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Noninvasive mechanical ventilation improves the immediate and long-term outcome of COPD patients with acute respiratory failure

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Noninvasive mechanical ventilation improves the immediate and long-term outcome of COPD patients with acute respiratory failure. M. Confalonieri, P. Parigi, A. Scartabellati, S. Aiolfi, S. Scorsetti, S. Nava, L. Gandola. ©ERS Journals Ltd 1996.

ABSTRACT: Noninvasive positive pressure ventilation (NPPV) has been proposed in COPD patients with acute on chronic respiratory failure (ACRF) in order to avoid endotracheal intubation and to improve immediate outcome, but long-term outcome of this therapeutic approach is still undefined.

We evaluated short- and long-term (1 year) outcome of early administration of NPPV in 24 patients with ACRF due to exacerbated COPD (Group A) in comparison with 24 matched historical-control patients treated conventionally (Group B). Patients of Group A were initially treated with NPPV *via* nasal mask in the presence of pH≤7.32, and/or P_{a,O_2}<7.98 kPa, and/or P_{a,CO_2}>7.18 kPa, plus signs of respiratory distress.

In-hospital survival rate was not significantly different in Group A *vs* Group B, but the patients treated with NPPV showed an earlier improvement in blood gases and a better pH and respiratory rate at discharge. Only 2 patients of Group A needed endotracheal intubation as compared with 9 of Group B. Hospital stay was significantly reduced in survivors of Group A *vs* Group B. Further severe relapses of ACRF in Group A were treated using NPPV. The number and length of further hospitalizations for pulmonary exacerbations were significantly higher in Group B compared with Group A. The survival rate at 12 months was significantly lower in Group B than in Group A (50% *vs* 71%).

In conclusion, NPPV administration in patients with ACRF due to exacerbated COPD improves not only immediate but also long-term outcome.

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Patients with severe chronic obstructive pulmonary disease (COPD), especially those who have chronic respiratory failure, are vulnerable to a wide range of insults that lead to acute respiratory distress (acute on chronic respiratory failure - ACRF) that requires hospital admission and often mechanical ventilation [1]. Conventional treatment of this common condition includes oxygen supplementation, drugs, removal of secretions and, when necessary, mechanical ventilation. Even if conventional treatment is rapidly undertaken, patients often require prolonged hospitalization with poor prognosis when mechanical ventilation is not provided [2, 3].

Noninvasive positive pressure ventilation (NPPV) has recently been tested in COPD patients in order to avoid endotracheal intubation, but it is still difficult to define its success in patients with acute respiratory failure [4, 5]. The majority of the studies dealing with NPPV in exacerbations of COPD were not controlled [5]; in fact, only three studies considered a control group. VITACCA *et al.* [6] compared 29 COPD patients treated with NPPV with 35 nonmatched COPD patients treated conventionally. BROCHARD *et al.* [7] studied two strictly matched patient groups. The only randomized controlled study was performed by BOTT *et al.* [8], using a volume-cycled nasal intermittent positive pressure ventilation mode. All these studies focused on the immediate outcome. This was improved in NPPV-treated patients. To our knowledge, no study has evaluated the long-term outcome of COPD patients treated with NPPV *versus* conventional therapy.

We recently reported our initial and encouraging experience in 28 consecutive patients with severe exacerbation of COPD treated with nasal bi-level positive pressure ventilation (BiPAP®) without a control group [9]. The aim of the present study was to evaluate the clinical efficacy of the early administration of nasal BiPAP in COPD patients with acute on chronic respiratory failure (ACRF) compared with conventional therapy, with regard to immediate and long-term outcome (6 and 12 months). The study design and setting is a prospective case series with strictly historically matched controls followed in a noninvasive monitoring unit located in a Division of Respiratory Diseases.

Methods

We compared the short-term (in hospital) and long-term (12 months) outcomes in 24 nonconsecutive patients suffering from acute decompensated COPD receiving early administration of nasal BiPAP (Group A), with the outcomes of 24 historically matched control patients (Group B) receiving conventional therapy [10]. Pharmacological therapy did not differ in the two study groups (steroids, β_2-agonists, ipratopium bromide, theophylline, antibiotics, diuretics and cardiovascular drugs, when needed). Doxapram and other respiratory stimulants were not used. Oxygen was supplied with caution (beginning with fractional inspiratory oxygen (F_{I,O_2}) 24–28% and monitoring blood gases), and airway clearing was provided, when needed. Blood gases were measured in all patients on admission on breathing room air and with oxygen supplementation, and also after approximately 1 h, after 1 day of treatment, at discharge, and during follow-up 4–5 measurements·y^{-1}.

An endotracheal intubation was possible at any time, in case of worsening of the respiratory conditions. Criteria for endotracheal intubation were similar in the two groups. "Traditional criteria" used in the historically-matched control group were equally applied to the patients of the prospective study, namely: Glasgow Coma Score (GCS) <9; severe hypercapnia (>9.3 kPa); acute decreasing pH <7.30; signs of severe respiratory distress.

The study was approved by the local Ethics Committee. Patients' informed consent to noninvasive ventilation was obtained.

Patients

Twenty four patients (15 males and 9 females) admitted in the period 1993–1994 because of exacerbation of COPD with ACRF were treated with early administration of noninvasive BiPAP ventilation plus medical therapy (Group A). These patients were treated with BiPAP in presence of: arterial oxygen tension (P_{a,O_2}) <7.98 kPa (breathing room air); and/or arterial carbon dioxide tension (P_{a,CO_2}) >7.18 kPa and/or pH<7.33; and/or GCS <13; and/or respiratory rate >30 breaths·min^{-1} plus other signs of respiratory distress (abdominal paradoxical movements, Hoover's sign, alternating abdominal and rib cage breathing, hypertonic secondary respiratory muscles, tachypnoea/bradypnoea).

The control patients (n=24; 16 males and 8 females) were selected from a group of 72 patients (Group B). They were admitted in the two preceding years for the same diagnosis and conventionally treated (O_2 + drugs + mechanical ventilation by endotracheal intubation, if needed).

Criteria of matching

For each patient treated with BiPAP, a matching control patient was selected according to the following criteria: admission P_{a,CO_2} within 0.665 kPa of the value for the treated patient when that value was <9.31 kPa, and within 1.33 when the value was ≥9.31 kPa; arterial pH on admission within 0.03 of the value for the treated patient; prognostic score on admission (Acute Physiology And Chronic Health Evaluation (APACHE) II score) within three points; and age within 10 yrs of that of the treated patient.

Noninvasive ventilatory support

A compact bi-level positive airway pressure ventilator (BiPAP, Respironics Inc., Murraysville, PA, USA) was used to provide pressure support ventilation (PSV) and external positive end-expiratory pressure (PEEP) could be added [11]. The device has a very sensitive flow trigger and, unlike conventional ventilators, it tolerates leaks. Inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) could be set independently. BiPAP was used in spontaneous/timed (S/T) mode, which means in spontaneous breathing (as a PSV) with the possibility of passing to timed mode (controlled timed ventilation without patient triggering) in case the respiratory rate decreased below a preset value [12]. We did not use the standard BiPAP exhalation device (Whisper-Swivel ™; Respironics Inc., Murraysville, PA, USA) that has been shown to cause CO_2 rebreathing [13], but the single patient use circuit with a continuous flow exhalation port (Respironics). Ventilation was regularly delivered using a continuous positive airways pressure (CPAP) nasal mask (Contour; Respironics) for a minimum period of 22 h on the first day of treatment; thereafter, the time of noninvasive ventilation was gradually reduced down to about 10–12 h·day^{-1}, until a stable and satisfactory blood gas equilibrium was achieved. Nocturnal NPPV was then employed for a few more days, according to the discontinuation criteria shown in figure 1.

Nursing care and patient assistance

All the patients were admitted into a noninvasive respiratory monitoring unit located in our Division of Respiratory Diseases. The nasal mask was applied by nurses after having chosen the patient's proper mask size. Patients were encouraged to keep their mouths closed and, if needed, strappings aimed at closing the mouth were tested. A constant patient-caregiver interaction was pursued during the first period of nasal ventilation. For at least 30 min a physician stayed beside the patient and, during the following 3–4 h, the patient was watched every 5–10 min (if the mask ventilation was well-tolerated). Patients' assistance and observation during ventilation was performed by nurses with the supervision of pneumonologists. A physician was responsible for the initial setting of pressures delivered by the ventilator. To facilitate acceptance by the patient of the ventilatory support *via* mask, a relative was allowed to stay near the patient to assist and to provide psychological support in the first hours/days. In fact, in the first hours after admission, hypercapnic patients experience most difficulty in tolerating ventilation masks.

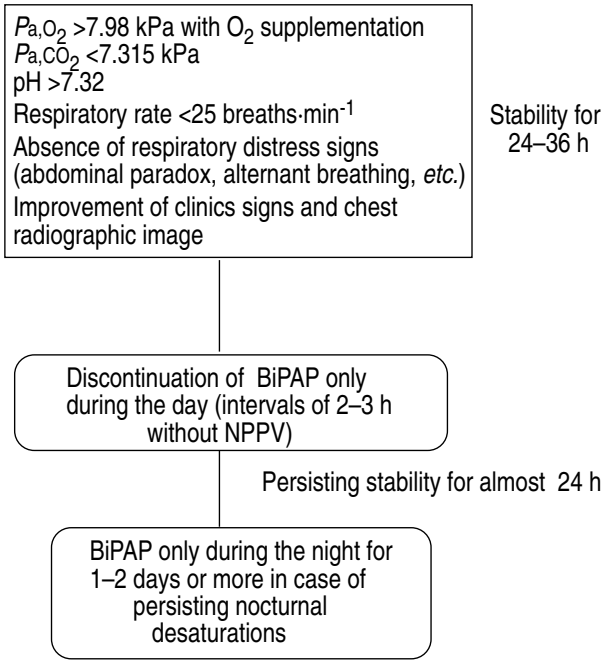

Fig. 1. – Criteria for discontinuation of noninvasive ventilation. P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; BiPAP: bi-level positive airway pressure; NPPV: noninvasive positive pressure ventilation.

Data recording

Immediate outcome. Evaluation of in-hospital mortality, occurrence of conventional mechanical ventilation by endotracheal intubation, need for tracheostomy, blood gas values and respiratory rate at discharge from hospital were recorded.

Duration of hospitalization (both in Intensive Care Unit (ICU) and pneumological ward). The discharge from the ICU in both groups of patients was decided by intensivists on the basis of respiratory autonomy from mechanical ventilation. Decision on the discharge from hospital was taken by pneumologists on the basis of achieving satisfactory clinical and blood gas stability. Clinical stability was defined as: 1) patient conscious and co-operative; 2) absence of hyperthermia; 3) stable haemodynamics (mean arterial blood pressure not varying by more than 10 mmHg in the preceding 3 days); 4) stable arterial blood gases when breathing room air and/or oxygen supplementation (not varying by more than 5% in the preceding 3 days).

Number and duration of further hospitalizations following 1 yr from baseline admission. Only admissions for respiratory exacerbations or directly related to the baseline admission were considered.

Out-patient follow-up. After hospital discharge, the study and control patients were routinely followed as outpatients by the same physicians working in the pneumological ward and, thus, medical management was not different in Group A and Group B.

Out-patient pneumological visit plus arterial blood gas analysis occurred during the first 20–30 days after hospitalization and was repeated 3–4 times·y^{-1}. Simple exacerbations without complications or ACRF were treated with antibiotics and/or oral steroids. This has been the standardized follow-up procedure in our department since 1988. During further hospitalizations, the therapy regimen did not change for the two groups of patients with the exception of the use of NPPV during some severe exacerbation episodes with ACRF affecting Group A patients (6 out of 14 episodes=43%).

Statistics

Baseline and follow-up data of noninvasively-ventilated patients and of controls were compared by analysis of variance (ANOVA) or Student's t-test and Mann-Whitney's nonparametric test. A comparison of in-hospital and long-term outcomes between the two groups of patients was made by a Chi-squared test with Yates' correction. The unpaired Student's t-test was carried out to evaluate group for group possible differences in hospitalization time in survivors. Comparisons between blood gas values on admission and at discharge in survivors were made by Student's paired t-test. Probability values less than 0.05 were considered significant. The Kaplan-Meier method was used to describe survival [14]. Differences in survival between groups were assessed using the log-rank test [15].

Results

Patients

Demographic and clinical characteristics of all the patients on admission are shown in tables 1 and 2. Patients treated with BiPAP and those treated conventionally matched perfectly, as shown in table 1.

The number of days during which BiPAP treatment was administered ranged 2–19, with a mean of 9.8±4 days. Mean IPAP was 15±2 cmH_2O (range 10–20) and mean EPAP was 4±0.8 cmH_2O (range 3–6).

Side-effects observed in patients treated with noninvasive ventilation are shown in table 3.

Immediate outcome

In-hospital survival rate was not significantly different in the treated *versus* the control group (88% *vs* 75%, p=0.477). Considering the avoidance of either death and endotracheal intubation as the most important treatment goal, the BiPAP treatment was successful in 20 patients (83%) compared with 13 patients (46%) of the conventionally treated group (p=0.035). Two of the conventionally treated patients were discharged with a tracheostomy.

Table 1. – Patients' data on admission (breathing room air) and short-term outcome (in hospital)

Pt No.	Age yrs	P_{a,O_2} kPa	P_{a,CO_2} kPa	pH	HCO_3^- mmol·L^{-1}	APACHE II	f_R br·min^{-1}	CGS	HR beats·min^{-1}	Hospital outcome
1A	73	5.719	9.976	7.34	40	21	52	12	100	Dead
1B	74	4.389	9.576	7.32	30	22	–	15	100	Success
2A	79	4.788	7.182	7.34	30	14	30	15	96	Success
2B	79	6.118	7.182	7.35	30	16	32	13	88	Dead
3A	66	5.719	10.108	7.28	36	25	32	11	60	Success
3B	58	6.517	9.044	7.28	32	25	48	10	110	Success
4A	66	3.857	9.044	7.27	29	14	12	13	92	Success
4B	73	4.389	9.044	7.27	32	17	40	12	100	Success
5A	71	4.921	9.709	7.29	36	19	46	15	76	Success
5B	73	4.522	9.443	7.31	34	20	40	13	96	Success
6A	67	4.788	8.645	7.30	34	21	38	12	95	Success
6B	67	5.320	7.980	7.30	29	21	–	13	88	Success
7A	66	5.852	7.448	7.35	24	20	34	15	95	Success
7B	66	4.788	7.980	7.33	32	21	–	15	100	Success
8A	75	5.054	9.709	7.29	36	20	40	13	100	Success
8B	75	5.985	10.64	7.26	38	19	20	15	120	Dead
9A	60	5.187	10.108	7.34	43	22	40	12	112	Success
9B	60	4.256	9.443	7.31	34	22	32	13	120	Success
10A	68	5.719	7.581	7.38	31	15	45	15	90	Success
10B	68	5.852	7.581	7.39	30	17	–	15	130	Success
11A	67	5.719	12.502	7.18	36	21	28	12	100	Success
11B	59	5.187	13.965	7.15	34	24	48	12	100	Success
12A	82	5.054	9.044	7.26	31	28	38	15	80	Success
12B	77	5.985	9.576	7.27	33	26	–	13	87	Success
13A	63	6.118	7.581	7.34	46	16	32	15	88	Success
13B	63	6.517	6.916	7.36	30	14	34	15	68	Success
14A	67	5.187	6.113	7.41	38	19	40	15	100	Success
14B	74	7.049	7.315	7.38	32	16	28	15	64	Success
15A	66	5.985	8.645	7.32	33	18	–	14	92	Success
15B	76	7.049	7.980	7.32	30	19	–	12	100	Success
16A	70	6.517	7.714	7.38	31	23	38	15	100	Success
16B	76	6.118	7.714	7.38	35	21	36	15	120	Dead
17A	60	6.251	7.581	7.41	36	15	28	15	100	Success
17B	64	5.586	7.980	7.43	39	15	32	15	80	Dead
18A	58	4.921	8.113	7.22	26	16	46	11	96	Success
18B	53	3.458	9.709	7.23	32	16	15	15	100	Success
19A	56	3.591	11.970	7.21	30	21	28	15	104	Dead
19B	67	5.719	10.640	7.19	30	22	28	12	84	Success
20A	72	5.985	7.714	7.22	22	17	46	15	98	Success
20B	73	6.650	8.379	7.22	26	14	32	14	100	Success
21A	74	7.448	9.576	7.14	24	26	48	15	120	Dead
21B	65	6.650	10.640	7.13	28	24	22	13	110	Dead
22A	65	7.182	10.640	7.23	37	23	44	13	100	Success
22B	66	6.118	10.374	7.24	37	22	24	13	115	Dead
23A	56	4.522	10.640	7.26	34	15	32	12	96	Success
23B	60	3.990	10.507	7.36	45	15	40	12	112	Success
24A	65	5.054	11.039	7.37	40	23	30	15	100	Success
24B	52	4.256	9.709	7.34	36	26	30	14	98	Success

The patients are numbered according to their historically-matched pairs; the letters A and B indicate their group. GCS: Glasgow Coma Score. br: breaths. P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; APACHE: Acute Physiology And Chronic Health Evaluation; f_R: respiratory rate; HR: heart rate;

Table 2. – Baseline patient values on admission

	Group A Added BiPAP	Group B Control	p-value
Age yrs	67±6	68±7	0.635
P_{a,O_2} kPa*	5.46±0.91	5.52±1.04	0.844
P_{a,CO_2} kPa*	9.18±1.49	9.11±1.58	0.884
pH*	7.29±0.07	7.29±0.07	0.921
HCO_3^-*	33.00±5.41	32.44±4.64	0.699
APACHE II score	19.67±3.91	19.17±3.99	0.663
f_R breaths·min^{-1}	36±8	31±7	0.090
Mean P_{sys} kPa	14.36±2.52	13.70±1.8	0.240
HR beats·min^{-1}	96±12	99±16	0.260
Last FEV_1 L†	1.03±0.49§	1.08±0.51‡	0.821
Last FVC L†	1.79±0.72§	1.83±0.60‡	0.915
Last FEV_1/FVC†	0.57±0.07§	0.59±0.06‡	0.259

Values are presented as mean±SD. *: breathing room air; †: clinical stability; §: assessed in 20 out of 24 patients; ‡: assessed in 18 out of 24 patients. BiPAP: bi-level positive airway pressure. P_{sys}: systemic blood pressure; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity. For further abbreviations see legend to table 1.

Only 2 (8%) out of the patients treated with nasal BiPAP needed mechanical ventilation by endotracheal tube, whereas 9 (38%) of the patients receiving conventional therapy underwent intubation and mechanical ventilation. Statistical analysis showed a significant difference (p=0.046) in the occurrence of endotracheal intubation between the groups. Two Group A patients and three Group B patients died after having been evaluated by the intensive care physicians and found to be ineligible for conventional mechanical ventilation because of their age and/or poor prognosis.

In-hospital survivors with both modalities of treatment showed statistically significant changes (p<0.001) between baseline and withdrawal data of blood gases (breathing room air) and respiratory rate at rest (fig. 2). It is notable that pH, P_{a,O_2} and P_{a,CO_2} improved earlier in BiPAP-treated patients than in controls (pH after 1 h (p<0.05) and after 24 h (p<0.03); P_{a,CO_2} after 1 and 24 h (p<0.001); P_{a,O_2} after 1 h (p<0.01), respiratory rate (f_R) after 1 and 24 h (p<0.001)). At discharge, a significant difference was still observed in pH and f_R (p<0.01 and p<0.001, respectively).

Duration of hospitalization

The mean duration of hospital assistance was 16±4 days (range 12–27 days) in the 21 Group A patients who had a favourable outcome, including one intubated patient, when compared with 31±16 days (range 14–65 days) in the 18 Group B patients who had favourable outcomes (p<0.001). The length of stay in the ICU was significantly shorter in the group of patients treated with BiPAP (1.2±4.3 *vs* 9.1±13.5 days; p=0.009).

Table 3. – Side-effects of mask ventilation, number of patients affected and mean duration of side-effects

Nasal mask ventilation side-effects	Pts affected n	Duration days	Notes
Nose abrasion	4	7	
Gastric distention	1	1	Side-effect reversed by use of nasogastric tube
Poor sleep	3	4	
Eye irritation	6	5	Decreased incidence after use of ComfortFlap®
Rhinitis	2	4	

Number of further hospitalizations for pulmonary exacerbations

The Group A patients had a total of 14 hospitalizations in a year after the baseline admission (mean 0.6±0.8 admissions·patient^{-1}), whilst Group B patients had a total of 26 hospitalizations in the year (mean 1.4±0.9·patient^{-1}). The difference between the groups was statistically significant (p=0.01).

Days spent in hospital per year were also significantly higher in Group B (450 days) than in Group A (153 days), with a mean of 25±22 days·y^{-1} per patient in Group B *versus* 7±10 days·year^{-1} per patient in Group A (p=0.003).

Blood gases during follow-up

Data on blood gas values during follow-up were available 1 month after the first hospital discharge for all Group A patients (18 out of 18) and for 15 out of 17 Group B patients. Mean pH was 7.39±0.04 in Group A and 7.37 ±0.03 in Group B; mean P_{a,CO_2} 4.83±1.2 kPa and 5.98± 0.83 kPa, and mean P_{a,O_2} 7.72±0.76 kPa and 7.64±0.93 kPa, respectively (no significant difference between the groups). Six months (range 4–8 months) after discharge these values were still not different. After 1 yr, blood gas values were available in 16 out of 17 Group A patients and in 9 out of 12 Group B patients, and again there were no significant differences between the groups.

Six and 12 months survival

Survival rate 6 months after admission was 71% in Group A and 54% in Group B, and after 1 yr was 71% in Group A and 50% in Group B. The differences between the groups were significant (p<0.05). The survival curves of the two groups are shown in figure 3. The cause of death is reported in table 4. Most of the deaths occurred within the first 120 days after the former hospital admission.

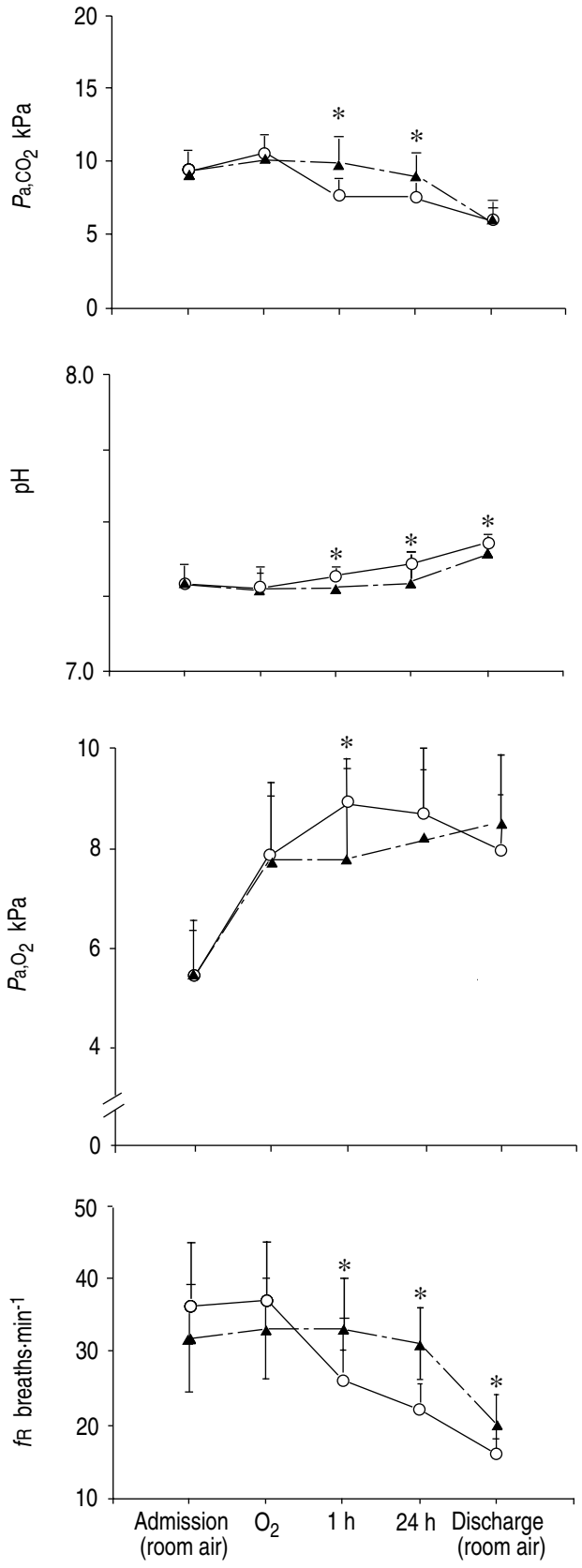

Fig. 2. – Blood gas data and respiratory rate (f_R) at different times in BiPAP treated patients (Group A) and in conventionally treated patients (Group B). ○—○: Group A patients; ▲---▲: Group B patients. For abbreviations see legend to figure 1.

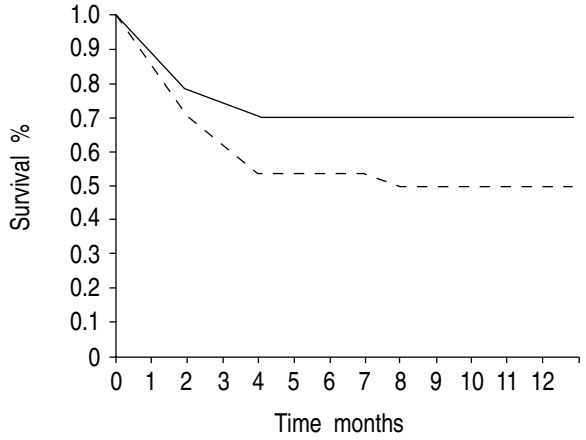

Fig. 3. – Survival of the two groups. —— : Group A (BiPAP treated patients); ·····: Group B (conventionally treated patients). BiPAP: bi-level positive airways pressure.

Table 4. – Cause of death and time of death after hospital admission in Group A and B patients (1 year observation period)

Patient No.	Cause of death	Time of death after admission months
Group A		
1A	Septic shock pneumonia	0.5 (in hospital)
6A	Exacerbation of COPD	3
9A	Exacerbation of COPD	2
12A	Pneumonia, cardiac failure	1
16A	Acute leukaemia	1
19A	MOF	0.8 (in-hospital)
21A	Stroke	0.2 (in-hospital)
Group B		
2B	Exacerbation of COPD	1.5 (in-hospital)
3B	Sudden death	1
7B	Pneumonia	2
8B	MOF	0.3 (in-hospital)
14B	Exacerbations of COPD	8
15B	Pneumonia	3
16B	Exacerbations of COPD	0.3 (in-hospital)
17B	Cardiac failure	0.3 (in-hospital)
20B	Pneumonia cardiac failure	3
21B	Exacerbation of COPD	1.3 (in-hospital)
22B	Exacerbations of COPD	3
24B	Pneumonia, MOF	0.2 (in-hospital)

COPD: chronic obstructive pulmonary disease; MOF: multiple organ failure.

Discussion

Our results confirm literature data concerning the efficacy of noninvasive positive pressure ventilation in avoiding endotracheal intubation and improving the immediate outcome of ACRF due to exacerbation of COPD in comparison with conventional treatment. The new data show that early administration of NPPV in severe relapses of ACRF may also improve the long-term outcome. This is

the fourth controlled study on immediate outcome [6–8], but is the first, to our knowledge, on long-term outcome after an acute episode of respiratory failure in COPD patients.

Our study demonstrated that the early use of BiPAP improved survival (at 6 and 12 months after admission) and reduced the number of further hospital admissions for respiratory exacerbations and the time passed in hospital during the next year. The prognosis of advanced COPD treated with conventional medical therapy is rather poor [2, 16] and is even worse when mechanical ventilation becomes necessary [17]. In the literature, survival rates at one year of patients who underwent invasive mechanical ventilation ranged 34–49% in different studies, [18–20]. The only long-term study on noninvasively ventilated patients [21] showed a survival rate at 1 yr very much higher than in other studies on patients treated conventionally either with medical therapy alone or by endotracheal mechanical ventilation. CORRADO and co-workers [22] used a negative pressure ventilation mode, the iron lung, to administer early treatment to COPD patients with acute respiratory failure (ARF) and at any relapse of ARF. Our results confirm the survival data of CORRADO and co-workers [22], although our patients treated with NPPV had a slightly lower survival rate at 1 yr. The difference may be explained by different ventilation modes, by difference in the size of the two study populations and by the fact that not all the relapses of ACRF in our study were treated with NPPV but only the severe ones. Obviously, it is not easy to explain the difference in survival rates on the basis of different treatment during one episode of ACRF. These differences may be due to the fact that the early use of NPPV shows an earlier improvement in blood gases.

Recently, MEECHAM JONES *et al*. [23] reported that nasal ventilation in acute exacerbations of COPD allows the safe use of supplemental oxygen with a well-controlled P_{a,CO_2} in most patients, but in those with severe hypercapnia only relatively small falls or even increases in P_{a,CO_2} are obtained with the initiation of NPPV. These results are apparently in contrast with ours and those of other authors [7, 8, 24]; the explanation may be that patients with the highest P_{a,CO_2} levels are often more difficult to ventilate and to obtain adequate co-operation with NPPV, but also that the exhalation devices might be important [13]. However, it is interesting to point out that in our study, at hospital discharge, the noninvasively ventilated patients showed a pH higher and a respiratory rate lower than conventionally treated patients. Both phenomena may be based on previous unloading of the respiratory pump for several days with resulting recovery [25]. However, any speculation about respiratory muscle fatigue is somewhat hazardous since there is no clear evidence in the literature regarding COPD patients, at least concerning chronic respiratory muscle fatigue [26]. Another advantage of noninvasive ventilation in comparison to the presently available conservative therapies is the significantly reduced work of breathing for the COPD patient [27].

It must be stressed that a distinct advantage of NPPV is avoidance of intubation in most patients and shortening of duration of hospitalization, thus reducing the possibility of several adverse effects associated with intubation and prolonged hospitalization. Invasive mechanical ventilation increases the risk of infectious complications, such as acute pulmonary exacerbations and pneumonia; in particular, it has been shown that the increased risk of developing pneumonia in patients receiving invasive ventilatory support is 1% per day of ventilation [28]. The presence of an endotracheal tube may, *per se*, bypass host defences, cause local trauma and inflammation and increase the risk of aspirating nosocomial pathogens from the upper airways [29]. A fundamental advantage of noninvasive ventilation may be the fact that it can preserve cough clearance, which is very important, especially for COPD patients with an exacerbated infection. In fact, insufficient cough clearance during invasive ventilation contributes greatly to the risk of infectious complications in COPD patients. No important and lasting side-effect was observed in the patients noninvasively ventilated.

Our study, given that it used historically-matched controls, presented well-known limits [30], even though it used strictly matching criteria. The principal problems related to the imperfect reproducibility of criteria for management and clinical decisions in historical groups. In our unit, except for the use of NPPV medical therapy strategies and follow-up procedures have not substantially changed over the last 4–5 yrs, being similar in Group A and Group B. It is also worth noting that: 1) the criteria for intubation in Group A were the same as those employed previously in Group B: and 2) the criteria for discharge from the ICU and from the pneumological ward have been quite homogenous in the course of the last few years. It should also be pointed out that even randomized controlled studies can present bias of distribution of the severity of the illness between the noninvasively ventilated patient group and the controls [31]. Furthermore, the lack of good matching can make a randomized trial less efficient than another trial not randomized but well-matched for several principal variables [32]. Our study population was, indeed, perfectly comparable for age, admission blood gases (breathing room air), severity score (APACHE II), and neurological status (GCS). It is notable that the matching criteria were similar to those employed by BROCHARD *et al*. [7], with the exception of APACHE II score [33] instead of the Simplified Acute Physiologic Score (SAPS). This kind of study may be useful as a "historical comparison" within the same Division of Respiratory Diseases, before and after the opening of an Intermediate Intensive Respiratory Care Unit.

Further, it is important to note that, besides the study of VITACCA and co-workers [6], our study is the second controlled one on the administration of PSV with an added PEEP in acute COPD patients, but it is the first one using BiPAP®. The most quoted paper concerning BiPAP *via* mask in acute respiratory failure is that by PENNOCK *et al*. [34], who reported the results of a noncontrolled study showing the feasibility of this ventilatory technique in a medical ward, especially for postsurgical patients. The background of the use of noninvasive bi-level positive pressure ventilation (PSV + PEEP) in exacerba-

tions of COPD with ACRF is based on physiological studies either on stable or acute patients. In patients with severe but stable COPD, it has been shown that BiPAP can improve respiratory pattern and blood gases, and unload ventilatory muscles during spontaneous breathing, reducing the effort of breathing and the oxygen cost [23]. NAVA *et al*. [35] demonstrated that nasal PSV improves diaphragmatic function in patients with severe stable COPD, and that this effect may be enhanced by the application of external PEEP. Recently, APPENDINI *et al*. [27] demonstrated that noninvasive ventilation delivered by CPAP added to PSV produces better results than CPAP or PSV alone with regard to the reduction of inspiratory effort, and as a consequence of working of breathing (WOB). Furthermore, the addition of a low external PEEP in severe COPD patients may counterbalance the positive pressure existing in the airways at the end of an expiration (autoPEEP), which is responsible for up to 70–80% of the total respiratory load [36, 37].

Our experience, and studies reported by PENNOCK and co-workers [38] and by CONWAY *et al*. [39], show the feasibility of nasal positive pressure ventilation in acutely decompensated COPD patients in a pneumological ward. It should be noted, that it is essential that conventional mechanical ventilation by endotracheal intubation would be available promptly. CHEVROLET *et al*. [40] described noninvasive ventilation in acute patients as a time-consuming and difficult procedure for the personnel of a general ward; we have found this to be the case only in the initial critical phase of noninvasive ventilation, but not so much when this phase has been overcome. BOTT *et al*. [8] did not observe that patients using NPPV consumed more nursing time than equally ill conventionally treated patients. Nevertheless, it is important to stress the need for experienced staff in this complex ventilatory technique [41]. In addition, the psychological support offered by the presence of patients' relatives might be very important, especially during the first hours of mask ventilation.

In conclusion, our results suggest that bi-level positive airway pressure delivered by mask can be added at an early stage to medical therapy plus oxygen supplementation in patients with acute on chronic respiratory failure due to decompensated chronic obstructive pulmonary disease in order to improve immediate and long-term outcomes.

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