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Iron lung *versus* conventional mechanical ventilation in acute exacerbation of COPD

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Iron lung versus *conventional mechanical ventilation in acute exacerbation of COPD. A. Corrado, R. Ginanni, G. Villella, M. Gorini, A. Augustynen, D. Tozzi, A. Peris, S. Grifoni, A. Messori, C. Nozzoli, G. Berni. ©ERS Journals Ltd 2004.*

ABSTRACT: The aim of this randomised study was to compare the effects of iron lung ventilation (ILV) with invasive mechanical ventilation (IMV) in patients with acute respiratory failure (ARF) due to exacerbation of chronic obstructive pulmonary disease.

Forty-four patients with ARF were assigned either to ILV (22 patients) or IMV (22 patients). Primary end-points were the improvement in gas exchange and complications related to mechanical ventilation.

On admission ILV and IMV groups did not differ in age, simplified acute physiology score II, arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}), arterial carbon dioxide tension (P_{a,CO_2}) and pH. Compared with baseline, ILV and IMV induced a similar and significant improvement in $P_{a,O_2}/F_{I,O_2}$, P_{a,CO_2} and pH after 1 h of treatment and at discontinuation of mechanical ventilation. Major complications tended to be more frequent in patients treated with IMV than in those treated with ILV (27.3% *versus* 4.5%), whereas mortality rate was similar (27.3% *versus* 18.2%). The ventilator-free days and the length of hospital stay were significantly lower in the ILV than in the IMV group.

This study suggests that iron lung ventilation is as effective as invasive mechanical ventilation in improving gas exchange in chronic obstructive pulmonary disease patients with acute respiratory failure, and is associated with a tendency towards a lower rate of major complications.

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Endotracheal intubation and mechanical ventilation in patients with chronic obstructive pulmonary disease (COPD) and acute or chronic respiratory failure are associated with several complications [1, 2]. Compared with standard medical therapy, noninvasive positive pressure ventilation (NIPPV) reduces the need for endotracheal intubation [3–5], the length of hospital stay [3], and the in-hospital mortality rate [3–6]. Recently, it was shown that in COPD patients with severe respiratory failure that failed medical therapy in the ward, NIPPV compared with invasive mechanical ventilation (IMV) resulted in a similar mortality rate, length of hospital stay and duration of mechanical ventilation [7].

It has been reported that COPD patients with severe respiratory acidosis and hypercapnic coma can be successfully treated with iron lung ventilation (ILV) [8]. A case-control study [9] suggested that ILV is as effective as IMV in the treatment of COPD patients with acute on chronic respiratory failure and is associated to a shorter duration of ventilation, and a similar length of hospital stay. Nevertheless, to date, no randomised study comparing ILV with IMV for the treatment of exacerbation of COPD has been carried out.

The aim of this prospective controlled, randomised, pilot study was to compare the effects of ILV and IMV on gas exchange and the rate of complications associated with mechanical ventilation in COPD patients with acute on chronic respiratory failure.

For editorial comments see page 361.

Methods

Study design

The study protocol was approved by the Ethics committee of the hospital and was performed according to the Helsinki Convention. Patients or their relatives gave written informed consent.

This pilot, prospective, randomised, controlled study was carried out from February 1, 1998 to December 31, 2000. The study took place in the emergency department of Careggi Hospital, Florence, which includes the emergency room (ER), the respiratory intensive care unit (RICU) and the general intensive care unit (GICU). The internal protocol of the institution established that in patients admitted to the emergency department, IMV should be performed in GICU and non-IMV in RICU.

All COPD patients with acute on chronic respiratory failure admitted to the ER were eligible for the study if they presented with an arterial carbon dioxide tension (P_{a,CO_2}) of >9.3 kPa and a pH of <7.25 while breathing room air or

during oxygen therapy with arterial oxygen saturation between 92–94%. The diagnosis of COPD was made according to European Respiratory Society criteria [10]. The patients were randomly assigned to one of the two arms (ILV or IMV) and transferred to RICU or GICU if the following conditions were fulfilled: 1) arterial blood gases performed in the ER after 1 h of optimal pharmacological and oxygen therapy showed no change or worsening in respiratory acidosis; 2) simultaneous availability of at least one bed both in the GICU and in the RICU; and 3) informed consent to participate in the study. The following exclusion criteria were adopted: associated major pathology such as stroke, acute myocardial infarction, acute respiratory distress syndrome, acute renal failure (needing haemodialysis), end-stage cancer, liver cirrhosis, pneumothorax, thoracic trauma, cystic fibrosis, shock, massive pulmonary embolism, acute asthma.

The patients who were not randomised due to lack of beds (point 2) underwent the same pharmacological and ventilatory treatment as the randomised patients and formed an observational group.

Randomised study

Randomisation. Randomisation was carried out using sealed envelopes containing random assignment codes; the codes were generated from tables of random numbers by an operator unaware of the aim of the study and the envelopes were kept in the ER.

Pharmacological treatment. All patients underwent standard pharmacological treatment (bronchodilators, antibiotics, corticosteroids, diuretics, heparin, adequate nutritional support, correction of electrolyte disorders). Bronchodilators in intubated patients were administered by a metered-dose inhaler (MDI) inserted in a spacer chamber (ACE; DHD Healthcare, Canastota, NY, USA) fitted in the inspiratory limb of the ventilatory circuit [11]. In conscious patients treated with ILV, bronchodilators were administered by an MDI inserted in a spacer chamber, whereas in unconscious patients, bronchodilators were administered by nebuliser. Oxygen was administered in order to obtain an arterial oxygen tension (P_{a,O_2}) level between 8.0–9.3 kPa. To verify the correct application of the protocol, a cross-check of the therapeutic regimen was supervised by one staff member of each setting. Sedative agents were not used for patients treated with ILV whereas intravenous midazolam (0.1 mg·kg^{-1}) or propofol (2 mg·kg^{-1}) were given for sedation during the first 6–8 h from the time of intubation in patients treated with IMV; no patient received paralysing drugs.

Chest physiotherapy. Chest physiotherapy was provided in RICU and GICU by the same staff of experienced therapists according to a standardised protocol.

Arterial blood-gases measurement. Arterial blood gases in randomised patients were recorded before the start and after 1 and 2 h of ventilatory treatment, after 30 min from any change in the ventilatory setting, and at least once a day.

Ventilation techniques. Patients assigned to ILV underwent ventilation by means of an iron lung (Coppa, Biella, Italy). Patients assigned to IMV underwent endotracheal intubation and were ventilated with PB 7200 (Puritan Bennett Co., Overland Park, KS, USA) or Servo Ventilator 300 (Siemens, Solna, Sweden).

Iron lung ventilation. The iron lung settings were similar to those previously reported [8, 12]. Briefly, the ventilator was set to deliver peak inspiratory pressures ranging -30–-40 cmH_2O and peak expiratory pressures from 10–15 cmH_2O. Inspiratory pressure was set in each individual patient in order to obtain a tidal volume (V_T) of ~6 mL·kg^{-1} intermittently recorded at the mouth by means of a Wright's ventilograph. In patients with spontaneous respiratory frequency <10 cycles·min^{-1}, the iron lung frequency and the ratio of inspiratory time to total breathing cycle time (t_i/t_{tot}) were set at 15 cycles·min^{-1} and 30%, respectively. In the other patients, the frequency and the t_i/t_{tot} ratio were individually set according to their spontaneous respiratory frequency in order to facilitate patient-ventilator synchrony. Oxygen was provided by nasal cannula or Venturi mask to increase P_{a,O_2} level to 8.0–9.3 kPa. Ventilator settings were adjusted on the basis of continuous oximetry and measurements of arterial blood gases. Ventilatory treatment started with a continuous session of $\geqslant$4 h according to subjective patient tolerance and to clinical improvement. Ventilatory treatment was then performed intermittently with sessions lasting 2–6 h, on the basis of the attending physician's judgement. ILV was withdrawn definitively if the patient maintained a respiratory rate of <30 breaths·min^{-1}, a P_{a,O_2} between 8.0–9.3 kPa with an inspiratory oxygen fraction (F_{I,O_2}) $\leqslant$40%, and a pH of >7.35 during spontaneous breathing.

Invasive mechanical ventilation. The initial ventilatory setting after intubation was in the assist pressure-controlled mode (APCV). When spontaneous breathing reappeared, 17 patients continued APCV (inspiratory pressure range 20–30 cmH_2O, positive end-expiratory pressure (PEEP) range 4–8 cmH_2O and respiratory frequency 15 cycles·min^{-1}) whereas five patients were changed to pressure-support ventilation (PSV; pressure-support range 20–28 cmH_2O, PEEP 3–7 cmH_2O) to improve patient-ventilator synchrony. Peak inspiratory pressure was set in each individual patient in order to obtain a V_T of 6 mL·kg^{-1}. F_{I,O_2} was set to increase P_{a,O_2} level between 8.0–9.3 kPa. Ventilator settings were adjusted on the basis of continuous oximetry and measurements of arterial blood gases.

Weaning was started when patients presented an improvement or resolution of the underlying cause of acute respiratory failure: $P_{a,O_2}/F_{I,O_2}$ >150 with PEEP $\leqslant$5 cmH_2O, temperature of <38°C, a haemoglobin level of >9 g·dL^{-1}, and no further need for vasoactive and sedative agents. Intermittent trials of spontaneous breathing by means of T-piece were adopted to withdraw mechanical ventilation. The duration was gradually increased and the trials were attempted at least twice a day, according to ESTEBAN *et al.* [13]. Patients able to breathe on their own for 2 h without signs of distress were promptly extubated.

Endotracheal intubation in the ILV group was performed when at least one of the following criteria was met within 2 h from the start of ventilatory treatment: 1) an increase or a decrease of <0.66 kPa from the baseline value in P_{a,CO_2}; 2) no change or worsening of pH from the baseline value; and 3) inability to maintain P_{a,O_2} >8 kPa despite F_{I,O_2} of 60%. Endotracheal intubation in the ILV group was also performed if the patients presented at least one of the following criteria: 1) respiratory arrest; 2) bradypnoea (respiratory frequency <8 cycles·min^{-1}); 3) psychomotor agitation requiring sedation; 4) haemodynamic instability (systolic pressure <70 mmHg); 5) decrease in the Glasgow coma score from the value on admission; 6) deterioration of arterial blood gases from the value on admission. Endotracheal intubation was not performed when patients or relatives (when patient was unconscious) refused this procedure.

Tracheostomy was performed if all attempts to disconnect

Table 1. – Data on admission of chronic obstructive pulmonary disease patients in acute respiratory failure treated with iron lung ventilation (ILV) or invasive mechanical ventilation (IMV)

	ILV	IMV	p-value
Patients n	22	22	
M/F	19/3	13/9	
Age yrs	72.2±6.1	74.5±7.5	0.259
Weight kg	67.7±13.9	68.1±16.2	0.93
Height cm	164.0±8.6	164.0±6.9	1
FEV1 % pred[#]	33.7±13.5	35.0±8.7	0.741
VC % pred[#]	61.1±12.9	57.5±9.3	0.294
FEV1/VC[#]	41.0±14.5	46.1±11.4	0.246
MRC dyspnoea scale[¶]	3 (2–4)	3.5 (2.0–4.0)	0.711
Glasgow Coma Score[+]	14 (3–15)	12 (7–15)	0.121
SAPS II[§]	32 (17–42)	35 (20–47)	0.194
$Pa,O_2/FI,O_2$	192.0±59.8	172.0±61.7	0.277
Pa,CO_2 kPa	12.8±2.1	13.3±2.4	0.531
pH	7.20±0.04	7.20±0.04	0.455
HCO_3 mM	36.2±4.8	37.4±8.2	0.663

Data are presented as mean±SD or median (range) unless otherwise stated. M: male; F: female; FEV1: forced expiratory volume in one second; VC: vital capacity; MRC: Medical Research Council; SAPS: simplified acute physiology score; Pa,O_2: arterial oxygen tension; FI,O_2: inspiratory oxygen fraction; Pa,CO_2: arterial carbon dioxide tension. [#]: functional measurements were obtained in stable conditions 1–12 months before or after the acute exacerbations; [¶]: from [16]; [+]: from [17]; [§]: from [18].

the patients from the ventilator failed on day 14 of mechanical ventilation.

Discharge criteria. The criteria established for discharging patients from RICU and GICU were that the patient was able to breath spontaneously for 48 h after the disconnection from ILV or after extubation for IMV group, haemodynamic stability and no need for artificial nutrition.

End-points. To assess the efficacy of ventilatory techniques in each individual patient, the primary end-points were considered to be the improvement in gas exchange and complications related to mechanical ventilation.

Secondary end-points were the ventilator-free days in each treatment group through day 28 following initiation of ventilatory treatment [14]; this method permits the dissociation of duration of mechanical ventilation from the impact of mortality, length of hospital stay and mortality rate.

Ventilator-associated pneumonia was defined according to the Centers for Disease Control and Prevention Criteria [15].

Statistical analysis

Continuous variables were compared using unpaired t-test and analysis of variance for normally distributed variables and the Mann-Whitney U-test for those that were non-normally distributed. A p-value of <0.05 was considered as statistically significant. All data are presented as mean±SD for normally distributed variables and as median (range) for non-normally distributed variables. Survival analysis was applied to the rate of discontinuation of mechanical ventilation and comparisons between groups were assessed by the log rank test. The data of the patients in the observational study were analysed in the same way as that adopted for the randomised patients.

Results

Enrolment

From a total of 4,718 COPD patients admitted to the emergency department in the period of the study, 592 (12.5%) suffered from acute on chronic respiratory failure. Of these, 96 (16.3%) fulfilled the criteria for the inclusion in the study, nevertheless 53 of them (55%) were not included due to lack of simultaneous availability of beds in both RICU and GICU.

Hence, a total of 44 patients (45%) were randomised (22 to ILV and 22 to IMV). The patients reported herein included no cases of readmission. Among the 53 patients who were not randomised, 42 (79%) were admitted to RICU and 11 (21%) to GICU.

Randomised study

Characteristics of the patients. The baseline characteristics of the patients on admission were similar in the two groups as reported in table 1. The causes of acute respiratory failure were COPD exacerbation (nine (40.9%) patients and seven (31.8%) patients, p= 0.755) [17], pneumonia (11 (50%) patients and 10 (45.4%) patients, p=1.0), and congestive heart failure (two (9.0%) patients and five (22.7%) patients, p=0.412) in ILV and IMV groups, respectively.

Primary end-points. Gas exchange. The arterial blood-gas values of both groups of patients are reported in table 2. Compared with baseline, both ILV and IMV induced a significant improvement in $Pa,O_2/FI,O_2$, Pa,CO_2 and pH after 1 h of treatment and at discontinuation of mechanical ventilation. There was no statistically significant difference in arterial blood gas values after 1 h and at discontinuation of mechanical ventilation between the two groups of patients.

Complications of mechanical ventilation. Major complications tended to be more frequent in patients treated with IMV than in those treated with ILV (27.3% *versus* 4.5%, p=0.09), as reported in table 3. Five patients treated with ILV developed minor complications (table 3).

Table 2. – Arterial blood-gas values in patients treated with iron lung ventilation (ILV) and invasive mechanical ventilation (IMV)

	ILV			p-value	IMV			p-value
	Admission	1 h	End of treatment		Admission	1 h	End of treatment	
$Pa,O_2/FI,O_2$	192±59.8	212.4±52.7	283.4±82.2	0.0001	172±61.7	224±76.5	269.2±63.8	0.0001
Pa,CO_2 kPa	12.8±2.1	10.3±2.1	7.6±0.5	0.0001	13.3±2.4	9.7±3.0	7.2±1.1	0.001
pH	7.20±0.04	7.30±0.07	7.39±0.03	0.0001	7.20±0.04	7.31±0.09	7.39±0.04	0.0001

Data are presented as mean±SD. Pa,O_2: arterial oxygen tension; FI,O_2: inspiratory oxygen fraction; Pa,CO_2: arterial carbon dioxide tension. p-Values are the results of one-way analysis of variance.

Table 3. – Complications and side-effects of mechanical ventilation

	ILV	IMV
Minor		
Back pain	3	0
Claustrophobia	1	0
Abdominal distension	1	0
Total	5	0[#]
Major		
Pneumothorax	1 (1)	1
Multiple organ failure	0	3[¶] (3)
Gastrointestinal bleeding	0	1
Pneumonia	0	1 (1)
Total	1 (1)	6[+] (4)

Data are presented as n (n with complications). ILV: iron lung ventilation; IMV: invasive mechanical ventilation. [¶]: all the three patients developed pneumonia. The total number of patients who developed pneumonia and died was four. [#]: p=0.06; [+]: p=0.09. Comparison of deaths due to complications p=0.342.

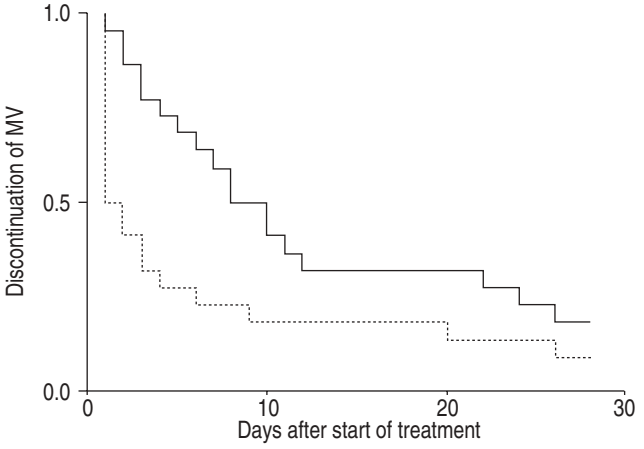

Fig. 1. – Kaplan-Meier curves for the rate of discontinuation of mechanical ventilation (MV) in the conventional MV (—) and negative pressure ventilation (·····) groups (p=0.0319 by log rank test).

Secondary end-points. Days free of mechanical ventilation. Figure 1 shows Kaplan-Meier curves demonstrating that the rate of discontinuation of mechanical ventilation as a function of time was significantly different between ILV and IMV groups (p=0.0319 by log rank test). Significant differences in ventilator-free days at 28 days were noted (ILV 26.5 (0–27), IMV 19 (0–27); p=0.002). The modality of ventilation (PSV or APCV) in patients treated with IMV did not influence the ventilator-free days at 28 days (PSV 17 (0–26), APCV 20 (0–27); p=1.0). The total number of hours of mechanical ventilation in survivors was significantly lower in ILV than in IMV group (p=0.0001; table 4).

Table 4. – Clinical outcomes in patients treated with iron lung ventilation (ILV) and invasive mechanical ventilation (IMV)

	ILV	IMV	p-value
Patients n	22	22	
Deaths in ICU	4/22 (18.2)	5/22 (22.7)	1.0
Deaths in hospital	4/22 (18.2)	6/22 (27.3)	0.719
Duration of MV[#] days	2 (1–6)	7 (1– 26)	0.0001
Rate of endotracheal intubation	4/22 (18.2)		
Rate of tracheostomy	1/22 (4.5)	5/22 (22.7)	0.188
Length of hospital stay[#] days	15 (6–55)	25 (11–65)	0.007

Data are presented as n/total n (%) or median (range) unless otherwise stated. ICU: intensive care unit; MV: mechanical ventilation. [#]: in survivors.

Hospital stay. The length of hospital stay was significantly longer in IMV than in ILV groups (p=0.007; table 4).

Mortality rate. ICU and hospital mortality rates were not significantly different in the two groups of patients (table 4). Mortality rate in patients with pneumonia as the cause of acute respiratory failure was 20% and 27% in ILV and IMV groups, respectively (p=1.0). The 18 patients (81.8%) treated with ILV and discharged from the hospital were alive after a median follow-up of 20 weeks (range 8–43). Four patients (18.2%) needed endotracheal intubation due to the failure of ILV. In the subgroup of four patients who died, three were previously intubated and one, although weaned from ILV, died from cardiac arrest. In the three intubated patients, the causes of death were pneumothorax in one patient and severe tachyarrhytmia with cardiac arrest in the other two.

The 16 patients (73%) treated with IMV and discharged from the hospital were alive after a median follow-up of 18 weeks (range 6–40). Among the six patients who died, four underwent tracheostomy due to difficulty in weaning. The causes of death were multiple organ failure in three patients, cardiogenic shock in one patient, pneumonia in one patient and sepsis in one patient. The rate of tracheostomy was of 22.7%. Among the tracheostomised patients, four (80%) died during hospitalisation after a median of 53.5 (range 22–84) days of hospital stay, whereas one (20%) survived and was discharged after 45 days of hospital stay.

Observational study

The characteristics of the patients and the main outcomes are reported in table 5.

Table 5. – Characteristics and outcomes of chronic obstructive pulmonary disease patients in acute respiratory failure not randomised and treated with iron lung ventilation (ILV) or invasive mechanical ventilation (IMV)

	ILV	IMV
Patients n	42[#]	11
M/F	24/18	7/4
Age yrs	77.0±6.9	73.0±9.1
$P_{a,O_2}/F_{I,O_2}$	210.0±96.0	182±91
P_{a,CO_2} kPa	13.1±2.2	12.0±1.7
pH	7.21±0.04	7.22±0.03
HCO_3 mM	38.0±13.0	39±8
MRC dyspnoea scale	4 (1–4)	4 (2–4)
Glasgow Coma Score	13 (3–15)	15 (3–15)
SAPS II	30 (16–40)	29 (15–38)
Mortality rate %	26	27.3

Data are presented as mean±SD or median (range) unless otherwise stated. M: male; F: female; P_{a,O_2}: arterial oxygen tension; F_{I,O_2}: inspiratory oxygen fraction; P_{a,CO_2}: arterial carbon dioxide tension; MRC: Medical Research Council; SAPS: simplified acute physiology score. [#]: nine patients (21.4%) required endotracheal intubation, two of these patients survived and seven died.

Discussion

This is the first prospective randomised trial that compares iron lung with conventional mechanical ventilation for the treatment of acute on chronic respiratory failure in COPD patients who failed an initial medical treatment lasting 1 h in the ER. The data show that ILV compared with IMV resulted in a similar improvement in arterial blood gases and pH, and in a trend towards a lower rate of major complications.

Before discussing these results and those concerning the secondary end-points, it is important to stress the limitations of the present study. The low number of observations could have induced β-type error, which may have influenced the lack of significant differences in complication rate. The simultaneous availability of at least one bed, both in RICU and GICU for randomisation, could have induced a bias, as some eligible patients were excluded. The treatment in the two different settings, different modalities of mechanical ventilation (PSV and APCV) employed in the IMV group, sedative drugs used only in the intubated patients, and the difference in motivation for discharging of the staff of the two settings could have influenced the results obtained, particularly the duration of mechanical ventilation and the length of hospital stay. Pharmacological treatment, including the way of oxygen delivery and chest physical therapy were previously standardised and a cross-supervision was adopted by one member of each staff in RICU and in GICU. Sedative drugs in patients treated with IMV were given only during the first 6–8 h from the time of endotracheal intubation and the different modalities of mechanical ventilation employed in the IMV group did not influence the ventilator-free days at 28 days. However, it is impossible to exclude that these confounding variables have influenced the present findings.

Finally, it is important to stress that this was intended as a pilot study to generate preliminary results to be tested by a larger multicentre study.

Randomised controlled studies [3–6] have demonstrated the superiority of mask ventilation in comparison with medical treatment in COPD patients with acute on chronic respiratory failure. A recent randomised study, comparing the effect of NIPPV and IMV, has extended the application of mask ventilation to COPD patients with hypercapnic respiratory failure who failed medical treatment in the ward [7]. One of the main findings was that the use of NIPPV resulted in a significant improvement in gas exchanges though the correction of these abnormalities was slower compared with IMV.

The present controlled study shows that ILV was as effective as IMV in improving gas exchanges and that the time of correction was not significantly different with the two methods of mechanical ventilation. Another important finding of this study was the trend towards a lower number of major complications in patients treated with ILV compared with IMV. This is due, in the authors′ opinion, to two factors. Firstly, ILV can be administered intermittently, avoiding the difficulty in weaning associated to IMV and reducing the length of mechanical ventilation. Secondly, avoiding endotracheal intubation the patients treated with ILV are exposed to a lower risk of infectious complications, in line with data obtained using mask ventilation [3, 7, 19, 20]. Confirming preliminary findings [8, 11], this study shows that ILV avoided endotracheal intubation in 82% of patients with a similar ICU and hospital mortality rates compared with IMV. The mortality rate found in the IMV group is in line with that reported in COPD patients by SENEFF *et al.* [21] and ESTEBAN *et al.* [22], 32% and 28%, respectively. Although the survival rate was not significantly different in the two groups, the management approach used in the RICU, including ILV, resulted in shorter mechanical ventilation time and hospital stay. These findings are due, in the authors′ opinion, to the fact that ILV can be administered intermittently avoiding the difficulty in weaning associated to IMV.

The better outcomes (rate of endotracheal intubation, duration of mechanical ventilation and length of hospital stay) reported in the present study in comparison with those reported by CONTI *et al.* [7] could be linked to different severity in the population studied; however, a randomised prospective controlled study that formally compares the two noninvasive ventilatory techniques is needed to clarify these aspects.

To conclude, iron lung ventilation was found to be as effective as conventional mechanical ventilation in chronic obstructive pulmonary disease patients with acute on chronic respiratory failure in improving gas exchange and was associated with a trend towards a lower rate of major complications. These promising findings justify a large multicentre controlled trial in order to compare the effects of iron lung ventilation and invasive mechanical ventilation in terms of clinical outcomes.

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