.52 ± 0.11	0.93 ± 0.18	<0.05	<0.001	<0.05
$V'E$ L·min^{-1}	9.6 ± 3.5	11.7 ± 2.3	15.2 ± 2.0	<0.01	<0.001	<0.001
Air leakage L·min^{-1}		10.62 ± 5.27	16.11 ± 7.88			<0.05

Data are presented as mean±SD, unless otherwise stated. SB: spontaneous breathing; Li: low-intensity; NPPV: noninvasive positive pressure ventilation; Hi: high-intensity; f_R: respiratory frequency; t_I: inspiratory time; t_E: expiratory time; t_{tot}: total time of respiratory cycle; V_T: tidal volume; $V'E$: minute ventilation; NS: nonsignificant.

difference between Hi-NPPV and Li-NPPV. NPPV also reduced SV, CO and cardiac index; the decrease was statistically more pronounced with Hi-NPPV than Li-NPPV. Similar changes were observed in the calculated oxygen delivery capacity and the oxygen delivery corrected by body surface area. A statistically significant correlation was observed between the per cent changes from baseline CO and absolute changes from baseline P_{pl} in the Hi-NPPV trial (r= -0.68, p<0.01). We found similar correlations between changes from baseline airway pressure and per cent changes from baseline CO during Hi-NPPV (r= -0.59, p<0.05).

There were no relationships between baseline left ventricular EFs and the per cent changes from baseline of CO.

DISCUSSION

The use of NIV in the treatment of chronic respiratory failure due to COPD has had mixed success [2] and for this reason, some researchers have hypothesised that ventilator pressures have been too low and developed a ventilatory technique called Hi-NPPV aimed to maximally reduce P_{a,CO_2} and improve clinical outcomes [5–7]. Previous studies suggest that this approach may not only improve gas exchange but also

other clinical parameters, including dyspnoea during physical activity, lung function and health-related quality of life [5, 7].

In the present study, we have assessed the acute physiological changes induced by Hi-NPPV and demonstrate that this novel approach is able to significantly improve P_{a,CO_2} compared with Li-NPPV, which is most probably related to a greater increase in expired V_T and $V'E$. Hi-NPPV is also associated with a marked reduction in PTPdi, an index of diaphragm oxygen expenditure, and in CO and SV, which could limit the application of Hi-NPPV in patients with pre-existing cardiac disease.

Before proceeding any further, we need to briefly discuss the main aim of Hi-NPPV, which is to maximally reduce the P_{a,CO_2} level. Presently, it is unclear whether hypercapnia per se influences the survival of these patients [5, 18, 19]. Moreover, potential adverse consequences of Hi-NPPV include diaphragm atrophy due to complete rest [20], as suggested by the near abolition of the P_{di} signal seen in most patients; the risk of this seems minimal, however, considering that the respiratory muscles of patients with severe COPD seem to be resistant to fatigue compared with normal subjects [21] and patients using Hi-NPPV are still breathing spontaneously most

TABLE 3	Respiratory mechanics					
Parameter	**SB**	**Li-NPPV**	**Hi-NPPV**	**p-value**		
				SB versus Li-NPPV	**SB versus Hi-NPPV**	**Li-NPPV versus Hi-NPPV**
P_{pl} cmH$_2$O	-15.1 ± 6.8	-6.73 ± 7.9	-2.05 ± 7.52	<0.001	<0.001	<0.001
P_{di} cmH$_2$O	17.9 ± 8.1	9.09 ± 2.4	2.83 ± 4.6	<0.001	<0.001	<0.01
PTPdi cmH$_2$O·s	14.9 ± 7.5	6.3 ± 5.9	1.6 ± 2.6	<0.001	<0.001	<0.01
PTPdi/min cmH$_2$O·s·min^{-1}	323 ± 149	132 ± 139	40 ± 69	<0.001	<0.001	<0.01
$C_{L,dyn}$ L·cmH$_2$O^{-1}	0.02 ± 0.014	0.03 ± 0.007	0.03 ± 0.009	NS	NS	NS
R_L cmH$_2$O·s·L^{-1}	22.3 ± 14.6	11.0 ± 8.4	11.9 ± 9.7	<0.01	<0.05	NS

Data are presented as mean±SD, unless otherwise stated. SB: spontaneous breathing; Li: low-intensity; NPPV: noninvasive positive pressure ventilation; Hi: high-intensity; P_{pl}: pleural pressure; P_{di}: transdiaphragmatic pressure; PTPdi: pressure–time product of the diaphragm; PTPdi/min: PTPdi per minute; $C_{L,dyn}$: dynamic lung compliance; R_L: pulmonary resistance; NS: nonsignificant.
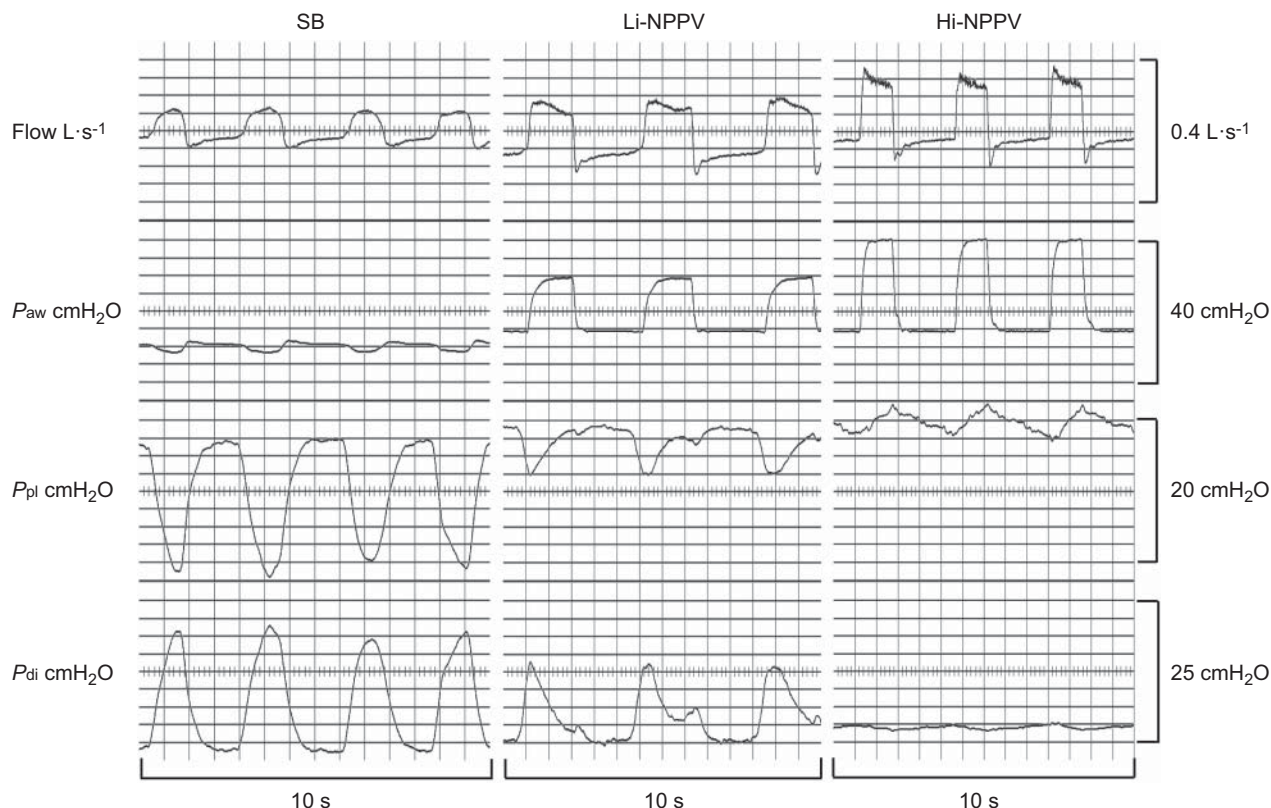
FIGURE 1. Respiratory mechanical parameters during spontaneous breathing (SB), low-intensity (Li) noninvasive positive pressure ventilation (NPPV) and high-intensity (Hi)-NPPV in a characteristic subject. P_{aw}: airway pressure; P_{pl}: pleural pressure; P_{di}: transdiaphragmatic pressure.

of the time, which should minimise atrophy [22]. Another possible detrimental consequence of Hi-NPPV is worsening of pulmonary hyperinflation. Because of the near total abolition of inspiratory muscle activity by Hi-NPPV, we could not calculate PEEPi,dyn using oesophageal tracings. However, the high V_T in the Hi-NPPV group combined with the increased expiratory time constant of COPD patients probably contributed to greater dynamic hyperinflation than with SB or Li-NPPV. Not only does this increase the risk of barotrauma, but it might also have adverse cardiovascular consequences, as will be discussed further herein.

The development of hypercapnic respiratory failure in COPD patients is mainly related to the occurrence of alveolar hypoventilation caused by a marked increase in the ratio of dead space volume (V_D) to V_T. This is a consequence of the reduced V_T that occurs as the failing patient develops a rapid shallow breathing pattern and increased V_D that results from a severe ventilation/perfusion (V'/Q') inhomogeneity [23]. NPPV helps to reverse this process by augmenting V_T and, potentially, reducing V'/Q' mismatch *via* application of positive airway pressure. In an animal study, NEUMANN and HEDENSTIERNA [24] found improvement of V'/Q' inhomogeneity during CPAP

Parameter	SB	Li-NPPV	Hi-NPPV	p-value		
				SB *versus* Li-NPPV	SB *versus* Hi-NPPV	Li-NPPV *versus* Hi-NPPV
TABLE 4 Blood gas parameters						
pH	7.38 ± 0.03	7.4 ± 0.03	7.42 ± 0.03	<0.05	<0.001	<0.01
Pa,CO_2 mmHg	59.3 ± 7.5	55.2 ± 6.9	49.4 ± 7.8	<0.001	<0.001	<0.01
Pa,O_2 mmHg	67.8 ± 7.1	65.8 ± 11.9	71.6 ± 19.1	NS	NS	NS
HCO_3^- mmol·L^{-1}	30.8 ± 2.9	30.7 ± 2.2	30.7 ± 2.4	NS	NS	NS
BE mmol·L^{-1}	8.3 ± 3.1	8.0 ± 2.7	7.6 ± 2.9	NS	NS	NS
FI,O_2 %	24.2 ± 2.5	24.3 ± 2.6	24.3 ± 2.7	NS	NS	NS

Data are presented as mean ± SD, unless otherwise stated. SB: spontaneous breathing; Li: low-intensity; NPPV: noninvasive positive pressure ventilation; Hi: high-intensity; Pa,CO_2: arterial carbon dioxide tension; Pa,O_2: arterial oxygen tension; BE: base excess; FI,O_2: inspiratory oxygen fraction; NS: nonsignificant.

TABLE 5	Mean values of main cardiovascular parameters and oxygen transport					
Parameter	SB	Li-NPPV	Hi-NPPV	p-value		
				SB *versus* Li-NPPV	SB *versus* Hi-NPPV	Li-NPPV *versus* Hi-NPPV
SAP mmHg	126 ± 22	118 ± 20	112 ± 21	<0.05	<0.01	NS
DAP mmHg	71 ± 7.7	69 ± 7.8	70 ± 8.2	NS	NS	NS
MAP mmHg	91 ± 11	87 ± 12	85 ± 12	NS	<0.05	NS
fC beats·min^{-1}	82 ± 15	81 ± 15	82 ± 14	NS	NS	NS
SV mL	70 ± 19.7	59 ± 16.5	51 ± 16.4	<0.001	<0.001	<0.001
CO L·min^{-1}	5.5 ± 1.14	4.7 ± 0.98	4.0 ± 0.96	<0.001	<0.001	<0.001
CO %[#]	100 ± 0.0	84.4 ± 6.5	72.5 ± 7.6	<0.001	<0.001	<0.001
CI L·min^{-1}·m^{-2}	3.23 ± 0.7	2.74 ± 0.6	2.33 ± 0.56	<0.001	<0.001	<0.001
SO$_2$ % baseline	92.6 ± 1.9	91.7 ± 4.5	93.4 ± 4.5	NS	NS	NS
DO$_2$ mL·min^{-1}	894 ± 176	740 ± 150	656 ± 166	<0.001	<0.001	<0.01
DO$_2$/m² mL·min^{-1}·m^{-2}	577 ± 110	462 ± 93	409 ± 104	<0.001	<0.001	<0.01

Data are presented as mean±SD, unless otherwise stated. SB: spontaneous breathing; Li: low-intensity; NPPV: noninvasive positive pressure ventilation; Hi: high-intensity; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; MAP: mean arterial pressure; fC: cardiac frequency; SV: stroke volume; CO: cardiac output. CI: cardiac index; SO$_2$: oxygen saturation; DO$_2$: oxygen delivery capacity; DO$_2$/m²: DO$_2$ corrected for body surface area; NS: nonsignificant.

ventilation and, in COPD patients, LORX *et al.* [25] evaluated airway and tissue mechanics using a low-frequency oscillation technique and observed improved homogeneity of ventilation in peripheral airways during application of increasing PEEP. The higher VT (and V'E) and greater airway pressure achieved with Hi-NPPV are probably responsible for the greater reversal of hypoventilation than with Li-NPPV, despite the greater air leaks associated with the higher inspiratory pressures.

Dyspnoea score was significantly reduced compared with SB, similarly with both modes of NPPV. Indeed, the presence of IEs, an index of patient/ventilator asynchrony, was also similar and very low with both settings. However, few of our patients (*i.e.* three out of 15) could not tolerate an inspiratory pressure >25 cmH$_2$O, so that we had to stop our stepwise increases at that level.

In contrast WINDISCH *et al.* [6] have shown that Hi-NPPV may be even better tolerated on a long-term basis, but the experience from our study suggests that the pressures applied should be individually and carefully titrated based on the patient's compliance and may need to be gradually increased over a longer period of time. Thus, no ''fixed recipes'' should be implemented.

A chief aim of Hi-NPPV, at least according to the philosophy of the proponents of this technique, is to achieve total control of the patient's spontaneous respiratory activity, but this has never been assessed. In our study, we have shown a dramatic reduction of PTPdi during Hi-NPPV by almost 90% from SB and 70% from Li-NPPV, and nine out of 15 patients achieved nearly a complete resting of the diaphragm. The mechanisms by which such a decrease was mediated were related not only to the higher inspiratory support, but also to the decreased duty cycle and higher inspiratory flow observed with Hi-NPPV. Decreasing the patient's inspiratory time and increasing the inspiratory flow rate have previously been shown to reduce the effort of the diaphragm in COPD patients [26]. In view of this, it may be surprising that the reduction in

respiratory rate from baseline that we observed during Li-NPPV was relatively small compared with some other physiological studies [3]. However, it should be noted that in the latter physiological study, patients were experienced users already enrolled in a home mechanical ventilation programme, whereas our patients were naïve users.

We observed significant differences in cardiovascular performance between the various settings. As expected, both NPPV settings increased intrapleural and intrathoracic pressure and lung volume compared with SB, and these independently influence right atrial filling (or pre-load) and impedance to right ventricular emptying (or afterload), which are the key determinants of cardiovascular performance. SB or partially assisted modes of ventilation (*i.e.* Li-NPPV) maintain negative pleural and intrathoracic pressure, which is transmitted to the right atrium. In contrast, controlled mechanical ventilation (*i.e.* Hi-NPPV in most cases) leads to a positive swing in Ppl during inspiration and, therefore, a higher right atrial pressure, which leads to decreased venous return and, consequently, a decreased right atrial pre-load. Moreover, the elevated lung volume during Hi-NPPV may have increased pulmonary vascular resistance [8, 9].

Our noninvasively obtained haemodynamic findings are consistent with previous observations made by MARANGONI *et al.* [27] and AMBROSINO *et al.* [28]. In both of these studies, cardiac output was reduced during NPPV, especially when PEEP was also applied. Notably, these studies did not evaluate the cardiovascular effects of higher inspiratory positive airway pressure values, as utilised by us during Hi-NPPV. It is also important to note that, lacking indices of organ perfusion, the clinical consequences of the reduction in cardiac output that we observed are unknown and not necessarily adverse. Heart rate did not change and the decreases in MAP are of questionable clinical significance. In fact, it is conceivable that at least part of the reduction in CO reflects the lower metabolic demand that would be expected as respiratory muscles undergo complete rest.

In conclusion, we have shown that Hi-NPPV in stable COPD patients is more effective than Li-NPPV at acutely improving gas exchange and reducing the patient's respiratory effort. Since it acts in most instances as a true controlled ventilation, it induces a positive pleural swing during inspiration, lowering CO and other indices of cardiac performance. The clinical significance of this effect needs further evaluation, especially in patients with pre-existing cardiovascular disease. Also, our observations are relevant only to acute physiological effects of Hi-NPPV and the long-term effects on sleep architecture, respiratory mechanics, gas exchange and cardiac performance require further study.

STATEMENT OF INTEREST

Statements of interest for N. Hill and S. Nava can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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