SERIES: 'CLINICAL PHYSIOLOGY IN RESPIRATORY INTENSIVE CARE'
Edited by A. Rossi and C. Roussos

Noninvasive mechanical ventilation in acute respiratory failure

N. Ambrosino

Noninvasive mechanical ventilation in acute respiratory failure. N. Ambrosino. ©ERS Journals Ltd 1996.
ABSTRACT: Mechanical ventilation (MV) has been indicated in the treatment of acute respiratory failure (ARF) if conservative treatment fails. Invasive MV is associated to a variety of complications. The recent innovations of noninvasive methods of MV (NMV) avoid the complications of invasive MV, whilst ensuring a similar degree of efficacy. A review of the literature from 1989 to 1995 shows that use of NMV in ARF has been reported in several studies involving more than 400 patients most of them COPD. NMV was successful from 51 to 91%, the severity of ARF being widely different among the different studies. Most of the studies compared effectiveness of NMV with historical groups of patients treated with "conventional" medical therapy whilst controlled studies of NMV *versus* ET intubation are lacking. Type of mask, mode of ventilation, compliance to treatment, type of patient and severity of disease may influence the success rate.

Success with NMV was associated with less severely abnormal baseline clinical and functional parameters and to less severe levels of acidosis assessed during an initial trial of NMV. Therefore, NMV may be useful in selected patients with ARF. Patients should have clinical and physiological evidence of ARF and should be sufficiently cooperative. It is commonly said that NMV should be avoided, and endotracheal (ET) intubation performed in patients with haemodynamic instability, uncontrolled arrhythmias, gastrointestinal bleeding , high risk for aspiration. With these limitations NMV in selected patients with ARF is well tolerated and may be useful in avoiding ET intubation in most cases of COPD and with a wide range of success rates in other disease. This in turn has several advantages in terms of avoiding complications of invasive MV, reducing the length of stay in ICU and probably the number of ICU readmissions. Side effects of NMV seem less severe than those induced by invasive MV.

In conclusion in selected patients a trial of noninvasive mechanical ventilation, as an adjunct to medical therapy, should be instituted at an early stage of ARF episodes before severe acidosis ensures, to avoid ET intubation.
Eur Respir J., 1996; 9; 795–807.

Respiratory Division, Clinica del Lavoro Foundation IRCCS, Centro Medico di Riabilitazione, Gussago (BS), Italy.

Correspondence: N. Ambrosino
Fondazione Salvatore Maugeri
Centro Medico di Riabilitazione di Gussago
Via Pinidolo 23 - 25064
Gussago (BS)
Italy

For more than 30 yrs, acute respiratory failure (ARF) has been one of the most frequent causes of admission to the Intensive Care Unit (ICU) [1]. The treatment of ARF is described as conservative if the patient is managed without intubation or tracheostomy and mechanical ventilation (MV). Many cases of ARF can be treated in a conservative way. MV *via* endotracheal (ET) tube or tracheostomy has been indicated if conservative treatment fails. Classic indications for MV are: deterioration of consciousness; cardiac or respiratory arrest; exhaustion or extreme fatigue [2]. The aims of MV are shown in table 1. MV makes it possible: 1) to obtain time for the cause of ARF to subside; and 2) to let the respiratory muscles (RM) rest and recover [3]. However, it is still difficult to predict which patients will require MV and when it should be instituted. Furthermore, there is no general agreement about which kind of ventilatory support is preferable.

Table 1. – Objectives of mechanical ventilation [3]

Improve pulmonary gas exchange
Reverse hypoxaemia
Relieve acute respiratory acidosis
Relieve respiratory distress
Decrease oxygen cost of breathing
Reverse respiratory muscle fatigue
Alter pressure-volume relations
Prevent and reverse atelectasis
Improve compliance
Prevent further injury
Permit lung and airway healing
Avoid complications

Complications of invasive mechanical ventilation

For several decades, mechanically-assisted intermittent positive pressure ventilation has been performed,

initially, by installing an artificial airway, the ET tube, and, in the event of prolonged ET intubation, later performing a tracheostomy. MV exposes the patient to a variety of complications resulting from the intubation procedure, during the course of ventilation, after removing the tube or due to tracheostomy [4]. A prolonged attempt at intubation may result, infrequently but dangerously, in cardiac arrest, generalized seizures and gastric distension. Self-extubation, mechanical dysfunction of the ET tube and cuff leaks may necessitate reintubation and result in increased mortality [5]. Injury to the pharynx, larynx and trachea can occur at the points of contact between the mucosa and the tube or cuff, resulting in ulceration, oedema, and haemorrhage with potential long-term complications, *i.e.* stenosis; furthermore, tracheostomy may result in loss of voice [6]. In patients requiring periodic MV, a deflated, fenestrated tracheostomy may impair RM performance during spontaneous breathing [7].

In addition to local damage, the ET tube places the patient at significant risk of developing nosocomial infections, mainly sinusitis and ventilator-associated pneumonia. Sinusitis due to nasotracheal intubation occurs from occlusion of the sinus ostia and is increasingly recognized as a cause of unexplained fever and sepsis in ventilated patients [8]. ET intubation is the single most important predisposing factor for nosocomial pneumonia as it bypasses the mechanical defences of the upper airways [9, 10]. It causes local injury, which predisposes patients to colonization of the trachea by pathogenic bacteria. In addition, the portion of the upper trachea between the inflated cuff and the vocal cords behaves as a reservoir for secretions originating from the sinuses, the nasal and oral cavity, the pharynx and the stomach. Such secretions can be introduced as a bolus into the lung by even minor ET tube manipulation [11]. Decrease in cardiac output (CO), barotrauma, and increase in work of breathing (WOB) due to the added space of the ET are additional problems of MV *via* an ET [12]. Up to 20% of mechanically-ventilated patients are not able to tolerate discontinuation of MV due to complete dependence on the machine and on the people who control them. Need for MV may lead to RM atrophy and related weaning difficulties [13, 14].

Noninvasive mechanical ventilation

The recent innovations of noninvasive methods of MV (NMV) in the treatment of chronic respiratory insufficiency has led to the attempt to avoid the complications of invasive MV, ensuring at the same time a similar degree of efficacy. Both intermittent negative pressure ventilation (INPV) and positive pressure ventilation by face or nasal mask have recently been used for this purpose. This review deals mainly with noninvasive positive pressure ventilation.

Negative pressure techniques

INPV came into use in the second half of the nineteenth century during poliomyelitis epidemics. Development of a subatmospheric pressure around the thorax and abdomen results in air being drawn into the lungs through the mouth and nose. When the pressure around the chest wall returns to that of the surrounding air, expiration occurs passively owing to the elastic recoil of the lungs and chest wall. Excellent reviews of negative pressure devices have been published [15, 16].

Several studies have pointed out the efficacy of INPV in reducing electrical and mechanical activity of the inspiratory muscles (IM), thus allowing them to rest [17]. Ventilation with an "iron lung" was found to show a linear relationship between the increase in venous pressure and the mean pressure applied to ventilate normal humans [18]. On the other hand, no significant change in CO and haemodynamics was found during INPV by cuirass ventilators in chronic obstructive pulmonary disease (COPD) patients [19]. All negative pressure ventilators restrict motion and back pain is a common problem. INPV has been associated with rib fractures, pneumothorax, obstructive sleep apnoeas and lower oesophageal sphincter dysfunction, both in normal subjects and in COPD patients [20–22].

Chronic hypercapnic respiratory insufficiency resulting from neuromuscular and skeletal disorders is the main indications for INPV [23, 24].

Studies that have been published on the effects of INPV in COPD patients during ARF episodes are presented in table 2. INPV has been used to avoid the need for ET intubation during episodes of ARF in neuromuscular and skeletal disorders [28]. On the other hand, during the poliomyelitis epidemic, mortality decreased from 87% to 40% when INPV was replaced by positive pressure ventilation [29].

The place of INPV in acute exacerbations of COPD is still discussed. Iron lung, cuirass and poncho-wrap ventilators have been successfully used in exacerbations of COPD [25–27, 30, 31]. A review of the papers listed in table 2 revealed that in no case was INPV used in place of invasive MV, the severity of ARF was defined

Table 2. – Published studies on the use of INPV in exacerbations of COPD

First author [Ref.]	COPD patients				INPV	Schedule	Control	Results		
	n	pH	P_{a,O_2} kPa	P_{a,CO_2} kPa				pH	P_{a,O_2} kPa	P_{a,CO_2} kPa
CORRADO [25]	9	7.33	5.7	9.0	Iron lung	8 h·day^{-1} for 7 days	7 stable	7.37	8.1	7.0
MONTSERRAT [26]	20	7.32	6.4	7.9	Poncho-wrap	6 h	6 h of rest	7.38	6.3	6.7
SAURET [27]	17	7.34	6.2	9.8	Poncho-wrap	6 h	none	7.39	7.0	8.6

INPV: intermittent negative pressure ventilation; COPD chronic obstructive pulmonary disease; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension.

by a mean pH not less than 7.32, and use of control populations was variable.

In conclusion, these studies on the effects of INPV during ARF in COPD patients may be considered preliminary and "physiological" rather than clinical: as a consequence, at the moment, there is no indication for the generalized use of INPV during ARF.

Positive pressure techniques

Intermittent positive pressure ventilation is aimed at delivering a tidal volume (V_T) and then allowing passive exhalation, either to atmospheric pressure or to a set positive airway pressure. The technique can be used to control ventilation entirely or to increase spontaneous respiratory efforts. Increasing gas exchange can be achieved for conscious subjects only if the ventilator cycles into inspiration in response to the initiation of a spontaneous breath by the patient, a process described as "triggering" ("assisted ventilation"). If there is no spontaneous inspiratory effort or it is too weak to trigger the ventilator, an automatic cycle must be imposed to ensure that gas exchange continues ("controlled ventilation"). The so-called assist/control mode can be used to ensure that breaths are triggered or imposed according to the capability of triggering the ventilator. Intermittent positive pressure ventilation delivered *via* a nasal, face or mouth mask (NIPPV) has been used in the short- and long-term treatment of chronic hypercapnic respiratory insufficiency from neuromuscular and thoracic disorders, from COPD and cystic fibrosis, with controversial results. It is usually delivered by standard volume-cycled ventilators in assisted or controlled mode [32].

Pressure support ventilation (PSV) is an assisted mode of ventilation supplying a set level of positive airway pressure during spontaneous inspiratory efforts. PSV can either totally or partially unload IM during spontaneous breathing. Total unloading occurs when the only effort made by the patient is to trigger the breath. PSV allows the patient to maintain control of inspiratory and expiratory time and to interact with a set pressure to determine the ultimate flow and V_T [33]. PSV *via* nasal mask (NPSV) has also been used in chronic respiratory insufficiency, in restrictive thoracic disease and COPD [34–36].

Physiological studies. NIPPV delivered in control mode is able to significantly reduce electromyographic (EMG) activity of the IM both in obstructive and in restrictive patients [37], the reduction being greater than with INPV [38]. Oesophageal (P_{oes}) and transdiaphragmatic pressures (P_{di}) are also reduced by NIPPV in control mode, confirming that NIPPV is also able to rest IM from a mechanical point of view [38].

In stable COPD patients, NPSV increases minute ventilation and V_T, and reduces breathing frequency (f_R), whilst improving gas exchange; it is able to reduce diaphragmatic EMG activity (E_{di}), P_{di} and the IM oxygen consumption as assessed by the pressure-time product (PTP_{di}) [39]. Similar results are reported during ARF episodes in COPD [40]. The addition of external positive end-expiratory pressure (PEEP) is able to further reduce diaphragmatic effort and oxygen consumption

both in stable COPD and during acute exacerbations [39, 41]. NPSV with and without PEEP may also be applied by means of portable ventilators [42]. In stable COPD, a reduction in CO and oxygen delivery has been observed with NPSV with and without PEEP, which was, however, of negligible clinical relevance [43].

Clinical studies of NIPPV in ARF of COPD

Success rate. MEDURI *et al.* [44] were the first to publish a report dealing with noninvasive face mask ventilation in patients with ARF. They treated six patients with hypercapnia and four with ARF meeting the clinical and objective criteria for MV, which was delivered with pressure control and PSV *via* a tightly strapped, clear face mask. No patient dropped out of the study because of inability to deliver adequate ventilation or to improve oxygen exchange; three patients (30%) eventually required ET intubation. The mask was generally well-tolerated. All patients had a nasogastric tube placed on suction, and none vomited or aspirated. The physiological response was considered similar to that which would have been achieved with conventionally delivered ventilation.

Since that time, NMV has been widely used in ARF episodes. A review of the literature from 1989 to 1995 shows that use of NMV in ARF has been reported in several studies involving more than 400 patients, most of them with COPD. NMV was successful in 51–91% of cases, the severity of ARF as assessed by the level of respiratory acidosis being widely different among the different populations under study [44–48]. Most of the studies compared effectiveness of NMV with historical groups of patients treated with "conventional" medical therapy, whilst controlled studies of NMV *versus* ET intubation are lacking. In these studies, success was defined as the ability of NMV to improve gas exchange, and to avoid ET intubation and death in the ICU. Some studies published on the clinical effects and success rate of NMV in COPD patients during ARF episodes are presented in table 3.

Modality of ventilation. In a subsequent open study, MEDURI *et al.* [49] treated 18 patients with hypercapnic ARF (83% from COPD or asthma) with NMV consisting of continuous positive airway pressure (CPAP) and NPSV or intermittent mandatory ventilation. NMV was successful in avoiding intubation in 13 of the 18 patients (72%). NPSV was set at 10–20 cmH$_2$O to achieve a frequency (f_R) <25 breaths·min^{-1} and a V_T >7 mL·kg^{-1}. The mean duration of NMV was 25 h, pH increased by 27%, arterial carbon dioxide tension (P_{a,CO_2}) decreased by 24%, and f_R decreased by 44%, with an ICU survival rate of 94%.

The most quoted paper dealing with NPSV during ARF is that by BROCHARD *et al.* [40], who in a study controlled with matched historical patients treated 13 COPD patients with ARF by means of NPSV 12–20 cmH$_2$O. NPSV induced an increase in pH of 38%, and a decrease in P_{a,CO_2} of 26%. Only one of their 13 patients (8%) needed ET intubation as compared with 11 of the 13 historical controls (84%) treated with conventional therapy. Two patients in each group died (15%). As compared with

Table 3. – Published studies on the effect of NMV during ARF in COPD patients

| First author [Ref.] | Patients | | | NMV | Schedule | Control | Results | | | Type of mask employed |
	n	pH	P_{a,CO_2} kPa				pH	P_{a,CO_2} kPa	Success %	
MEDURI [49]	18	7.29	9.5	CPAP + NPSV	25 h PS 10–20 cmH$_2$O VT 7 mL·kg^{-1}	Open	7.37	7.2	72	Face
BROCHARD [40]	13	7.29	8.5	NPSV	7.6 h for 2–8 days PS 12 –20	13 Historical	7.40	6.3	76	Face
FOGLIO [50]	25	7.33	9.7	NIPPV	4×1 h for 6 days·week^{-1} (3 weeks) VT 15 mL·kg^{-1} I:E 1:3	24 ST Retrospective	7.36	7.6	51	Nasal
BENHAMOU [51]	20	7.28	9.2	NIPPV	At first 12 h + night, then individually	Open	7.34	8.4	60	Nasal tailored
VITACCA [52]	13	7.25	11.4	NIPPV	69 h	35 ST	7.40	7.5	77	Face
	16	7.29	10.1	NPSV	57 h	Historical	7.35	8.0	87	
BOTT [53]	30	7.35	8.5	NIPPV	7.6 h for 5–9 days	30 ST Prospective randomized control	7.38	7.6	83	Nasal
FERNANDEZ [54]	14	7.19	12.1	NPSV	8±4 h	Open	7.31	8.8	79	Face
KRAMER [55]	11	7.27	12.0	NPSV	3.8±1.4† days	12 ST Prospective randomized	NR	9.7**	91	
BROCHARD [56]	43	7.27	9.2**	NPSV	6 h	42 ST Prospective randomized	7.31	8.9**	74	Face

NR: nonreported; **: from the figure. NMV: noninvasive mechanical ventilation; ARF: acute respiratory failure; CPAP continuous positive airway pressure; NPSV: pressure support ventilation *via* nasal mask; NIPPV: noninvasive intermittent positive pressure ventilation; ST: standard therapy; PS: pressure setting; VT: tidal volume; I:E: inspiratory/expiratory ratio. For further abbreviations see legend to table 2. †: mean±SD.

the controls, patients treated with NPSV needed a shorter mean duration of ventilatory assistance (3 *vs* 12 days) and a briefer stay in the ICU (7 *vs* 19 days). No side-effects were noted during this study, and with NPSV <25 cmH$_2$O the patients did not observe inflation of the stomach.

NIPPV by nasal mask was used by FOGLIO *et al.* [50] in a retrospective study on 25 COPD patients with acute exacerbations, in which patients unable to tolerate NMV were the control population treated with standard medical therapy. NIPPV was delivered by means of a "domiciliary" volume-cycled ventilator in controlled mode with a VT of 15 mL·kg^{-1}, and an inspiratory/expiratory (I/E) ratio of 1:3. NIPPV was applied for 1 h four times a day for 6 days a week. Improvements in blood gases, maximal inspiratory pressure (MIP) and airflow obstruction were similar to those in control patients. The relevant side-effects are listed in table 4.

NIPPV by means of a volume-cycled ventilator in controlled mode and delivered through a customized nasal mask was used by BENHAMOU *et al.* [51] to evaluate the possible role of NMV in ARF episodes when invasive MV was questionable. They studied 30 patients (mean age 76 yrs), in all of whom clinical or physiological parameters indicated the need for MV, but ET intubation was either not applied because of the age and the physiological condition of the patients, or was postponed. NMV

was continuous during the first 12 h and the following nights, and was then intermittent during the day. Twenty one patients (70%) improved clinically within a few hours. Progressive correction of arterial blood gases (ABG) was observed. Eighteen patients (60%) were able to be successfully weaned from NMV. Clinical tolerance was said to be satisfactory in 23 (76%) patients and poor in seven patients (24%). These authors claimed a success in 60%, but two more deaths after weaning reduced the number of patients able to be discharged home to 16 (53%).

NPSV and NIPPV by face mask were compared in the treatment of ARF in 16 and 13 COPD patients, respectively, by VITACCA *et al.* [52]. Both NPSV and NIPPV improved ABG. Thirteen percent of patients submitted to NPSV and 22% of patients submitted to NIPPV required ET intubation. These authors retrospectively compared the need for ET intubation of these patients (as a whole 17%) with 35 COPD patients in ARF treated with medical therapy in the same institution, 16 (45%) of whom required ET intubation.

BOTT *et al.* [53] reported the first prospective randomized clinical trial of NIPPV compared with conventional therapy in patients with acute exacerbations of COPD. Thirty patients were randomized to receive NIPPV and 30 patients received conventional therapy. Nasal ventilation was more effective than conventional therapy in lowering (by 15%) P_{a,CO_2} and reversing acidosis. Four

Table 4. – Side-effects during noninvasive positive pressure ventilation assessed in published studies

Side-effect	MEDURI [49]	FOGLIO [50]	BENAHMOU [51]	VITACCA [52]	KRAMER [55]
Type of mask	Face	Nasal	Nasal tailored	Face	Nasal
Aspiration	5.6				
Gastric distension		8		3.4	
Mask discomfort		32		7	18
Nose lesion	5.6	20	7	21	18
Dry nose		20		3.4	
Eye irritation		16	17		
Air leaks		16		3.4	18
Atelectasis			10		
Claustrophobia				3.4	

Percentage values are presented. First authors only are named.

patients allocated to receive NIPPV did not receive this therapy because they were unable to tolerate it or due to lack of co-operation (due to neurological status). A comparison of the 26 patients who were treated with NIPPV compared with the 30 patients who received conventional therapy demonstrated a significant reduction in mortality (1 of the 26 (3.8%) *versus* 9 of the 30 (30%)). However, when the four patients who did not tolerate NMV were included, the mortality with NMV increased to 3 out of 30 (10%), being not significantly modified on an intention-to-treat basis. Breathlessness was significantly improved in the treated group. The difference in survival for the two groups led the authors to recommend NIPPV in all patients admitted with an acute exacerbation of COPD and ventilatory failure who do not respond promptly to conventional therapy. It is worthwhile mentioning that many control group patients in the study by BOTT *et al*. [53] died without being endotracheally intubated, which may have influenced mortality.

FERNANDEZ *et al*. [54] studied 12 COPD patients during 14 episodes of acute exacerbation of chronic respiratory failure, who failed to improve with intensive medical therapy and showed impairments in severe respiratory acidosis and/or hypercapnic encephalopathy leading their attending physicians to recommend MV. In these circumstances, a trial of NPSV with a level of pressure support adjusted to obtain a $V\text{T} >400$ mL was attempted. If the patient deteriorated, ET intubation and standard MV were performed. Mean $P\text{a,CO}_2$ decreased by 27%, and arterial pH increased. Three episodes were unsuccessful (21%) and one of the patients (8%) died in the intensive care unit (ICU).

In a recent randomized, prospective trial of NMV *versus* standard therapy, KRAMER *et al*. [55] used a simple portable ventilator to deliver NPSV in the patient flow-triggered/time triggered (S/T) mode through a nasal mask to COPD and non-COPD patients with ARF. Ventilation was initiated using a backup rate of 12 breaths·min^{-1}. The inspiratory positive airway pressure was set at 8 cmH$_2$O and the expiratory positive airway pressure at 2 cmH$_2$O. The need for intubation was reduced from 73% in the standard therapy group to 31% in the NPSV group. Among COPD patients, the reduction was even more relevant with 67% of control patients requiring intubation compared with 9% of NPSV patients.

In the largest multicentric, randomized, prospective study of NMV *vs* standard medical therapy in 85 COPD patients, BROCHARD *et al*. [56] showed that the use of 20 cmH$_2$O of NPSV significantly reduced the need for ET

(11 out of 43 (26%) *vs* 31 out of 42 (74%) for NPSV and standard therapy, respectively). In the subgroup successfully treated with NPSV, a significant improvement was noted in the respiratory rate as well as in arterial oxygen tension ($P\text{a,O}_2$) at 1 h (by 61%) and $P\text{a,CO}_2$ at 12 h (by 14%). In addition, the frequency of complications was significantly lower in the NPSV group (16 *vs* 48%). The in-hospital mortality rate was also significantly reduced with NPSV (4 out of 43 *vs* 12 out of 42). Ten of the 12 deaths in the standard-treatment group and 3 of the 4 in the NPSV group occurred during mechanical ventilation. These authors concluded that in selected patients with acute exacerbations of COPD, NMV can reduce the need for ET, the length of the hospital stay and the in-hospital mortality rate.

Other uncontrolled studies of noninvasive positive pressure ventilation during ARF in COPD patients have recently been reported [57–59].

CPAP and PEEP. Use of external PEEP or CPAP is a key therapy in the management of ARF due either to impaired gas exchange (acute lung failure) or inability of the IM to sustain adequate alveolar ventilation (acute exacerbations of COPD). The major aims of PEEP are considered to be the improvement in oxygenation and the unloading of IM in the two cases, respectively. In acute exacerbations of COPD, dynamic pulmonary hyperinflation and its systematic corollary, *i.e.* intrinsic PEEP (PEEPi) caused by expiratory flow limitation and prolonged expiration, are invariably present. As a consequence, inspiration does not begin with the start of inspiratory effort because PEEPi has to be offset by the IM before either spontaneous or mechanical breathing can start [60]. In addition to studies in intubated patients [61, 62], CPAP and PEEP have recently been shown to reduce the WOB in patients with acute exacerbation of COPD. In these patients, an added PEEP can counterbalance, at least in part, the inspiratory threshold load resulting from PEEPi. Most studies on added PEEP have focused on its physiological effects, and few controlled trials have dealt with the effects of PEEP on clinical outcome [41, 63–65].

APPENDINI *et al*. [41] delivered, through a nasal mask, 15 min periods of CPAP at 80% of dynamic PEEPi (PEEPi,dyn), NPSV of 10 cmH$_2$O and a combination of both to seven COPD patients with ARF (mean $P\text{a,O}_2$ 7.5 kPa, $P\text{a,CO}_2$ 10.2 kPa, pH 7.34). Both NPSV and NPSV+ CPAP but not CPAP alone induced a reduction in $P\text{a,CO}_2$

of about 7.3%. More interestingly, NPSV decreased diaphragmatic effort as assessed by PTPdi. NPSV combined with CPAP induced a further reduction in PTPdi by counterbalancing PEEPi,dyn, which was reduced. On the basis of these results, the authors suggested the use of low levels of PEEP (80–90% of PEEPi,dyn) to treat acute exacerbation of COPD by means of mask PSV.

MIRO et al. [64] used mask CPAP in seven patients with hypercapnic ARF, in an attempt to avoid ET intubation. Mask CPAP was started at 5 cmH$_2$O and then increased to a maximum of 10 cmH$_2$O depending on the clinical response. In five patients (71%), CPAP significantly improved ABG but one of them was withdrawn from mask ventilation due to necrosis from the face mask and was, therefore, intubated. In two out of the seven patients, ABG deteriorated even with CPAP of 10 cmH$_2$O and one of these (14%) was intubated. No barotrauma or adverse haemodynamic effects were associated with CPAP.

FERNANDEZ et al. [54] were able to add PEEP (5.7±0.8 cmH$_2$O) to counterbalance "suspected" but not assessed PEEPi in four out of their 14 cases of ARF treated by NPSV. No increase in the leakage around the mask occurred. In these patients, the use of external PEEP only diminished the apparent inspiratory effort. In some cases, patients spontaneously referred to an alleviation of dyspnoea when PEEP was added. Unfortunately, no objective measurement is reported.

Duration of NMV and length of stay in the ICU. A review of the literature shows NMV was used 4–20 h·day^{-1} for 1–9 days. In the controlled study by BOTT et al. [53], both patients undergoing NMV and the control group remained in hospital for 9 days. In the study by BROCHARD et al. [40], the need for ventilatory assistance was 3±1 and 12±11 days for the group treated by a noninvasive and invasive approach, respectively. Patients in their study remained in ICU 7±3 *versus* 19±12 days for NMV and ET intubation, respectively. FERNANDEZ et al. [54] reported an ICU stay of 5±2 *versus* 17±8 days for NPSV and ET intubation, respectively. In a recent retrospective study by VITACCA et al. [66], duration of NMV ranged 4 h to 11 days (mean 2.6±2.0 days) in comparison to invasive MV which lasted 19±10 days (range 2–84 days). Patients submitted to NMV remained in the ICU for 10±8 days, whilst patients undergoing ET intubation remained in the ICU for 24±12 days. Patients in the study by KRAMER et al. [55] used the ventilator for an average of

3.8±1.4 days, and among patients who used NPSV successfully the average duration of use during the first 24 h was 20.1± 0.4 h. In that study, NPSV did not significantly reduce duration of ventilator use, hospital length of stay, mortality or charges in comparison to standard therapy. In the recent multicentric prospective, randomized study by BROCHARD et al. [56], the mean hospital stay was significantly shorter for patients receiving NPSV (23±17 *vs* 35±33 days).

Mortality. Conventional medical treatment of COPD patients with ARF was associated with an overall mortality ranging 12–29% [67, 68]. Table 5 shows the immediate mortality in the ICU of COPD patients with ARF treated with either invasive or noninvasive MV. Comparison of rates between studies is difficult as the criteria for inclusion of patients, settings of MV, medical treatment and medical practices (*e.g.* less or more frequent use of mechanical ventilation in different countries) are different. As a whole, the survival rate of NMV seem better, although it is conceivable that patients submitted to invasive MV would have been more severe [25, 40, 49, 51–54, 56, 69–76].

Determinants of success. Since promising results have been observed with NIPPV and NPSV, NMV is increasingly being used in the treatment of ARF in COPD patients. The success rate of these techniques is different according to different authors, even in the same department [50, 52]. The type of mask employed, mode of ventilation, compliance to treatment, patient characteristics and severity of disease treated may influence the success rate [77]. Up to the present time, controlled studies of NMV *versus* ET intubation are lacking, so that the use of NMV as an alternative to ET intubation, might, in case of failure, be considered as unduly delayed ET intubation. It is, therefore, important to identify parameters able to predict the outcome of NMV.

In the study by MEDURI et al. [49], a significant initial (after 1 h of treatment) improvement in Pa,CO$_2$ (>16% decrease) and in pH (>7.30) but not pulmonary function in a stable state predicted success. BENAHMOU et al. [51] studied the initial characteristics in a group of patients successfully weaned from NMV and in a group of patients who died or who were secondarily intubated. These two groups did not differ in terms of age, previous respiratory tract disease, cause for the acute decompensation,

Table 5. – Mortality rate of COPD patients in ICU

First author	[Ref.]	Pts n	Mortality %	First author	[Ref.]	Pts n	Mortality %
NUNN	[69]	11	54	MEDURI	[49]	18	6
GILLESPIE	[70]	54	24	BROCHARD	[40]	13	15
SPICHER	[71]	13	46	BENHAMOU	[51]	20	25
KAELIN	[72]	35	22	VITACCA	[66]	29	13
MENZIES	[73]	95	21	BOTT	[53]	30	10
GRACEY	[74]	7	42	FERNANDEZ	[54]	12	8
STAUFFER	[75]	67	45	AMBROSINO	[76]	47	7
BROCHARD	[56]	31	32	BROCHARD	[56]	43	9
				CORRADO (INPV)	[25]	105	11

ICU: Intensive Care Unit; MV: mechanical ventilation. For further abbreviations see legend to table 1.

initial ABG, Simplified Acute Physiological Score (SAPS) [78], and level of consciousness on inclusion in the study. However, initial agitation appeared to be a poor prognostic factor. In the study by BOTT *et al.* [53], patients who died were more acidotic on admission than patients who survived (pH 7.31 *versus* 7.35) and more hypercapnic (Pa,CO$_2$ 9.4 *vs* 8.4 kPa), although both groups were equally hypoxic (Pa,O$_2$ 5.1 *vs* 5.3 kPa). FERNANDEZ *et al.* [54] failed to demonstrate significant differences between patients not needing and those needing ET in terms of diagnosis, age, clinical status as assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II score [79], ABG and haemodynamics, either on admission or before and after NMV.

SOO HOO *et al.* [80] evaluated the efficacy of nasal mechanical ventilation in COPD patients and hypercapnic respiratory failure and tried to identify predictors of its success or failure in a prospective study of 12 patients treated during 14 episodes of ARF (mean pH 7.25±0.09; mean Pa,CO$_2$ 9.7±2.1 kPa). NMV was performed with a volume ventilator and was successful in 50% of cases. There was no differences in age, prior pulmonary function and ABG, admission ABG, or respiratory rate between those patients successfully treated and those patients who failed NIPPV. Unsuccessfully treated patients appeared to have a greater severity of illness, as indicated by a higher APACHE II score (mean 21±4 *vs* 15±4). Unsuccessfully treated patients were edentulous, had pneumonia or excess secretions, and had pursed-lip breathing, factors that prevented adequate mouth seal and contributed to greater mouth leakage than in successfully treated patients. Successfully treated patients were able to adapt more rapidly to the nasal mask and ventilator with greater and more rapid reduction in Pa,CO$_2$ correction of pH, and reduction in respiratory rate. BROCHARD *et al.* [56] found that NPSV was less effective in the patients with more severe clinical disturbances as assessed by SAPS, and encephalopathy score. In that study, gas exchange was not different between patients treated successfully and unsuccessfully with NPSV.

With the aim of identifying simple parameters recorded in a hospital setting useful for the early prediction of whether or not COPD patients may be successfully treated with NMV, we have recently retrospectively analysed 59 episodes of ARF in 47 COPD patients treated with NMV by means of either NPSV (25 cases) or NIPPV (34 cases) delivered through either a nasal (31 cases) or a facial (28 cases) mask. According to survival and to the need for ET intubation, each episode was considered as successful (46 episodes; 78%) or unsuccessful (13 episodes; 22%). NMV was able to significantly reduce Pa,CO$_2$ in both groups. NPSV was successful in 84% and NIPPV in 73%. Clinical and radiological evidence of pneumonia was the cause of ARF in 39% of unsuccessful episodes but only in 9% of successful ones. Success with NMV was associated with less severely abnormal baseline clinical and functional parameters, and to less severe levels of acidosis assessed during an initial trial of NMV. The logistic regression analysis demonstrated that baseline pH maintained a significant predictive effect, indicating that all other variables were in some way dependent on it. By this analysis, baseline pH showed a sensitivity of 97% and a specificity of 71%. The severity of the episode of ARF as assessed by clinical and functional compromise and the level of acidosis and hypercapnia during an initial trial of NMV, therefore, have an influence on the likelihood of success with NMV and may prove useful in deciding whether to continue with this treatment [76]. Facial masks were successful in 78% and nasal masks in 77% (unpublished data); therefore, the mode of ventilation and type of mask used do not seem to influence the outcome of NMV in acute exacerbations of COPD. Both AMBROSINO *et al.* [76] and BROCHARD *et al.* [56] found that NMV was less likely to be effective in patients with more severe physiological disturbances at the outset, suggesting that once decompensation has been well-established the cycle of deterioration may not be broken with the use of NMV [81].

On the other hand, in patients with ARF from causes other than COPD, WYSOCKI *et al.* [82, 83] proposed NPSV by face mask as an alternative to ET intubation. Only in hypercapnic but not in normocapnic patients was NPSV associated with a reduction in the rate of ET intubation, in the length of ICU stay and in the mortality rate. In both groups of patients, gas exchange improved after 1 h on NPSV. PENNOCK *et al.* [84] in similar patients could not find any pretreatment parameters that favoured successful outcome.

Long term survival. Survival at 1 yr in COPD patients undergoing ET intubation and MV is variable but nevertheless quite low [70–75, 85–94]. Survival rates at one year obtained in different studies of COPD patients who underwent MV are shown in table 6. Recently, VITACCA *et al.* [66] have retrospectively evaluated the short- and long-term prognosis in COPD patients submitted to NMV for ARF. Thirty nine patients submitted to NMV through face masks (mean pH 7.28; Pa,CO$_2$ 10.9 kPa) were compared to 27 historical control patients (mean pH 7.26; Pa,CO$_2$ 9.9 kPa) submitted to MV through ET intubation when clinical and functional conditions had further deteriorated because the medical therapy failed and NMV was not available at the time. The mortality rate was 20 and 26% in ICU, 18 and 48% at 3 months, and 30 and 63% at 1 yr, in NMV patients and in controls, respectively. The number of new ICU admissions during the follow-up was 0.12 *versus* 0.30 per patient annually in NMV and patients undergoing ET intubation, respectively.

CORRADO *et al.* [25] showed that the overall survival rate during the first year of their patients treated by

Table 6. – One year mortality rate in patients undergoing invasive and noninvasive mechanical ventilation

First author	[Ref.]	Pts n	MV modality	Mortality %
CORRADO	[25]	105	INPV	18
GILLESPIE	[70]	54	ET	44
KAELIN	[72]	35	ET	59
MENZIES	[73]	95	ET	66
GRACEY	[74]	7	ET	61
STAUFFER	[75]	67	ET	44
NAVA	[85]	42	ET	45
VITACCA	[66]	27	ET	63
VITACCA	[66]	30	NIPPV/NPSV	30

ET: endotracheal (intubation). For further abbreviations see legends to tables 2 and 3.

means of iron lung was 82%. These patients made monthly visits to the hospital. This fact, rather than the difference in modality of ventilation (mask ventilation *versus* iron lung) might explain the better 1 yr survival of patients in the study by CORRADO *et al*. [29], underlining the usefulness of a regular programme of outpatient control.

Diseases other than COPD

MARTIN *et al*. [95] showed that in induced asthma CPAP reduced the load on the IM, improving their efficiency and decreasing the energy cost of their action. In patients with severe acute asthma, SHIVARAM *et al*. [96] reported that low levels of CPAP (5 and 7.5 cmH$_2$O) by nasal mask produced a significant decrease in breathing frequency and dyspnoea compared with a control group. Neither group of patients showed significant changes in spirometry or blood gases. That different modalities of NMV may have a role in the management of patients with severe acute asthma is still to be confirmed by clinical controlled studies [97].

NMV has been used as an effective and "dignified" method of supporting patients with end-stage disease and ARF [98, 99]. Other studies dealing with medical or surgical patients with different aetiologies (from hypothyroidism to cardiogenic pulmonary oedema) and ages have also been published. Generally, improvement in ABG is reported both with NIPPV and NPSV [100–105]. CPAP delivered by face mask in patients with severe cardiogenic pulmonary oedema resulted in earlier physiological improvement and in reduction of the need for ET intubation and MV, in comparison to standard medical therapy. However, no significant difference was found in in-hospital mortality or the length of the hospital stay [103]. More recently, LIN *et al*. [106] confirmed that serial incremental CPAP therapy improves oxygenation and gas exchange, decreases intrapulmonary shunt and relieves the need for ET intubation in patients with acute cardiogenic pulmonary oedema. These authors failed to show any significant beneficial changes in mortality rate and hospital stay. A recent prospective randomized study by WYSOCKI *et al*. [82] suggested a lack of efficacy of NMV in non-COPD patients. PENNOCK *et al*. [84] were able to transfer the use of NPSV delivered by simple portable ventilators from an experimental setting [98] to the normal care providers of patients with ARF of different causes (80% of them surgical) with a success rate of 80%. NPSV, CPAP and continuous negative external pressure have been used in the treatment of ARF in infectious complications of acquired immune deficiency syndrome (AIDS) and lung transplantation [107, 108]. Some uncontrolled studies of ARF have also included patients with chest wall disease [49, 51, 57, 102].

Weaning from invasive mechanical ventilation

Weaning from invasive MV may be difficult in patients with increased WOB or impaired ventilatory drive. Various techniques have been used to aid weaning, including PSV. Most methods require maintenance of ET intubation and supervision in an ICU, thus causing the cost of care to increase [109, 110]. NMV was used in patients with weaning difficulties from invasive MV by means of NIPPV and NPSV after a median of 31 days of invasive MV [111]. Eighteen out of 22 patients were successfully transferred to NMV and discharged home a median of 11 days after starting this type of ventilation. Other cases of successful substitution of NIPPV for ET ventilation have been reported [112, 113].

Advantages and limitations of NIPPV

The main advantages of mask ventilation are shown in table 7. The theoretical advantages of mask ventilation include: improvement in patient comfort, reduction in the need for sedation; avoidance of the complications of ET intubation; possibility of delivering ventilation intermittently; capacity for normal swallowing, feeding and speech; physiological air warming and humidification; a physiological cough; easier weaning; meanwhile maintaining the option of ET intubation unchanged [47, 48].

Side effects. Most studies report the prevalence of side-effects only anecdotally. Studies with an assessment of side-effects are shown in table 4. Care is needed to ensure that the mask fits and is comfortable. Tolerance to the ventilator is important. BENHAMOU *et al*. [51] reported "bad tolerance" to the respirator in 17% of their cases. VITACCA *et al*. [52] found that compliance to NMV was better with NPSV and fewer side-effects were observed with this modality in comparison to NIPPV. In the study by KRAMER *et al*. [55], 2 out of 11 patients (18%) failed NPSV because of nasal mask intolerance. Several commercial models are available in multiple sizes or can be constructed to conform to facial contours. A poorly fitting mask is bound to leak. Commercial masks have been associated with air leaks in 16 and 18% of patients, respectively [50, 55]. Furthermore, the amount of leakage can change and the nasal mask is easily removable. The positive pressures delivering air to the patient are felt on the face with the nasal mask, a sensation that can be uncomfortable and eye irritation and/or conjunctivitis have been reported in 16 and 17% of patients, respectively [50, 51].

All these differences can contribute to an inspiratory volume that may be changing and that is not necessarily directly proportional to the ventilator pressure as it would be with an intubated patient. To avoid air leaks, some masks incorporate a large high-compliance, low-pressure inflatable cuff for facial sealing. Some masks are filled with silicone to minimize dead space and to avoid air

Table 7. – Advantages of mask ventilation

Intermittent delivery of ventilation
No need for ET intubation
Use of different modalities of ventilation
Normal swallowing, feeding and speech
Physiological air-warming and humidification
Physiological cough
Easier weaning
Unchanged possibilities of ET intubation

ET: endotracheal

leaks, and thin pieces of foam rubber are used to adjust the face mask for a tighter fit. Customized masks are individually moulded to the patient's nose in silicone paste mixed in a slow catalyser. The mask is usually prepared rapidly (about 15–30 min) [51, 100].

Commercial and customized masks are secured to the head with Velcro or elastic straps. Keeping the mouth closed has been shown to be necessary to rest IM effectively [37], and the usual source of inadvertent volume loss is through the mouth in patients who sleep with their mouth open. An elasticated chin strap secured to the bands holding the mask to the head is often sufficient to control the leaks but it is rarely successful in edentulous patients. Efforts to secure the mask more firmly put pressure on the bridge of the nose, where the skin ulcerates very easily and necrosis may result. Mild skin lesions were reported in 5.6% of patients by MEDURI et al. [49], and in other studies skin reddening and/or abrasion was reported in 20% of patients [52], and nasal bridge ulcerations in 18% of patients [55]. However, in the largest series by BROCHARD et al. [56] facial skin necrosis was reported in only 1 out of 43 (2.3%) patients. The use of wound care dressing on the bridge of the nose under the mask may avoid the skin abrasions [84]. Different types of commercial nasal masks are available, some of them involving only nostrils and avoiding contact with nose skin.

Gastric distension is almost unavoidable with facial masks, and a nasogastric tube is usually inserted before initiating face mask ventilation and placed on suction. Even so, MEDURI et al. [49] reported one case (5.6%) of aspiration [49]. However, BROCHARD et al. [40] reported that when using a level of pressure support lower than 25 cmH$_2$O no gastric inflation was observed. Nasal masks may be related to gastric distension [50].

Type of mask. It is not clear whether face masks are more effective. Theoretically, face masks allow less air leakage through the mouth, while nasal masks preserve speech and swallowing, but no prospective study has directly compared their efficacy. Although previous reports suggest that facial masks could be more efficient in ARF [40, 47, 49, 52], PENNOCK and co-workers [84, 101] successfully used a nasal mask for NMV in ARF from various causes. The number of failures due to lack of accommodation to the mask in several reports [40, 47, 49, 101] support the need for a well-tolerated and a tighter fitted mask specifically designed for this noninvasive technique. The type of the mask (nasal or facial) does not seem to play a role in the outcome of NMV. Recently, a mask that covers the whole anterior surface of the face and delivers effective ventilation *via* the nasal and oral routes, having a more extensive patient-mask interface and not obstructing the patient's field of vision, has been introduced and evaluated but needs further clinical studies [114].

Nursing. Clearing the airways should precede mask ventilation in patients with a great amount of secretions. The effectiveness of NIPPV with all modalities depends on strict staff supervision for nurses and physiotherapists. CHEVROLET et al. [115] treated six patients with NIPPV

during an episode of ARF due to restrictive and obstructive pulmonary disorders. They used a volume-cycled ventilator in assist/control mode and found that NIPPV was successful in avoiding ET intubation in only three patients suffering from a restrictive pulmonary disorder, whereas the procedure was unsuccessful in patients with obstructive disorders. Moreover, in all patients, acute NIPPV was very time-consuming for the nursing staff. In patients with restrictive disorders, a nurse needed to monitor a patient submitted to NIPPV for 41% of the duration of ventilation. In patients with obstructive disorders, a nurse needed to monitor for 91% of the NIPPV time! However, no comparison with the time consumed to deliver standard therapy is reported, and BOTT et al. [53] found that the amount for nursing care required to treat ARF with NIPPV was not different in comparison to patients undergoing standard therapy.

In a study by KRAMER et al. [55], respiratory therapists tended to spend more time at the bedside of patients receiving NPSV than that of control patients (100±27 *versus* 44±15 min over an 8 h period) but the difference was not statistically significant. Furthermore, there was a significant drop in the amount of time therapists spent at the bedside of NPSV patients during the second 8 h period. In addition, therapists and nurses rated the difficulty of caring for patients receiving NPSV as no greater than for control patients. PENNOCK et al. [84] suggested that a 15–30 min period of patient-caregiver interaction when initiating ventilator support can substantially improve patient comfort and acceptance, and reduce the need for nursing care.

General considerations

Selection criteria. As a whole, these studies show that NMV may be useful in selected patients with ARF. Based on criteria used in the studies evaluated, patients should have clinical and physiological evidence of ARF, including acute respiratory acidosis, tachypnoea, use of accessory muscles of inspiration and/or abdominal paradox. Patients should be sufficiently co-operative to follow instructions related to use of the mask. It is commonly said that NMV should be avoided and ET intubation performed in patients with haemodynamic instability, uncontrolled arrhythmias, gastrointestinal bleeding, high risk for aspiration, but no specific study is available to support this (table 8) [47]. It is worth noting that in the study by BROCHARD et al. [56] only 31% of all the patients with COPD admitted during the study period met the criteria for enrolment.

Pros and cons. With these limitations, NMV in selected patients with ARF is well-tolerated and may be useful in avoiding ET intubation in most cases of COPD and with a wide range of success rates in other diseases.

Table 8. – Contraindications to mask ventilation

Coma
Unco-operative patient
Haemodynamic instability
Gastrointestinal bleeding
Recent upper abdominal surgery
Need for frequent aspiration
Excessive airway secretions

Several pros and cons must be noted.

1. Most of the studies on NMV have historical control populations and only three adequately controlled published trials have shown an advantage of NMV compared with conventional medical therapy [53, 55, 56]. Historical comparison of two different patient populations must be interpreted with caution because treatment strategies may change with time and such studies are considered to favour the treatment group [116]. On the other hand, a retrospective study gives information about a "real" setting of operations in an ICU.

2. With the above limitations, NMV seems to be able to reduce the need for ET intubation in ARF. This, in turn, has several advantages in terms of avoiding complications of invasive MV, reducing the length of stay in an ICU and, probably, the number of ICU readmissions. On the other hand, prospective, randomized, controlled studies of noninvasive *versus* ET intubation are lacking.

3. Side effects of NMV seem less severe than those induced by ET MV. On the other hand, NMV may be impeded by these complications. Prevalence of some of these complications, in particular aspiration, are still to be completely assessed and their consequences evaluated.

4. The findings relating to time consumption by nursing staff [115] may be of great concern, as the use of NMV could pose a greater strain on resources than would standard practice alone. This finding was not confirmed by BOTT *et al*. [53], or by KRAMER *et al*. [55]. Other studies have suggested a reduced length of stay in the ICU of patients treated with NMV in comparison to ET intubated patients [40, 54, 56, 66]. Furthermore, one report suggested a reduction in ICU readmission when patients avoided invasive MV [66]. This observation might support a reduction in the cost of treatment of these patients, but again studies of economics are lacking. In one study reporting costs [55], no significant difference between NPSV and control patients was found in hospital charges (3.7±1.1 and 4.0±1.5 thousand dollars for NPSV and control, respectively), or in total expenses (37.6±7.9 and 33.9±6.9 thousand dollars, respectively).

5. Noninvasive ventilatory support as a substitute for intubation and mechanical ventilation has several limitations. When a patient is intubated, the caregiver can set the ventilator parameters as prescribed and assume that the ventilator will perform appropriately. NMV affords less control. Mask ventilation with "domiciliary" ventilators sacrifices control of the airway, choice of pressure or volume delivery waveform, sometimes control of the level of inspiratory trigger, most alarms, *etc*. If the delivery of ventilator support in a specific patient requires any of these features, the choice of noninvasive ventilation with a simplified ventilatory support system is not appropriate. On the other hand, the many features of modern positive pressure ventilators are not necessary in all patients requiring MV [84].

Future studies

Further studies are needed: 1) to evaluate the ability of NMV (if any) to be used as an alternative to ET intubation; 2) to evaluate the most appropriate selection of patients and time of intervention; 3) to find the best level of NPSV and PEEP in different kinds of patients; 4) to define the best type of mask and most appropriate ventilator in different situations (ICU, Intermediate Intensive Care Unit, pulmonary ward, *etc*.); and 5) to evaluate the costs of NMV in comparison to conventional therapy and to invasive MV.

In conclusion, some authors claim that noninvasive mechanical ventilation to treat acute respiratory failure should be considered investigational and reserved for carefully selected patients [47]. Our opinion is rather that, in selected patients, a trial of noninvasive mechanical ventilation should be instituted at an early stage in episodes of acute respiratory failure as an adjunct to medical therapy, before severe acidosis ensues, in order to avoid endotracheal intubation.

References

1. Derenne JP, Fleury B, Pariente R. Acute respiratory failure of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988; 138: 1006–1033.
2. Petty TL. Chronic airflow obstruction. *In*: Petty TL ed. Intensive and Rehabilitative Respiratory Care. Philadelphia, Lea and Febiger, 1982; pp. 222–245.
3. Tobin MJ. Mechanical ventilation. *N Engl J Me*d 1994; 130: 1056–1061.
4. Pingleton S. Complications of acute respiratory failure. *Am Rev Respir Dis* 1988; 137: 1463–1493.
5. Rashkin MC, Davis T. Acute complications of endotracheal intubation. *Chest* 1986; 89: 165–167.
6. Heffner JE, Miller KS, Sahn SA. Tracheostomy in the intensive care unit. Part 2. Complications. *Chest* 1986; 90: 430–436.
7. Criner G, Make B, Celli B. Respiratory muscle dysfunction secondary to chronic tracheostomy tube placement. *Chest* 1987; 91: 139–141.
8. Deutschman CS, Wilton P, Sinow J, Dibbell D, Konstantinides FN, Cerra FB. Paranasal sinusitis associated with nasotracheal intubation: a frequently unrecognized and treatable source of sepsis. *Crit Care Med* 1986; 14: 11–114.
9. Torres A, Aznar R Gatell JM, *et al*. Incidence, risk and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respir Dis* 1990; 142: 523–528.
10. Fagon JY, Chastre J, Hance A, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993; 94: 281–287.
11. Kingston GW, Phang PT, Leathley MJ. Increased incidence of nosocomial pneumonia in mechanically-ventilated patients with subclinical aspiration. *Am J Surg* 1991; 161: 589–592.
12. Shapiro M, Wilson RK, Casar G, Bloom K Teague RB. Work of breathing through different sized endotracheal tubes. *Crit Care Med* 1986; 14: 1028–1031.
13. Le Bourdelles G, Vires N, Bockzowki, Seta N, Pavolovic D, Aubier M. Effects of mechanical ventilation on diaphragmatic contractile properties in rats. *Am J Respir Crit Care Med* 1994; 149: 1539–1544.
14. Tobin MJ, Alex CG. Discontinuation of mechanical ventilation. *In*: Tobin MJ (ed). Principles and Practice of Mechanical Ventilation. NY, McGraw-Hill, 1994; pp. 1177–1206.
15. Hill N. Clinical applications of body ventilators. *Chest* 1986; 90: 897–905.
16. Ambrosino N, Rampulla C. Negative pressure ventilation in COPD patients. *Eur Respir Rev* 1992; 2: 353–356.

17. Nava S, Ambrosino N, Zocchi L, Rampulla C. Diaphragmatic rest during negative pressure ventilation by pneumo-wrap: assessment in normal and COPD patients. *Chest* 1990; 98: 857–865.

18. Beck GJ, Seanor HE, Barach AL, Gats D. Effects of pressure breathing on venous pressure: a comparative study of positive pressure breathing applied to the upper respiratory passageway and negative pressure to the body of normal individuals. *Am J Med Sci* 1952; 224: 169–173.

19. Ambrosino N, Cobelli F, Torbicki, *et al*. Hemodynamic effects of negative-pressure ventilation in patients with COPD. *Chest* 1990; 97: 850–856.

20. Levy RD, Cosio MG, Gibbons L, Macklem PT, Martin JG. Induction of sleep apnoea with negative pressure ventilation in patients with chronic obstructive lung disease. *Thorax* 1992; 47: 612–615.

21. Marino WD, Pitchumoni CS. Reversal of negative pressure ventilation-induced lower esophageal sphincter dysfunction with metoclopramide. *Am J Gastroenterol* 1992; 87: 190–194.

22. Zibrak JD, Hill NS, Federman EC, Kwa SL, O'Donnell C. Evaluation of intermittent long-term negative pressure ventilation in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988; 138: 1515–1518.

23. Shneerson JM. Noninvasive and domiciliary ventilation: negative pressure techniques. *Thorax* 1991; 46: 131–135.

24. Levine S, Henson D. Negative pressure ventilation. *In*: Tobin MJ, ed. Principles and Practice of Mechanical Ventilation. NY: McGraw-Hill, 1994; pp. 393–411.

25. Corrado A, Bruscoli G, Messori A, *et al*. Iron Lung treatment of subjects with COPD in acute respiratory failure: evaluation of short- and long-term prognosis. *Chest* 1992; 101: 692–696.

26. Montserrat JM, Martos JA, Alarcon A, Celis R Plaza V, Picado C. Effect of negative pressure ventilation on arterial blood gas pressures and inspiratory muscles strength during an exacerbation of chronic obstructive lung disease. *Thorax* 1991; 46: 6–8.

27. Sauret JM, Guitart AC, Rodriguez-Frojan G, Cornudella R. Intermittent short-term negative pressure ventilation and increased oxygenation in COPD patients with severe hypercapnic respiratory failure. *Chest* 1991; 100: 455–459.

28. Libby DM, Briscoe WA, Boyce B, Smith JP. Acute respiratory failure in scoliosis of kyphosis: prolonged survival and treatment. *Am J Med* 1982; 73: 532–538.

29. Lassen HCA. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special references to treatment of acute respiratory insufficiency. *Lancet* 1953; 1: 37–41.

30. Marks A, Bocles J, Morganti L. A new ventilatory assister for patients with respiratory acidosis. *N Engl J Med* 1963; 268: 61–67.

31. Corrado A, Bruscoli G, De Paola E, Ciardi-Duprè GF, Baccini A, Taddei M. Respiratory muscle insufficiency in acute respiratory failure of subjects with severe COPD: treatment with intermittent negative pressure ventilation. *Eur Respir J* 1990; 3: 644–648.

32. Calverley PMA. Domiciliary ventilation in chronic obstructive lung disease. *Thorax* 1992; 47: 334–336.

33. MacIntyre N. Nishima M, Usada Y, Tokioka H. Takezawa J, Shimada Y. The Nagoya conference on system design and patient-ventilator interactions during pressure support ventilation. *Chest* 1990; 97: 1463–1466.

34. Hill NS, Eveloff SE, Carlisle CC, Goff SG. Efficacy of nocturnal nasal ventilation in patients with restrictive thoracic disease. *Am Rev Respir Dis* 1992; 145: 365–371.

35. Strumpf DA, Millman RP, Carlisle CC, *et al*. Nocturnal positive-pressure ventilation *via* nasal mask in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991; 144: 1234–1239.

36. Waldhorn RE. Nocturnal nasal intermittent positive pressure ventilation with Bi-level positive airway pressure (BiPAP®) in respiratory failure. *Chest* 1992; 145: 365–371.

37. Carrey Z, Gottfried S, Levy R. Ventilatory muscle support in respiratory failure with nasal positive pressure ventilation. *Chest* 1990; 97: 150–158.

38. Belman MJ, Soo Hoo GW, Kuei JH, Shadmer R. Efficacy of positive *vs* negative pressure evaluation in unloading the respiratory muscles. *Chest* 1990; 98: 850–856.

39. Nava S, Ambrosino N, Rubini F, *et al*. Effect of nasal pressure support ventilation and external PEEP on diaphragmatic activity in patients with severe stable COPD. *Chest* 1993; 103: 143–150.

40. Brochard L, Isabey D, Piquet J, *et al*. Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. *N Engl J Med* 1990; 323: 1523–1530.

41. Appendini F, Patessio A, Zanaboni S, *et al*. Physiological effects of positive end-expiratory pressure and mask pressure support during exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994; 149: 1069–1076.

42. Ambrosino N, Nava S, Bertone P, Fracchia C, Rampulla C. Physiologic evaluation of pressure support ventilation by nasal mask in patients with stable COPD. *Chest* 1992; 101: 385–391.

43. Ambrosino N, Nava S, Torbicki A, *et al*. Hemodynamic effects of pressure support ventilation and PEEP by nasal route in patients with chronic hypercapnic respiratory insufficiency. *Thorax* 1993; 48: 523–528.

44. Meduri GU, Conoscenti CC, Menashe PH, Nair S. Noninvasive face mask ventilation in patients with acute respiratory failure. *Chest* 1989; 95: 865–870.

45. Ambrosino N, Nava S, Rubini F. Noninvasive mechanical ventilation in the treatment of acute respiratory failure in chronic obstructive pulmonary disease. *Monaldi Arch Chest Dis* 1993; 48: 144–154.

46. Elliott M, Moxham J. Noninvasive mechanical ventilation by nasal or face mask. *In*: Tobin MJ, ed. Principles and practice of mechanical ventilation. NY, McGraw-Hill, 1994; pp. 427–453.

47. Meyer TJ, Hill NS. Noninvasive positive pressure ventilation to treat respiratory failure. *Ann Intern Med* 1994; 120: 760–770.

48. Sassoon CSH. Noninvasive positive pressure ventilation in acute respiratory failure: review of reported experience with special attention to use during weaning. *Respir Care* 1995; 40: 282–288.

49. Meduri GU, Abou-Shala N, Fox RC, Jones CB, Leeper KV, Wunderink RG. Noninvasive face mask mechanical ventilation in patients with acute hypercapnic respiratory failure. *Chest* 1991; 100: 445–454.

50. Foglio C, Vitacca M, Quadri A, Scalvini S, Marangoni S, Ambrosino N. Acute exacerbations in severe COLD patients: treatment using positive pressure ventilation by nasal mask. *Chest* 1992; 101: 1533–1538.

51. Benhamou D, Girault C, Faure C, Portier F, Muir JF. Nasal mask ventilation in acute respiratory failure: experience in elderly patients. *Chest* 1992; 102: 912–917.

52. Vitacca M, Rubini F, Foglio K, Scalvini S, Nava S, Ambrosino N. Noninvasive modalities of positive pressure ventilation improve the outcome of acute exacerbations in COLD patients. *Intens Care Med* 1993; 19: 450–455.

53. Bott J, Carroll MP, Conway JH, *et al*. Randomized controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1 993; 341: 1555–1557.

54. Fernandez R Blanch LI, Valles J, Baigorri F, Artigas A. Pressure support ventilation *via* face mask in acute respiratory failure in hypercapnic COPD patients. *Intens Care Med* 1993; 19: 456–461.

55. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 1995; 151: 1799–1806.

56. Brochard L, Mancebo J, Wysocki M, *et al*. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333: 817–822.

57. Elliott MW, Steven MH, Phillips GD, Branthwaite MA. Noninvasive mechanical ventilation for acute respiratory failure. *Br Med J* 1990; 300: 358–360.

58. Confalonieri M, Aiolfi S, Gandola L, Scartabellati A, Della Porta R, Parigi P. Severe exacerbations of chronic obstructive pulmonary disease treated with BiPAP by nasal mask. *Respiration* 1994; 61: 310–316.

59. Meecham Jones DJ, Paul EA, Grahame-Clarke C, Wedzicha JA. Nasal ventilation in acute exacerbations of chronic obstructive pulmonary disease: effect of ventilator mode on arterial blood gas tensions. *Thorax* 1994; 49: 1222–1224.

60. Rossi A, Polese G, Brandi G, Conti G. Intrinsic positive end-expiratory pressure (PEEPi). *Intens Care Med* 1995; 21: 522–536.

61. Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. *J Appl Physiol* 1988; 65: 1488–1499.

62. Petrof BJ, Legare M, Goldberg P, Milic-Emili J, Gottfried SB. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive airway disease. *Am Rev Respir Dis* 1990; 141: 281–289.

63. De Lucas P, Tarancon C, Puente L, Rodriguez C, Tatay E, Monturiol JM. Nasal continuous positive airway pressure in patients with COPD in acute respiratory failure: a study of the immediate effects. *Chest* 1993; 104: 1694–1697.

64. Miro AM, Shivaram U, Hertig I. Continuous positive airway pressure in COPD patients in acute hypercapnic respiratory failure. *Chest* 1993; 103: 266–268.

65. Rossi A, Ranieri M. Positive end-expiratory pressure. *In*: Tobin MJ, ed. Principles and Practice of Mechanical Ventilation. New York, McGraw-Hill, 1994; pp. 259–303.

66. Vitacca M, Clini E, Rubini F, Foglio K Nava S, Ambrosino N. Noninvasive mechanical ventilation in severe COLD and acute respiratory failure: short- and long-term prognosis. *Intens Care Med* 1996; (in press).

67. Bardsley PA, Tweney J, Morgan N, Howard P. Oral almitrine in treatment of acute respiratory failure and cor pulmonale in patients with an exacerbation of chronic obstructive airways disease. *Thorax* 1991; 46: 493–498.

68. Jeffrey AA, Warren PM, Flenley DC. Acute hypercapnic respiratory failure in patients with chronic obstructive lung disease: risk factors and use of guidelines for management. *Thorax* 1992; 47: 34–40.

69. Nunn JF, Milledge JS, Singaraya J. Survival of patients ventilated in an intensive therapy unit. *Br Med J* 1979; 1: 1525–1527.

70. Gillespie DJ, Marsh HMM, Divertie MB, Meadows JA. Clinical outcome of respiratory failure in patients requiring prolonged (>24 hours) mechanical ventilation. *Chest* 1986; 90: 364–369.

71. Spicher JE, White DP. Outcome and function following prolonged mechanical ventilation. *Arch Intern Med* 1987; 147: 421–425.

72. Kaelin RM, Assimacopoulos A, Chevrolet JC. Failure to predict six month survival of patients with COPD requiring mechanical ventilation by analysis of simple indices: a prospective study. *Chest* 1987; 92: 971–978.

73. Menzies R Gibbons W, Goldberg P. Determinants of weaning and survival among patients with COPD who require mechanical ventilation for acute respiratory failure. *Chest* 1989; 95: 398–405.

74. Gracey DR Naessens JM, Krishan I, Marsh HMM. Hospital and posthospital survival in patients mechanically-ventilated for more than 29 days. *Chest* 1992; 101: 211–214.

75. Stauffer JL, Fayter N, Graves B, Cromb M, Lynch JC, Goebel P. Survival following mechanical ventilation for acute respiratory failure in adult men. *Chest* 1993; 104: 1222–1229.

76. Ambrosino N, Foglio K Rubini F, Clini E, Nava S, Vitacca M. Noninvasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. *Thorax* 1995; 50: 755–757.

77. Brochard L (Editorial). Noninvasive ventilation: practical issues. *Intens Care Med* 1993; 19: 431–432.

78. Le Gall JR, Loirat P, Alperovitch A, *et al*. A simplified acute physiology score for ICU patients. *Crit Care Med* 1984; 12: 975–977.

79. Knaus WA, Draper EA, Wagner DP, *et al*. Apache II: a severity of disease classification system. *Crit Care Med* 1985; 13: 818–829.

80. Soo Hoo GW, Santiago S, Williams A. Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: determinants of success and failure. *Crit Care Med* 1994; 22: 1253–1261.

81. Elliot MW (Editorial). Noninvasive ventilation in chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333: 870–871.

82. Wysocki M, Tric L, Wolff MA, Gertner J, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure. *Chest* 1993; 103: 907–913.

83. Wysocki M, Tric L, Wolff MA, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure: a randomized comparison with conventional therapy. *Chest* 1995; 107: 761–768.

84. Pennock BE, Crawshaw L, Kaplan PD. Noninvasive nasal mask ventilation for acute respiratory failure: institution of a new therapeutic technology for routine use. *Chest* 1994; 105: 441–444.

85. Nava S, Rubini F, Zanotti E, *et al*. Survival and prediction of successful ventilator weaning in COPD patients requiring mechanical ventilation for more than 21 days. *Eur Respir J* 1994; 7: 1645–1652.

86. Petheram IS, Branthwaite MA. Mechanical ventilation for pulmonary disease: a six year survey. *Anesthesia* 1980; 35: 467–473.

87. Swinburne AJ, Fedullo AJ, Bixby K Lee DK, Wahl GW. Respiratory failure in the elderly: analysis of outcome after treatment with mechanical ventilation. *Arch Intern Med* 1993; 153: 1657–1662.

88. Rieves RD, Bass D, Carter RR, Griffith JE, Norman JR. Severe COPD and acute respiratory failure: correlates for survival at the time of tracheal intubation. *Chest* 1993; 104: 854–860.

89. Rello J, Ausina V, Ricart M, Castella J, Prats G. Impact of previous antimicrobial therapy on the etiology and

outcome of ventilator-associated pneumonia. *Chest* 1993; 104: 1230–1235.

90. Warren PM, Flenley DC, Millar JS, Avery A. Respiratory failure revisited: acute exacerbations of chronic bronchitis between 1961–1968 and 1970–1976. *Lancet* 1980 1: 467–471.

91. Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. *Am Rev Respir Dis* 1986; 133: 792–796.

92. Sluiter HJ, Blokzijil EJ, Vandijl W, *et al.* Conservative and respirator treatment of acute respiratory insufficiency in patients with chronic obstructive lung disease: a reappraisal. *Am Rev Respir Dis* 1972; 105: 932–943.

93. Potgieter PD, Rosenthal E, Benatar SR. Immediate and long-term survival in patients admitted to a respiratory ICU. *Crit Care Med* 1985; 13: 798–802.

94. Sukulmachantra Y, Dinakara P, Williams MH. Prognosis of patients with chronic obstructive pulmonary disease after hospitalization for acute ventilatory failure: a 3 year follow-up study. *Am Rev Respir Dis* 1966; 93: 215–222.

95. Martin JG, Shore S, Engel LA. Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. *Am Rev Respir Dis* 1982; 126: 812–817.

96. Schivaram U, Miro AM, Cash ME, *et al.* Cardiopulmonary responses to continuous positive airway pressure in acute asthma. *J Crit Care* 1993; 8: 87–92.

97. Branthwaite MA. An update on mechanical ventilation for severe acute asthma. *Clin Intens Care* 1990; 1: 4–6.

98. Meduri GU, Fox RC, Abou-Shala N, Leeper KV, Wunderink RG. Noninvasive mechanical ventilation *via* face mask in patients with acute respiratory failure who refused endotracheal intubation. *Crit Care Med* 1994; 22: 1584–1590.

99. Freichels TA. Palliative ventilatory support: use of noninvasive positive pressure ventilation in terminal respiratory insufficiency. *Am J Crit Care* 1994; 3: 6–10.

100. Robert D, Gaussorgues P, Leger P, *et al.* Ventilation mécanique au masque dans les poussées d'insuffisance respiratoire chronique. *Réan Soins Intens Méd Urg* 1989; 5: 401–406.

101. Pennock BE, Kaplan PD, Carlin BW, Sabangan JS, Macgovern JA. Pressure support ventilation with a simplified ventilatory support system administered with a nasal mask in patients with respiratory failure. *Chest* 1991; 100: 1371–1376.

102. Marino W. Intermittent volume cycled mechanical ventilation *via* nasal mask in patients with respiratory failure due to COPD. *Chest* 1991; 99: 681–684.

103. Bersten AD, Holt AW, Vedig AE, Skowronski GA, Baggley CJ. Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure delivered by face mask. *N Engl J Med* 1991; 325: 1825–1830.

104. Lapinski SE, Mount DB, Mackey D, Grossman RF. Management of acute respiratory failure due to pulmonary edema with nasal positive pressure support. *Chest* 1994: 105: 229–231.

105. Piper AJ, Parker S, Torzillo PJ, Sullivan CE, Bye PTP. Nocturnal nasal IPPV stabilizes patients with cystic fibrosis and hypercapnic respiratory failure. *Chest* 1992; 102: 846–850.

106. Lin M, Yang Y, Chiang H, Chang M, Chiang BN, Chitlin MD. Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary edema: short-term results and long-term follow-up. *Chest* 1995; 107: 1379–1386.

107. Gachot B, Clair B, Wolff M, Regnies B, Vachon F. Continuous positive airway pressure by face mask or mechanical ventilation in patients with human immunodeficiency virus infection and severe *Pneumocystis carinii* pneumonia. *Intens Care Med* 1992; 18: 155–159.

108. Ambrosino N, Rubini F, Callegari G, Nava S, Fracchia C. Noninvasive mechanical ventilation in the treatment of infectious complications of lung transplantation. *Monaldi Arch Chest Dis* 1994; 49: 311–314.

109. Brochard L, Rauss A, Benito S, *et al.* Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1994; 150: 896–903.

110. Esteban A, Frutos F, Tobin MJ, *et al.* A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med* 1995; 332: 345–350.

111. Udwadia ZF, Santis GK Steven MH, Simonds AK. Nasal ventilation to facilitate weaning in patients with chronic respiratory insufficiency. *Thorax* 1992; 47: 715–718.

112. Goodenberger DM, Couser JI Jr, May JJ. Successful discontinuation of ventilation *via* tracheostomy by substitution of nasal positive pressure ventilation. *Chest* 1992; 102: 1277–1279.

113. Restrick LJ, Scott AD, Ward EM, Feneck RO, Cornwell WE, Wedzicha JA. Nasal intermittent positive pressure ventilation in weaning intubated patients with chronic respiratory disease from assisted intermittent, positive pressure ventilation. *Respir Med* 1993; 87: 199–204.

114. Criner GJ, Travaline JM, Brennan KJ, Kreimer DT. Efficacy of a new full face mask for noninvasive positive pressure ventilation. *Chest* 1994; 106: 1109–1111.

115. Chevrolet JC, Jolliet P, Abajo B, Toussi A, Louis M. Nasal positive pressure ventilation in patients with acute respiratory failure: difficult and time-consuming procedure for nurses. *Chest* 1991; 100: 775–782.

116. Sacks H, Chalmers TC, Smith H Jr. Randomized *versus* historical controls for clinical trials. *Am J Med* 1982; 72: 233–240.