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Physiological changes during low and high "intensity " noninvasive ventilation

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ABSTRACT

In a physiological randomized cross-over study, performed in stable hypercapnic COPD patients, we have assessed the short term effects of two settings of non-invasive ventilation, one aimed at maximally reducing $PaCO_2$ level (Hi-NPPV:27.6±2.1 cmH_2O of IPAP, 4±0 cmH_2O of EPAP and respiratory rate of 22/min) and one according to the usual parameters used in earlier studies (Li-NPPV:17.7±1.6 cmH_2O of IPAP, 4±0 cmH_2O of EPAP and respiratory rate of 12/min). Both modes of ventilation significantly improved gas exchange compared to spontaneous breathing (SB), but to a greater extent using Hi-NPPV (pCO_2:59.3±7.5, 55.2±6.9 and 49.4±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±149 cmH_2O*sec/min during SB to 132±139 cmH_2O*sec/min during Li-NPPV and 40±69 cmH_2O*sec/min during Hi-NPPV, while in 9/15 patients completely abolished spontaneous breathing activity. Hi-NPPV also induced a marked reduction in cardiac output measured noninvasively with a Finometer, compared to 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 cardiac output, which needs to be considered when Hi-NPPV is applied to patients with pre-existing cardiac disease.

INTRODUCTION

A recent systematic review on the use of long-term non-invasive ventilation (NIV) in stable hypercapnic chronic obstructive pulmonary disease (COPD) patients, was inconclusive since, despite improvement in lung hyperinflation, gas exchange and

diaphragmatic effort, no major long-term clinical advantages were observed in the randomized 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 cmH20, that is very close to the average values employed in most of the randomized long-term trials [3, 4].

Higher inspiratory pressures (28 cmH20) and respiratory rates (20 breaths/min) were recently adopted to ventilate chronic hypercapnic COPD patients in order to achieve the maximal $PaCO_2$ reduction. This type of approach, called high-intensity positive pressure mechanical ventilation (Hi-NPPV), has been shown to improve spontaneous diurnal blood gases more than the traditional lower pressures approach (Li-NPPV). A long-term randomized study will be necessary to determine the effect of Hi-NPPV on long term survival [5-7].

No data are available, however, to assess physiologic 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 [8, 9].

In this randomized cross-over study, we investigated the acute physiologic changes of Hi-NPPV vs 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 our Department of Respiratory Rehabilitation 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 hemodynamic stability. The patients' characteristics, including Pulmonary Function Tests and Arterial Blood Gases at the time of the study, are shown in Table 1. Enrollment criteria were the presence of chronic hypercapnic respiratory failure (i.e. pH>7.35, $PaCO_2 \geq 50$ mmHg), while exclusion criteria were the presence of cancer, neuromuscular disease or an Ejection Fraction (EF) recorded during an echocardiography study < 40% (the mean of EF in enrolled patients was 58.9%±11% SD) . 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 un our before beginning of each trial.

The patients were studied in a semi-recumbent 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 randomized trials, each with different ventilatory settings over 30 minutes, separated by a return to spontaneous breathing for 10 minutes. The randomization of the trials was obtained by a computerized program, developed "ad hoc", in order to evenly distribute the sequence. The patients were ventilated with a respirator with a dedicated "NIV platform" (*HARMONY* Philips, *VIVO-50* Breas, 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, and blinded to the protocol, to avoid any possible airleaks. 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 program. They were therefore familiarized with NIV in the preceeding few days, using our usual clinical protocol [3] aimed at reducing $PaCO_2$ > 10% while on ventilation ($PaCO_2$ at hospital admission during spontaneous breathing = 62.3±8.2 mmHg and 56.3±7.5 during the NIV adaptation trial), achieving an expired tidal volume of 6-8 ml/Kg and a reduction of transdiaphragmatic pressure (Pdi) by 50% of baseline during the measurement of respiratory mechanics. These settings were chosen by the attending clinician, unaware of the aim of the study. The mean inspiratory support was 17.7 ± 1.6 cmH_2O (range: 15-20 cmH_2O) with an external continuous positive airway pressure of 4 cmH_20 and a back-up rate of 12 breaths/min.

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 at 0,5 cm H_2O/min. This allowed us to reach mean inspiratory pressure values very close to those of Windisch et al (27.6±2,1 cmH_2O used in our study vs ~28 cmH20 used in previous studies)[5, 6], aiming at maximally decreasing $PaCO_2$ by stepwise increases in inspiratory pressure [5-7]. As with Li-NPPV the external PEEP level was fixed at 4 cmH_2O and respiratory rate

was set to match the spontaneous breathing rate, usually 20 to 22 breaths/min.

Measurements.

Arterial blood gases were obtained from a radial artery during spontaneous breathing and at the end of each ventilatory trial. Flow at the airway opening was measured with a heated pneumotachograph (Hans-Rudolf 3700, Kansas, USA) and a differential pressure transducer (Honeywell ± 300 cm H_2O; Freeport IL, USA) placed between the mask and the Y-piece of the ventilator. Tidal volume (VTi) was obtained by integration of the flow. Breathing pattern was measured from the flow signal. Expired tidal volume (VTexp) was used for data analysis. We also measured the difference between expired and inspired tidal volume to quantify the amount of air-leaks.

Airway pressure (Honeywell ± 300 cm H_2O; Freeport IL, USA) was measured from a side port between the pneumotachograph and the face mask.

Esophageal and gastric pressures (Honeywell ± 300 cm H_2O; Freeport IL, USA) were measured with an esophageal balloon positioned at the lower third of the esophagus, filled with 0.5 ml of air and a gastric balloon filled with 1 ml of air. The proper position of balloon was verified using the occlusion test. Transdiaphragmatic pressure (Pdi) was calculated as the difference between gastric (Pga) and esophageal (Pes) pressure.

Pressure time integrals of the diaphragm were calculated per breath (PTPdi/b) and per minute (PTPdi/min). $PEEPi_{,dyn}$ was obtained from Pdi signal, as the value of Pdi at the moment of zero flow [11, 12]. Ineffective Efforts (IE) were analyzed from the Pdi traces and expressed as percentage of total breaths measured.

We also measured cardiovascular parameters using a non-invasive device (Finometer pro, Finapres Medical System BV, Netherlands; www.finapres.com)[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 cardiac output 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 the following: systolic arterial pressure (SAP mmHg), diastolic arterial pressure (DAP mmHg), mean arterial pressure (MAP mmHg), heart rate (HR beat/min), stroke volume (SV ml) and cardiac output (CO l/min).

Dyspnea was assessed using the Borg' scale, with a range of zero to ten, 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 last 3 minutes of recordings were considered for analysis.

Statistical analysis

All signals were collected using a personal computer equipped with an A/D board, and stored at a sampling rate of 100 Hz. Results are presented as mean $\pm$ standard deviation (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 Graph pad Prism and Medcalc softwares. 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 of 15 patients were randomized to receive Li-NPPV as the first intervention.

Breathing pattern

As shown in Table 2, compared to baseline conditions, both Hi-NPPV and Li-NPPV significantly increased expired tidal volume and minute ventilation, 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 (Ti/Tot) lower, whereas no statistical difference was observed in breathing frequency.

Respiratory mechanics

Mean values of respiratory mechanics are illustrated in Table 3. Tidal Pdi, PTPdi/breath and PTPdi/min were significantly reduced compared to spontaneous breathing, but the decrease in all these parameters was significantly greater using Hi-NPPV vs Li-NPPV. Indeed, in 9/15 patients the Pdi trace was flat and the Ppl became even positive during Hi-NPPV, suggesting a "true" controlled ventilation (as illustrated in Figure 1). For this reason, data on PEEPi,dyn are not presented. Only two of the six patients with a measurable Pdi had ineffective efforts (IE), both during Li-NPPV (8.0±5.5% of the total breaths) and Hi-NPPV (1.2±2.8%). Lung resistance (RL) 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 shown in Table 4. Despite different ventilatory settings, pH and $PaCO_2$ improved significantly vs baseline conditions, the changes being significantly less pronounced using Li-NPPV.

Dyspnea score

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

Cardio-vascular parameters and oxygen transport

The mean values of main cardiovascular parameters and oxygen transport are presented in Table 5. Mechanical ventilation induced a significant decrease in systolic arterial pressure, but without any difference between Hi-NPPV and Li-NPPV. NPPV also reduced stoke volume, cardiac output, and cardiac index, statistically more pronounced with Hi-NPPV than Li-NPPV. Similar changes were observed in the calculated oxygen transport and the oxygen transport corrected by body surface area (DO_2/m^2). A statistically significant correlation was observed between the % changes from baseline cardiac output and absolute changes from baseline Ppl in the Hi-NPPV trial ($r=-0.68$, $p<0.01$**). We found similar correlations between changes from baseline Paw and % changes from baseline cardiac output during Hi-NPPV ($r= -0,59$; $p<0.05$*).

There were no relationships between baseline left ventricular ejection fractions and the

% changes from baseline of cardiac output .

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 hypothesized that ventilator pressures have been too low and developed a ventilatory technique called high intensity NIV (Hi-NPPV) aimed to maximally reduce $PaCO_2$ 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 (HRQL) [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 $PaCO_2$ compared to Li-NPPV, most likely related to a greater increase in expired tidal volume and minute ventilation. Hi-NPPV is also associated with a marked reduction in PTPdi, an index of diaphragm oxygen expenditure, and in Cardiac Output and Stroke Volume, that could limit the application of Hi-NPPV in patients with pre-existing cardiac disease.

Before proceding any further, we need to briefly discuss the main aim of Hi-NPPV, which is to maximally reduce the $PaCO_2$ level. Presently, it is unclear whether hypercapnia per se influences the survival of these patients [5, 18, 19]. On the other hand, potential adverse consequences of Hi-NPPV include diaphragm atrophy due to complete rest [20] as suggested by the near abolition of the Pdi 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 to normal subjects [21] and patients

using Hi-NPPV are still breathing spontaneously most of the time, which should minimize 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 couldn't calculate the amount of PEEPidyn using esophageal tracings. However, the high tidal volumes in the Hi-NPPV group combined with the increased expiratory time constant of COPD patients probably contributed to greater dynamic hyperinflation than with spontaneous breathing or Li-NPPV. Not only does this increase the risk of barotrauma, but it might also have adverse cardiovascular consequences (see below).

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 (V_D) to tidal volume (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 (Va/Q) inhomogeneity [23]. NPPV helps to reverse this process by augmenting V_T and, potentially, reducing Va/Q mismatch via application of positive airway pressure. In an animal study, Neumann et al [24] found improvement of V/Q inhomogenity during CPAP ventilation and, in COPD patients, Lorx et al [25] evaluated airway and tissue mechanics using a low frequency oscillation technique and observed improved homogenity of ventilation in peripheral airways during application of increasing levels of PEEP. The higher V_T (and minute ventilation) 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.

Dyspnea score was significantly reduced compared to spontaneous breathing, similarly with both modes. Indeed, the presence of IE, an index of patient/ventilator asynchrony, was also similar and very low with both settings. However, few of our patients (i.e. 3/15) could not tolerate an inspiratory pressure >25 cmH_20, so that we had to stop our stepwise increases at that level.

In contrast Windisch et al have shown that Hi-NPPV may be even better tolerated on a long-term basis [6], but the experience from our study suggests that the pressures applied should be individually and careful titrated based on patient's compliance and may need to be gradually increased over a longer period of time. Thus no "fixed recepies" 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 was never assessed. In our study we have shown a dramatic reduction of PTPdi during Hi-NPPV by almost 90% from spontaneous breathing and 70% from Li-NPPV, and 9/15 patients achieved nearly a complete resting of the diaphragm. The mechanisms by which such a decrease was mediated were not only related to the higher inspiratory support, but also to the decreased duty cycle and higher inspiratory flow observed with Hi-NPPV. Decreasing the patient's Ti and increasing the inspiratory flow rate have previously been shown to reduce the diaphragm's effort 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 to some other physiologic studies [3]. However, it should be noted that in the latter physiologic study, patients were experienced users already enrolled in an home mechanical ventilation program whereas our patients were naive users.

We observed significant differences between the various settings in cardiovascular performance. As expected, both NPPV settings increased intrapleural and intrathoracic pressure and lung volume compared to SB and these independently influence right atrial filling (or preload), 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 of Ppl during inspiration and therefore a higher right atrial pressure (P_{RA}) which leads to decreased venous return and therefore a decreased right atrial preload**.** Moreover, the elevated lung volume during Hi-NPPV may have increased pulmonary vascular resistance [8, 9].

Our noninvasively obtained hemodynamic findings are in line 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. Of note, these studies did not evaluate the cardio-vascular effects of higher IPAP values as utilized 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 mean arterial pressure are of questionable clinical significance. In fact, it is conceivable that at least part of the reduction in cardiac output 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 cardiac output 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 physiologic effects of Hi-NPPV and the long-term effects on sleep architecture, respiratory mechanics, gas exchange and cardiac performance require further study.

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Fig. 1. Respiratory mechanical parameters during SB, Li-NPPV and Hi-NPPV in an characteristic subject.

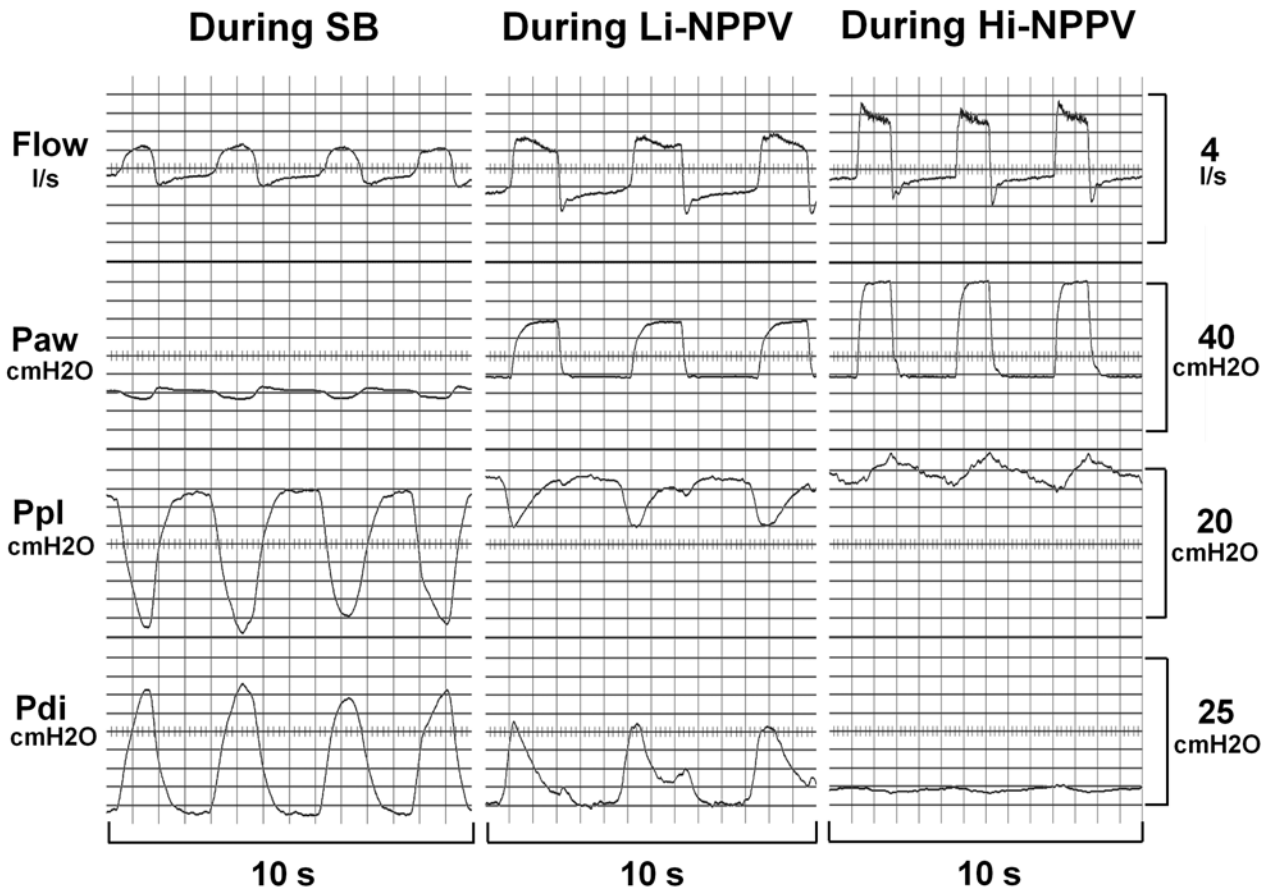

Table 1. Patients' characteristics including pulmonary function tests and arterial blood gases

Patient n	Age (year)	Sex (M/F)	BMI (kg/m2)	pH	pCO_2 (mmHg)	pO_2 (mmHg)	FEV1 (l) % predicted	FVC (l) % predicted	FEV1/ 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	N.A.	N.A.	N.A.
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	N.A.	N.A.	N.A.
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	**71.8**	**----**	**24.5**	**7.38**	**59.3**	**67.8**	**0.61 23.6%**	**1.68 53.8%**	**44.7**
SD	**± 7.8**	**----**	**± 5.7**	**± 0.03**	**± 7.5**	**± 7.1**	**± 0.15 ±8.11%**	**±0.56 ± 14.5%**	**± 23.13**
M: male; F: female; SD: standard deviation; N.A.: not available; BMI: body mass index									

Table 2. Breathing pattern

Parameter	SB	Li-NPPV	Hi-NPPV	Significance level		
				SB vs. Li-NPPV	SB vs. Hi-NPPV	Li-NPPV vs. Hi-NPPV
RR (breaths/ min)	24.8 ± 8.4	21.3 ± 6.3	22.9 ± 3.3	NS	NS	NS
Ti (s)	1.25 ± 0.3	1.1 ± 0.19	0.74 ± 0.1	NS	p<0.05	p<0.001
Te (s)	1.46 ± 0,75	1.98 ± 0,77	1.93 ± 0,34	NS	NS	NS
Ti/Ttot	0.48 ± 0.09	0.37 ± 0.08	0.27 ± 0.05	p<0.001	p<0.001	p<0.001
VT (l)	0.4 ± 0.1	0.56 ± 0.11	0.67 ± 0.13	p<0.001	p<0.001	p<0.001
VT/Ti (l/s)	0.33 ± 0.08	0.52 ± 0.11	0.93 ± 0.18	p<0.05	p<0.001	p<0.05
Ve (l/min)	9.6 ± 3.5	11.7 ± 2.3	15.2 ± 2.0	p<0.01	p<0.001	p<0.001
Air-leaks (l/min)		10.62±5.27	16.11±7.88	-	-	p<0.05

RR:respiratory rate, TI: inspiratory time; Ti/Ttot: duty cycle, VT: expired tidal volume; VT/Ti: mean inspiratory flow; Ve: minute ventilation; SB: spontaneous breathing; NS: not significant.

Table 3. Respiratory mechanics

Parameter	SB	Li-NPPV	Hi-NPPV	Significance level		
				SB vs. Li-NPPV	SB vs. Hi-NPPV	Li-NPPV vs. Hi-NPPV
Ppl (cmH_2O)	-15.1 ± 6.8	-6.73 ± 7.9	2.05 ± 7.52	p<0.001	p<0.001	p<0.001
Pdi (cmH_2O)	17.9 ± 8.1	9.09 ± 2.4	2.83 ± 4.6	p<0.001	p<0.001	p<0.01
PTPdi (cmH_2O*s)	14.9 ± 7.5	6.3 ± 5.9	1.6 ± 2.6	p<0.001	p<0.001	p<0.01
PTPdi /min (cmH_2O*s/min)	323 ± 149	132 ± 139	40 ± 69	p<0.001	p<0.001	p<0.01
Cldyn (l/cmH_2O)	0.02 ± 0.014	0.03 ± 0.007	0.03 ± 0.009	NS	NS	NS
RL (cmH_2O*s/l)	22.3 ± 14.6	11.0 ± 8.4	11.9 ± 9.7	p<0.01	p<0.05	NS

Ppl: pleural pressure; Pdi: tansdiafragmatic pressure; PTPpl: pleural pressure-time product ; PTPdi: diaphragmatic pressure-time product; Cldyn: dynamic compliance; RL: lung resistance; SB: spontaneous breathing; NS: not significant.

Table 4. Blood gas parameters

Parameter	SB	Li-NPPV	Hi-NPPV	Significance level

				SB vs. Li-NPPV	SB vs. Hi-NPPV	Li-NPPV vs. Hi-NPPV
pH	7.38 ±0.03	7.4 ± 0.03	7.42 ±0.03	p<0.05	p<0.001	p<0.01
$PaCO_2$ (mmHg)	59.3 ± 7.5	55.2 ± 6.9	49.4 ± 7.8	p<0.001	p<0.001	p<0.01
PaO_2 (mmHg)	67.8 ± 7.1	65.8 ±11.9	71.6 ±19.1	NS	NS	NS
HCO_3 (mmol/l)	30.8 ± 2.9	30.7 ± 2.2	30.7 ± 2.4	NS	NS	NS
BE (mmol/l)	8.3 ± 3.1	8.0 ± 2.7	7.6 ± 2.9	NS	NS	NS
FiO_2 (%)	24.2 ± 2.5	24.3±2.6	24.3±2.7	NS	NS	NS
SB: spontaneous breathing; NS: not significant						

Table 5. The mean values of main cardio-vascular parameters and oxygen transport

Parameter	SB	Li-NPPV	Hi-NPPV	Significance level		
				SB vs Li-NPPV	SB vs Hi-NPPV	Li-NPPV vs Hi-NPPV
SAP (mmHg)	126 ± 22	118 ± 20	112 ± 21	p<0.05	p<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	p<0.05	NS
HR (beat/min)	82 ± 15	81 ± 15	82 ± 14	NS	NS	NS
SV (ml)	70 ± 19.7	59 ± 16.5	51 ± 16.4	p<0.001	p<0.001	p<0.001
CO (l/min)	5.5 ± 1.14	4.7 ± 0.98	4.0 ± 0.96	p<0.001	p<0.001	p<0.001
CO %	100 ± 0.0	84.4 ± 6.5	72.5 ± 7.6	p<0.001	p<0.001	p<0.001
CI ($l/min/m^2$)	3.23 ± 0.7	2.74 ± 0.6	2.33 ± 0.56	p<0.001	p<0.001	p<0.001
SO_2 %	92.6 ± 1.9	91.7 ± 4.5	93.4 ± 4.5	NS	NS	NS
DO_2 (ml/min)	894 ± 176	740 ± 150	656 ± 166	p<0.001	p<0.001	p<0.01
DO_2/m_2 ($ml/min/m^2$)	577 ± 110	462 ± 93	409 ± 104	p<0.001	p<0.001	p<0.01
SAP: systolic arterial pressure; DAP: diastolic arterial pressure; MAP: mean arterial pressure; HR: heart rate; SV: stroke volume; CO: cardiac output.; CO% = CO*100/CObaseline; CI: cardiac index; DO_2 : oxygen transport; SB: spontaneous breathing; NS: not significant.						