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Non-invasive modalities of positive pressure ventilation improve the outcome of acute exacerbations in COLD patients

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Abstract. *Objective:* 1) To compare the clinical usefulness of both non-invasive pressure support ventilation (NPSV) and non-invasive intermittent positive pressure ventilation in assist-control (A/C) mode (NIPPV) in chronic obstructive lung disease (COLD) patients with acute hypercapnic respiratory failure: 2) to compare retrospectively the usefulness of non-invasive mechanical ventilation (NMV) with standard medical therapy alone.
Design: Prospective randomized retrospective study.
Setting: 2 Respiratory intermediate intensive units.
Patients: 29 COLD patients (age: 62±8 years) with chronic respiratory failure were hospitalized in a department for rehabilitation during acute relapses of their disease. They were transferred to our intermediate intensive care unit (IICU) and submitted randomly to either NPSV (16 patients) or NIPPV (13 patients).
Measurements and results: Blood gas analysis, dynamic flows, clinical variables, success rate, time of ventilation, side effects and subjective score of compliance to therapy. Therapy was considered successful when endotracheal intubation was avoided and patients were returned to their condition prior to exacerbation. No statistically significant difference was found between NPSV and NIPPV in success rate (NPSV 87.5%; NIPPV 77%) or in time of ventilation (NPSV: 69±49; NIPPV: 57±49 h). A better compliance to non-invasive mechanical ventilation (NMV) was found in NPSV patients than in NIPPV patients; side effects were observed less frequently in the NPSV group. Comparison of the success rate of NMV was retrospectively performed with 35 control COLD patients with chronic respiratory insufficiency who had undergone an acute relapse of their disease in the 2 years preceding the institution of the IICU and had been treated with oxygen and medical therapy alone. Patients submitted to NMV showed a greater success rate than control (82 versus 54%) after a period of ventilation ranging from 4–216 h.
Conclusion: Non-invasive mechanical ventilation performed either by NPSV or NIPPV may improve the outcome of acute exacerbations of COLD, as compared to medical therapy alone. NPSV seems to be more acceptable to patients in comparison with NIPPV.

Key words: Acute respiratory failure – Mechanical ventilation – Intermediate intensive care unit

Patients with chronic obstructive lung disease (COLD) may suffer from acute exacerbations of their disease as shown by a worsening of their clinical status and blood gases. Acute exacerbations of COLD may lead to acute respiratory failure (ARF) often necessitating endotracheal intubation and mechanical ventilation (MV). Up to 2 years ago these patients were treated in our institution with medical therapy and possibly transferred to an ICU in another hospital for endotracheal intubation. The recent institution in our department of an intermediate intensive care unit (IICU) allowed us to treat patients with non-invasive mechanical ventilation (NMV).

Non-invasive intermittent positive pressure ventilation (NIPPV), and pressure support ventilation (NPSV) have been used in patients requiring endotracheal intubation and in relatively less severe patients [1–6]. To our knowledge no study has been performed to compare these two forms of NMV in treatment of ARF.

The aim of this study was therefore 1) to compare the clinical usefulness of both NIPPV and NPSV in COLD patients during an acute hypercapnic respiratory failure and 2) to compare retrospectively the usefulness of NMV to standard medical therapy alone.

Methods

Patients

COLD patients ($n = 29$; 18 male) defined according ATS criteria [7], with chronic respiratory insufficiency, and usually followed in our institution, were studied. Demographic and functional characteristics of the patients when in stable state are shown in Table 1. They were all hypoxemic and hypercapnic on long term oxygen therapy. In our pulmonary rehabilitation department they had undergone acute relapses of their

Table 1. Demographic and last functional characteristics of population in study in stable state before exacerbation

	Age (years)	FVC (ml)	FEV_1 (ml)	FEV_1/FVC (%)	pH*	PaO_2* (mmHg)	$PaCO_2$* (mmHg)
Ventilated ($n = 29$)	62 ± 10	1436 ± 650	706 ± 250	49 ± 10	7.36 ± 0.02	49 ± 6	55 ± 4
Control ($n = 35$)	61 ± 7	1550 ± 710	820 ± 302	52 ± 12	7.36 ± 0.01	51 ± 7	53 ± 6
	NS	NS	NS	NS	NS	NS	NS

* Data recorded on air in spontaneous breathing

disease and were transferred to our IICU where they were randomly submitted either to NPSV (16 patients) or to NIPPV in A/C mode (13 patients). NMV was instituted when patients met the following criteria: rapid deterioration in neurological status (Glasgow Coma Scale ≤ 9) [8], acute onset of severe hypercapnia ($PaCO_2 > 65$ mmHg), acute decrease in values of pH (< 7.35) [4], tachypnoea and/or abdominal paradox. Ventilation was added to standard IV medical therapy (aminophylline, steroids, and β2 agonists) and to O_2 therapy.

All patients were submitted to NMV using a pressure triggered ventilator (EVITA Drager Moislinger Allee Lubeck, Germany) by means of a tightly fitted face mask (Crystalcone, Harol, UK).

The ventilatory settings were: 1) NPSV – the maximal tolerated inspiratory pressure support able to achieve an expiratory tidal volume (V_T) > 8 ml/kg (this values ranged from 14–22 cmH_2O with a positive end expiratory pressure (PEEP) of 5 cmH_2O. The initial setting of inspiratory flow rate was 60 l/min and it was decreased if the patient did not tolerate it (not less than 40 l/min). All patients, at the start of ventilation, received the faster flow profile curve (with a short inspiratory flow time) to improve maximal patient comfort. If the ventilation time was prolonged the flow profile curve was decreased with a longer inspiratory flow time to decrease the peak pressure.
2) NIPPV in A/C mode – a V_T of 12 ml/kg, a respiratory frequency (RR) of 15, a PEEP of 5 cmH_2O, a trigger level of minus 0.5 cmH_2O, a pressure limitation of 40 cmH_2O and I/E ratio of 1/3. For all patients a supplementary oxygen was added to mix with the ventilator inspiratory flow in order to achieve a $SaO_2 > 90\%$. Good supervision performed by physicians, physiotherapists and nurses was mandatory during the study [9].

Nursing workload was particularly concentrated towards correct choice of size and type of mask, good position and fitting maintenance of the mask, clinical and monitoring evidence of deterioration in cardiorespiratory function, control during ventilation intervals required to expectorate, drink or rest, observation of side effects and a frequent change of patients' posture.

NMV was prescribed continuously; nevertheless, when patients had to expectorate, drink or rest, ventilation was stopped for 15–30 min. Anaesthetic and sedative prescription was avoided during ventilation. NMV was definitively withdrawn when patients:
1) reached levels of pH > 7.35 in spontaneous breathing without further neurological worsening for at least 24 h (successful therapy)
2) needed endotracheal intubation (unsuccessful therapy).
The causes of relapse and the Apache II score [10] were recorded for all patients prior to the beginning of the study.

Historical group

The success rate of the therapy in all COLD patients with chronic respiratory failure ($n = 25$; 26 male) who had undergone severe acute relapses during the 2 years before IICU institution in our hospital and had only been treated with medical therapy, was compared retrospectively to the outcome of 29 ventilated patients. Historical and ventilated groups were compared for diagnosis, age, weight, blood gas analysis, Apache score and neurological status as assessed by the clinical report.

Measurements

In patients submitted to NMV pH, $PaCO_2$, PaO_2/FIO_2 and bicarbonate, were obtained by means of arterial radial puncture during spontaneous breathing on oxygen prior to the beginning of ventilation (baseline); respiratory rate (RR) and heart rate (HR) were recorded at the same time by means of a monitor system (Kolormon-Kontron Instruments-Watford UK). Intermediate measurements were performed either during NMV or in spontaneous breathing according to the actual patient's requirement in the interval 2–4 h, 6–8 h, at 12, 24, 48, 72 and 96 h. The same measurements were also performed after withdrawal from MV for at least 48 h (follow up).

In 10 of the 29 ventilated patients dynamic lung volumes could be assessed at the bedside at the same times (Pocket monitor Micro Medical Instruments, Kent UK), when clinical conditions permitted. The time of withdrawal of ventilation, the patient's subjective compliance to ventilation by means of an arbitrary score (1 = bad; 2 = quite bad; 3 = sufficient; 4 = good; 5 = very good) and side effects were also recorded.

For 35 control patients baseline blood gas analysis was obtained and only in 25 were dynamic lung volumes also measured.

Statistical analysis

Baseline data of NPSV, NIPPV and control group were compared using an unpaired *t*-test; they were also compared for success rate in time using a Mantel-Cox test.

In ventilated groups pre-ventilation measurements (Baseline: T0) were compared to data obtained at the time of withdrawal (T1) and between T1 and the last value collected (T2) by using analysis of variance (ANOVA). The differences between the average compliance score versus ventilation was tested using an unpaired *t*-test.

The data of side effects during the two different ventilation modalities were tested with a chi-square Fisher test. Significance was taken at $p < 0.05$. The study was approved by the local ethical committee and by the ethical committee of the Clinica del Lavoro Foundation Pavia.

Results

The diagnosis of the 29 ventilated patients at the moment of IICU admission was mostly infectious relapse (20 patients), pneumonia (7 patients) and pulmonary embolism (2 patients).

Baseline functional and clinical characteristics for ventilated and control groups are shown in Table 2. There were no significant differences in age, weight, PaO_2/FIO_2 and Apache score at baseline between the ventilated and control groups; the ventilated group showed worse values in $PaCO_2$, in pH levels and severity of airway obstruction. The successful rate of the 2 different ventilation modalities showed the following: NPSV = 87.5% and NIPPV = 77%.

Of the 16 NPSV patients 2 (12.5%) and 3 (23%) of the 13 NIPPV patients needed endotracheal intubation after an average time of ventilation of 84 ± 10 h for NPSV and 74 ± 9 h for NIPPV group. There were 2 (67 and 69 years respectively) of these 5 patients who showed a pulmonary embolism diagnosed by a lung scan which complicated the COLD and caused their death in our hospital; 2 patients (70 and 75 years) died despite endotracheal

Table 2. Ventilated and control patients characteristics at the beginning of the study

	Control ($n = 35$)		Ventilated ($n = 29$)		
			Total	NPSV ($n = 16$)	NIPPV ($n = 13$)
Weights (kg)	60 ± 12	NS	53 ± 9	54 ± 8	52 ± 10
pH	7.32 ± 0.02	$p < 0.003$	7.27 ± 0.07	7.29 ± 0.04	7.25 ± 0.11
$PaCO_2$ (mmHg)	69 ± 9	$p < 0.001$	83 ± 20	76 ± 11	92 ± 27
PaO_2/FIO_2	1.94 ± 0.49	NS	1.89 ± 0.65	1.89 ± 0.71	1.88 ± 0.62
Respiratory rate (a/min)	30 ± 9	NS	33 ± 8	33 ± 7	32 ± 10
Heart rate (b/min)	115 ± 16	NS	119 ± 19	119 ± 20	118 ± 19
APACHE II score	20 ± 8	NS	21 ± 6	19 ± 6	23 ± 7
FEV_1 (ml)	672 ± 255	$p < 0.001$	387 ± 140	364 ± 127	482 ± 209
FVC (ml)	1390 ± 640	$p < 0.003$	1053 ± 470	890 ± 326	1704 ± 409

Data recorded in spontaneous breathing

intubation and invasive ventilation performed in another ICU to where they had been transferred from our department; only 1 patient (52 years) was successfully discharged from an ICU located near our hospital after having performed tracheotomy.

Figure 1 shows changes over time in the number of the ventilated patients in the two groups. Successful patients of NPSV group were ventilated with an average time of 69 ± 49 h (range 6 – 216 h) without any statistical difference in comparison with the successful NIPPV group: 57 ± 49 h (range 4 – 144 h).

The mean number of hours of ventilation per day for each single patient decreased from 16 ± 3 on the first day to 10 ± 4 on the second day. At the same time nurse workload appeared concentrated in the first day of ventilation; it decreased simultaneously with patient co-operation improvement.

Patients who were successfully ventilated with both modalities showed significant changes between baseline and withdrawal data for pH (7.29 ± 0.03 to 7.35 ± 0.02 and 7.25 ± 0.09 to 7.40 ± 0.04 for NPSV and NIPPV respectively), $PaCO_2$ (77 ± 11 to 61 ± 5 mmHg and 87 ± 20 to 57 ± 10 mmHg for NPSV and NIPPV respectively), PaO_2/FIO_2 (1.95 ± 0.69 to 2.41 ± 0.62 and 1.65 ± 0.36 to 2.23 ± 0.46 for NPSV and NIPPV respectively) respiratory frequency and heart rate (Fig. 2). The majority of patients showed a rapid disappearance of dyspnea, tachycardia and neurological symptoms from the first hours of ventilation. Figure 2 shows the effect was also maintained after withdrawal of ventilation; in fact all successful patients remained oriented and alert.

The patients of two groups able to perform spirometry showd the same positive trend in time for FEV_1 (335 ± 114 to 710 ± 205 ml/s for NPSV and 315 ± 134 to 677 ± 210 ml/s for NIPPV, $p < 0.001$) and FVC (693 ± 340 to 1370 ± 617 ml for NPSV and 769 ± 543 to 1326 ± 603 ml for NIPPV, $p < 0.001$).

The average compliance score versus ventilation was 4 ± 0.8 for NPSV group and 3 ± 1 for NIPPV group ($p < 0.02$). In NPSV group, 4 out of 16 patients showd a very good (score 5) compliance in comparison with NIPPV group in which only 1 out of 13 did.

Table 3 shows side effects recorded during ventilation time for the two groups; the number of patients who presented side effects was higher in NIPPV group in comparison with NPSV group ($p < 0.01$). No such effects were so severe as to discontinue ventilation. All succesfully ventilated patients were thereafter discharged in stable conditions.

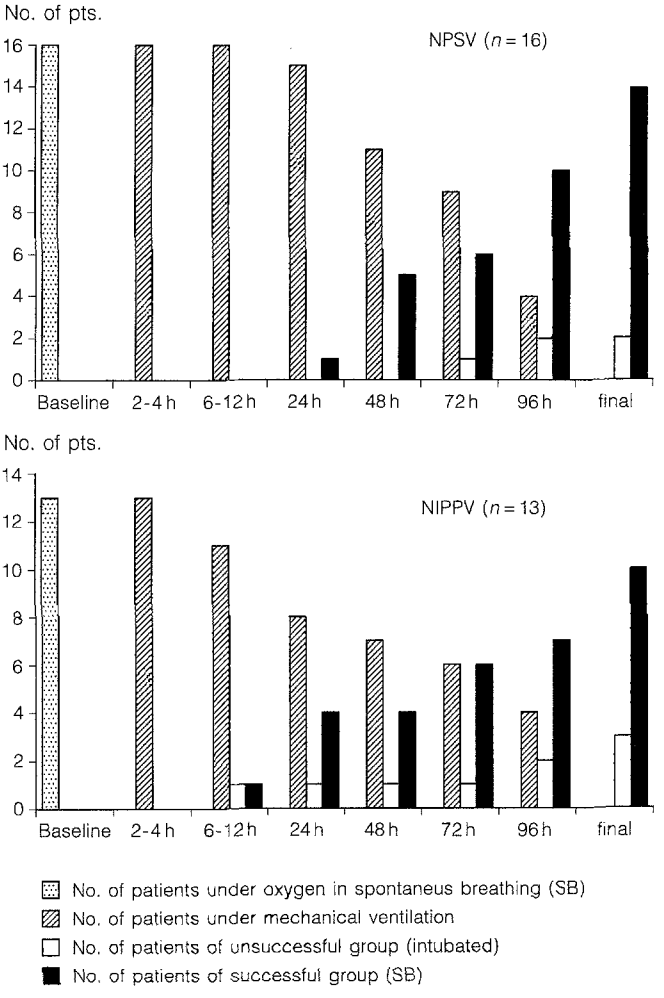

Fig. 1. Changes over time in the number of the ventilated patients

The 35 historical controls presented ARF due to episodes of infectious relapse in 23 and to pneumonia in 12

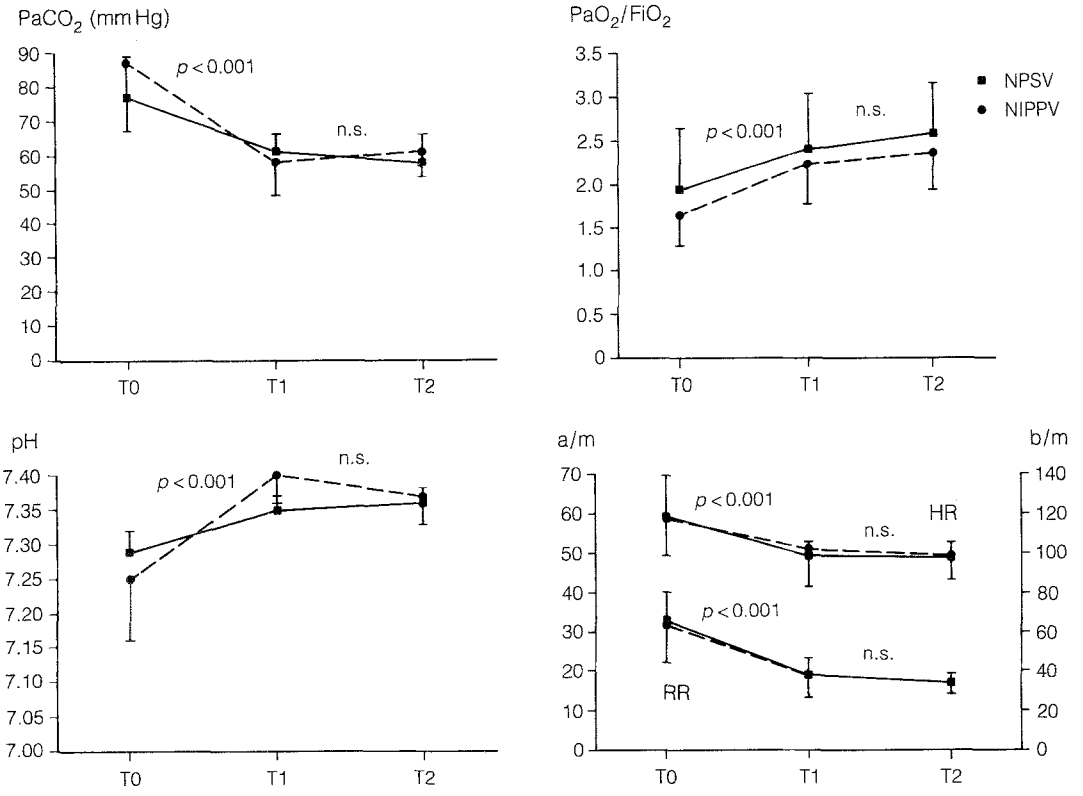

Fig. 2. Changes in physiological variables over time. For abbreviations see the text

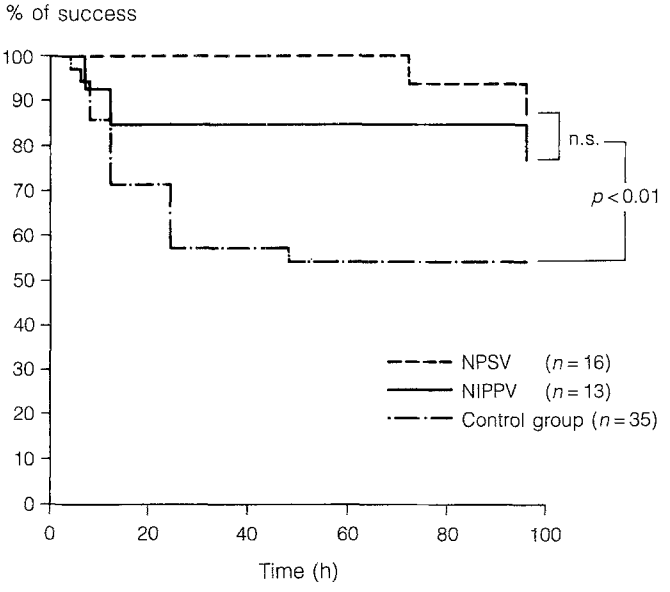

Fig. 3. Success rate of the two ventilation methods in comparison with medical approach

patients; they had been treated in our rehabilitation department with the same standard medical therapy (drugs and oxygen); 16 of them (46%) needed endotracheal intubation and ICU admission after an average time of medical treatment of 16±11 h.

Significant differences in success were found between the total group of ventilated patients (82%) and control group (54%) ($p<0.01$, Fig. 3).

Discussion

This prospective randomized study shows that both NPSV and NIPPV may improve the outcome of exacerbations; better compliance versus NPSV rather than NIPPV was found.

This study also shows in a retrospective way that noninvasive mechanical ventilation added to standard medical therapy is more effective than medical therapy alone in avoiding endotracheal intubation during episodes of ARF in COLD patients with chronic respiratory insufficiency. The effects of positive pressure ventilation via nasal or facial mask have been studied in clinical trials on patients with ARF of different etiologies [1–6].

To our knowledge our study is the first to compare the effectiveness of NPSV and NIPPV in ARF due to COLD. No difference in success rate, time of ventilation and ventilation induced changes in blood gases, respiratory frequency and HR was found. The NPSV group tolerated

Table 3. Number of patients who presented side effects during ventilation ($n = 29$)

	NPSV ($n = 16$)	NIPPV ($n = 13$) ($p<0.01$)
Nose abrasion	2	4
Nose pain	1	1
Gastric distension		1
Bad sleeping		2
Mask leakage		1
Claustrophobia		1
Rhinitis	1	

ventilation better than NIPPV one as demonstrated by the better compliance score and fewer side effects recorded in the assisted ventilation group. The hypothetical explanation of these last results could be that NPSV is an assisted mode of ventilation supplying at set level of positive airway pressure during spontaneous inspiratory efforts. NPSV can either totally or partially unload ventilatory muscles during spontaneous breathing [11–12]. Total unloading occurs when the only effort made by the patient is to trigger the breath. Those authors also demonstrated that NPSV reduced both the effort of breathing and the oxygen cost. Respiratory frequency is reduced and tidal volume increased.

NIPPV in control mode is also able to reduce phasic electromyographic activity of the diaphragm in patients with COLD [13]. On the other hand when NIPPV rate is allowed to be determined by patient triggering (A/C mode as in our patients) with a set backup rate, it has been demonstrated that inspiratory muscles continue to perform work even after the ventilator has been triggered [14].

Some authors believe these techniques to be not easy, time consuming for nurses, requiring some expertise and reasonable co-operation on the part of the patients [9]. Other papers reported improvements in ventilatory function which obviated, in some cases, the need for conventional mechanical ventilation with its side effects [15]. In our study 24 out of 29 studied patients were successfully treated with noninvasive ventilation (82%); Pennock, using NPSV by a simplified ventilator, reported a 76% success rate in 31 consecutive patients with ARF of various etiologies, support lasting from 2 h to 6 days [2]. The natural history of COLD patients treated by Brochard et al. [5] were more similar to ours. These authors compared NPSV to historical intubated patients and found that after two to eight days patients submitted to NPSV had a success rate of 92%. Meduri et al. [4] used NPSV for 2 h to 4 days with a sucess rate of 67%. Our COLD patients were treated with NPSV from 6 h to 9 days and showed a success rate of 87.5% rather similar to other authors' experience. Our patients were ventilated by means of NIPPV from 4 h to 6 days and showed a success rate of 77% similar to that reported by Marino [6] and Benhamou [16]; they presented a success rate in NIPPV group of 69% and 60% respectively with a time of ventilation ranging from 1–3 days and from 2 h to 60 days respectively.

We had previously [3] treated NIPPV patients with acute exacerbations of COLD not needing endotracheal intubation and found that NIPPV was not more effective than standard medical therapy alone. The differences between the two studies could be ascribed mainly to patient selection. In the former study patients showing neurological signs of requiring mechanical ventilation were excluded, while in the present study patients were selected on the basis of necessity of mechanical ventilation. A second reason, still to be demonstrated, is the fact that the patients of our previous study were submitted to mechanical ventilation through a nasal mask while in the present study ventilation was applied by a face mask. Meduri and Brochard used face masks, while Pennock, Marino and Benhamou used nasal maks; differences and relative usefulness of nasal and facial masks are still debated [17].

Although we did not measured the actual intrinsic PEEP, we added positive end expiratory pressure to both modalities of ventilation: it has been shown in COLD patients, during both controlled [18] and assisted [19–29] invasive mechanical ventilation that extrinsic PEEP may counterbalance the intrinsic PEEP these patients commonly suffer from [21–22].

The control group of our study was retrospective and this is an important limitation. The two groups were not perfectly matched as regarding pH and $PaCO_2$ which were more compromised in the ventilated groups. This could introduce a bias in the evaluation of results, but this bias should have favoured the control group which indeed had a worse outcome.

On the other hand this could not be necessarily a negative factor, as it permitted us to compare our treatment schedules in two different periods of time; the present is characterized by the availability in our hospital of an IICU to perform non-invasive techniques of ventilation [23–24]. The availability of an IICU, adding facilities in monitoring patients, may further improve the effectiveness of these techniques.

In our study non-invasive MV resulted as more effective than oxygen and medical therapy alone in avoiding endotracheal intubation. In previous studies on patients with COLD and ARF, medical therapy resulted in mortality ranging from 6–34% and in the use of assisted ventilation ranging from 3–65%. Comparison of these papers is difficult due to differences in the selection of patients, medical therapy and degree of monitoring applied [25–29].

Nose abrasion was the most frequent side effect reported in other papers [3, 4, 6]; we confirmed this event in our patients, too. Gastric distension was observed only in one patient of NIPPV group. The main side effects we reported were skin abrasion on the nose or pain caused by the straps which hold the mask. Our results showed that no invasive ventilation approach seemed to increase conventional nurse workload (NW) performed during invasive ventilation (endotracheal and tracheotomy tube) confirming what found by Chevrolet [9]. Nevertheless in our opinion the increased NW appeared concentrated in the first or second day avoiding the prolonged NW during ventilation and weaning requested by the endotracheal intubation.

This study offers an indication on the usefulness of an IICU in a respiratory department. The retrospective comparison between the two periods in our department (pre- and post-IICU institution) demonstrates that the need for endotracheal intubation and admission to an ICU was reduced by almost three times. The non-invasive ventilation techniques could be considered, in selected patients, as a concrete possibility to buy time before aggressive ventilation is performed with endotracheal intubation.

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