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Noninvasive mechanical ventilation in acute hypoxaemic respiratory failure

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ABSTRACT: In acute hypoxaemic respiratory failure (HRF), oxygenation, reduction in the work of breathing and in dyspnoea may be achieved by delivering noninvasive mechanical ventilation (NIMV).

Several uncontrolled and 13 randomized controlled studies (RCS) were reviewed. Uncontrolled studies confirmed the feasibility and the possibility to improve arterial blood oxygenation with NIMV. The 13 RCS compared NIMV *versus* a conventional approach in a total of 720 patients with HRF. Endotracheal intubation was required in 186 of the 358 patients (median (95% confidence interval (CI)) 51%, (40–63%)) assigned to a conventional approach and in 107 of the 362 patients (29% (20–39%)) assigned to NIMV. Eleven of the 13 RCS found a reduction in the rate of endotracheal intubation with NIMV with an absolute risk reduction of 31% (30–33%).

Ten of the 13 RCS found a reduction in the mortality rate which was 30% (19–40%) in the control group and 19% (13–26%) in the NIMV group. The mean absolute risk reduction was 15% (10–20%).

In conclusion, noninvasive ventilation appears to be a useful method in avoiding endotracheal intubation and probably in reducing the morbidity of patients with hypoxaemic respiratory failure.

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Acute hypoxaemic respiratory failure (HRF) refers to pathological states in which arterial blood oxygenation is severely impaired. In HRF, the objective of mechanical ventilation (MV) is to achieve and to maintain an acceptable level of arterial blood oxygenation by increasing the inspiratory oxygen concentration. The objective is also to reduce the work and the cost of breathing by unloading respiratory muscles, and, eventually, to reduce the dyspnoea. MV has been traditionally administered through an endotracheal tube (ET) which is an invasive device associated with potential complications and discomfort. A less invasive procedure able to achieve comparable objectives is to use MV with a nasal or a facial mask.

Based on published studies several uncontrolled and 13 randomized controlled studies (RCS), the aim of the present review is to summarize the rationale and the physiological effects of noninvasive mechanical ventilation (NIMV) in HRF but also to analyse the effects on the rate of endotracheal intubation and on the patients outcomes. Some specific HRF situations, technological and logistic aspects of NIMV as well as

complications and side-effects will also be reviewed to give practical guidelines for use in patients with HRF.

Definitions

Ventilatory modalities

Noninvasive ventilation (NIV) could be realized by various techniques such as external negative pressure, chest wall oscillation, and positive-pressure ventilation. The present article will focus on NIMV only which refers to the application of a positive airway pressure to unload inspiratory respiratory muscles. Positive airway pressure may be obtained by delivering inspiratory volume (volume-controlled ventilation) or directly by delivering a positive pressure (pressure-controlled ventilation). The latter could be obtained by four different ways: first by delivering inspiratory positive airway pressure (IPAP), second by delivering expiratory positive airway pressure (EPAP), third by delivering IPAP and EPAP at a comparable level to realize a continuous positive airway pressure (CPAP),

fourth by delivering IPAP and EPAP at a different level (IPAP>EPAP) to realize a bilevel positive airway pressure (BiPAP) ventilation.

Hypoxic respiratory failure

As stated earlier, in the present paper NIMV in HRF will be discussed exclusively. A continuum however exists between pure HRF and pure hypercapnic respiratory pump failure resulting in some mixing hypoxaemic-hypercapnic forms of respiratory failure. For instance patients with cardiogenic pulmonary oedema (CPO) are conventionally classified as patients with HRF. However, in the study of BERSTEN *et al.* [1] patients with CPO and receiving CPAP had a carbon dioxide tension in arterial blood (P_{a,CO_2}) of 58 ± 8 mmHg (mean \pm SD). This was also the case in the recent study from MEHTA *et al.* [2] in which patients with CPO treated with BiPAP had a P_{a,CO_2} of 56 ± 15 mmHg suggesting that patients with CPO could have a failure in part of the respiratory pump, that could not be reversed with oxygen supplementation only.

The rationale for noninvasive mechanical ventilation in hypoxaemic respiratory failure

Basically, in patients with HRF the rationale for using NIMV is not different than for using invasive MV. As stated by a recent international consensus conference [3], the rationale for using MV in HRF, *via* an ET or *via* a mask, is to improve oxygenation by delivering high oxygen concentration, by unloading respiratory muscles, by recruiting alveoli and increasing lung volumes. The question is on the rationale of noninvasive instead of invasive ventilation and the following responses could be proposed: 1) NIMV is able to improve oxygenation as well as invasive MV. Several uncontrolled studies [4] as well as recent randomized controlled studies [5] reported an improvement in oxygenation with NIMV. In the report from MEDURI *et al.* [4], arterial blood gas correction or improvement was observed in 31 of the 41 patients (76%) with HRF. In the randomized controlled study of ANTONELLI *et al.* [5], the oxygen tension in arterial blood/inspiratory oxygen fraction ratio ($P_{a,O_2}:F_{I,O_2}$) increased significantly from 116 ± 24 – 230 ± 76 mmHg with NIMV and from 124 ± 25 – 211 ± 68 mmHg with conventional ventilation (fig. 1). 2) NIMV is able to unload respiratory muscles as well as invasive MV. Several studies performed in chronic obstructive pulmonary disease (COPD) patients with acute respiratory failure (ARF) found that NIMV was able to unload inspiratory muscles [6]. Indirect evidence suggests that it could also be the case in patients with HRF [7]. However, leak around the mask or through the mouth can reduce NIMV efficacy [8]. In addition, mouth leak during NIMV can increase nasal airway resistances [9] and NIMV by itself could increase the glottis resistances [10]. Both mechanisms can reduce the NIMV efficacy to unload respiratory muscles. 3) NIMV is able to recruit alveoli and to increase lung volume as well as invasive MV.

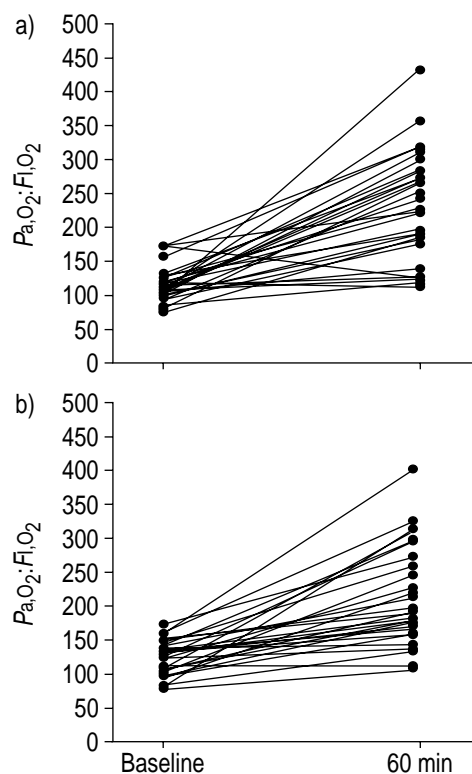


Fig. 1.—The ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ($P_{a,O_2}:F_{I,O_2}$) at baseline and after 1 h of mechanical ventilation in patients with acute respiratory failure in a) the noninvasive ventilation ($n=32$, baseline mean \pm SD: 116 ± 24 , 60 min 230 ± 76 , $p < 0.001$); and b) conventional ventilation groups ($n=32$, baseline mean \pm SD: 124 ± 25 , 60 min 211 ± 68 , $p < 0.001$). From [5] with permission.

Again several uncontrolled studies reported the recruitment effects of NIMV especially by using CPAP. However, a direct comparison with invasive MV failed to confirm the comparable efficacy which can be also reduced by leaks around the mask and upper airway resistances. 4) NIMV may be indicated (and better than invasive MV) in some forms of rapidly reversible HRF. This may be the case in CPO not from severe ischaemic disease [11, 12], or in status asthmaticus [13]. In these situations, supporting the failing respiratory function transiently with NIMV may be better than using invasive MV. Unfortunately, in these situations, direct comparison between invasive MV and NIMV is lacking. 5) In immunosuppressed patients, invasive MV is associated with high risk of ventilator-associated pneumonia and high mortality rate. In these patients, NIMV may be a safer modality to support ventilation, by avoiding or delaying invasive MV [14]. 6) NIMV may be an alternative, in patients refusing invasive MV, or for those in whom the physician in charge decided that invasive MV may be unethical [15, 16].

Finally, the rationale for using NIMV in patients with HRF is to reduce the complications related to the endotracheal device and more specifically nosocomial pneumonia. The possibility with NIMV to prevent nosocomial pneumonia in patients needing MV was

recently reported in a prospective epidemiological survey [17]. In a cohort of 320 consecutive patients, 75% of whom with acute HRF, the density of ventilator associated pneumonia was significantly reduced from 0.85 per 100 days of tracheal intubation to 0.16 per 100 days of NIMV ($p=0.004$). NOURDINE *et al.* [18] also found a lower incidence of nosocomial infections other than pneumonia and a lower mortality rate in a group of 129 patients with respiratory failure from various aetiologies, treated with NIMV. Using a multivariate analysis, they found that NIMV was significantly associated with a lower rate of nosocomial infections. This has also been confirmed by a recent matched case-control study conducted in a medical intensive care unit (ICU) [19] showing that in 50 patients with acute exacerbation of COPD or CPO, the rates of nosocomial infections and of nosocomial pneumonia were significantly lower in patients who received NIV than in those treated with MV (18% *versus* 60% and 8% *versus* 22%; $p=0.001$ and $p=0.04$, respectively). Similarly, the daily risk of acquiring an infection (19 *versus* 39 episodes per 1,000 patient-days; $p=0.05$), the proportion of patients receiving antibiotics for nosocomial infection (8% *versus* 26%; $p=0.01$), mean duration of ventilation (6 *versus* 10 days; $p=0.01$), mean length of ICU stay (9 *versus* 15 days; $p=0.02$), and crude mortality (4% *versus* 26%; $p=0.002$) were all lower among patients who received NIV than those treated with MV [19].

The physiological effects of noninvasive mechanical ventilation in hypoxaemic respiratory failure

In patients with HRF, the physiological effects of EPAP or CPAP have been more extensively investigated than the effects of IPAP or BiPAP. In any case, the mean positive airway pressure (MPAP) is the most important determinant of arterial oxygenation. During volume or pressure-controlled ventilation, MPAP can be estimated by the following equation:

$$\text{IPAP} \times t_I/t_{\text{tot}} + \text{EPAP} \times t_E/t_{\text{tot}} \quad (1)$$

where t_I , t_E , and t_{tot} are the inspiratory, expiratory and total cycle times respectively. Therefore, the addition of IPAP to a preset level of EPAP (to realize a BIPAP ventilation) increases MPAP proportionally. EPAP or CPAP also allow the recruitment of under-ventilated alveoli by increasing lung volume at end expiration and prevent derecruitment phenomena. The application of mask CPAP in healthy volunteers facilitates the expiratory flow and shortens the expiratory time by active reflex mechanisms [20]. Increments of CPAP levels (5, 10, and 15 cmH₂O) cause a proportional increase in minute ventilation, resulting primarily from an increase in tidal volume (V_T) at 5 cmH₂O and an increase in respiratory rate at 15 cmH₂O (from a shortening of t_E irrespective of any alteration in t_I [20]). CPAP also causes a level-dependent reduction in cardiac stroke volume starting at 5 cmH₂O with a facial mask and 10 cmH₂O with a nasal mask.

Both EPAP alone and BIPAP improved oxygenation

in hypoxaemic patients before and after extubation (breathing through a face mask) [21, 22]. In post-thoracotomy, patients receiving 10 cmH₂O of invasive CPAP, the switch to face mask CPAP resulted in higher arterial oxygen saturation (S_{a,O_2}) without differences in haemodynamic parameters [22]. In 22 trauma patients [21], transfer from ET to face mask NIMV at similar EPAP (5.8±2.5 and 5.2±2.2 cmH₂O) and IPAP (13±5 and 12.8±1.7 cmH₂O) resulted in similar blood gases and respiratory pattern (fig. 2). In hypercapnic patients, MEDURI *et al.* [23] reported that minute ventilation (\dot{V}_E), \dot{V}_T , P_{a,CO_2} and the $P_{a,O_2}:F_{I,O_2}$ ratio were similar during invasive MV and NIMV after extubation. These reports strongly suggest that the physiological effects of NIMV can be compared to the physiological effects of MV with endotracheal intubation, *i.e.* improving oxygenation and unloading inspiratory respiratory muscles.

Clinical experiences

Nonrandomized retro-prospective studies

MEDURI *et al.* [24] have reported one of the first clinical applications of NIV in patients with ARF. Among the 10 patients reported in this study, four had HRF, two CPO, and two acute respiratory distress syndromes (ARDS). The $P_{a,O_2}:F_{I,O_2}$ ratio was <125 mmHg in all the patients, all survived and only one required endotracheal intubation because NIMV was not tolerated. Subsequently, PENNOCK *et al.* [25] reported a group of 31 patients, most of them with postsurgery HRF, in whom NIMV was applied with a 70% success rate. WYSOCKI *et al.* [26], reported 17 patients (14 with HRF) in whom NIMV was able to avoid invasive MV with a 47% success rate. Since these pilot studies, reports by several other authors have confirmed the feasibility of NIMV in patients with HRF. Most of them found a significant improvement in gas exchange with NIMV. The largest retrospective study found an improvement in gas exchange in 55 out of 68 patients (80%) with HRF from various aetiologies [4]. These uncontrolled studies in combination confirmed the feasibility and the possibility to improve gas exchange with NIMV in patients with HRF.

Randomized controlled studies

Thirteen RCS have compared NIMV *versus* a conventional approach in patients with HRF [1, 2, 5, 14, 27–35]. A total of 720 patients with HRF were included. Endotracheal intubation was required in 186 of the 358 patients (median (95% CI) 51% (40–63%)) assigned to a conventional approach and in 107 of the 362 patients (29% (20–39%)) assigned to NIMV. Eleven of the 13 RCS found a reduction in the rate of endotracheal intubation with NIMV with an absolute risk reduction of 31% (30–33%). Accordingly, five patients should receive NIMV to avoid endotracheal intubation in one. Ten of the 13 RCS

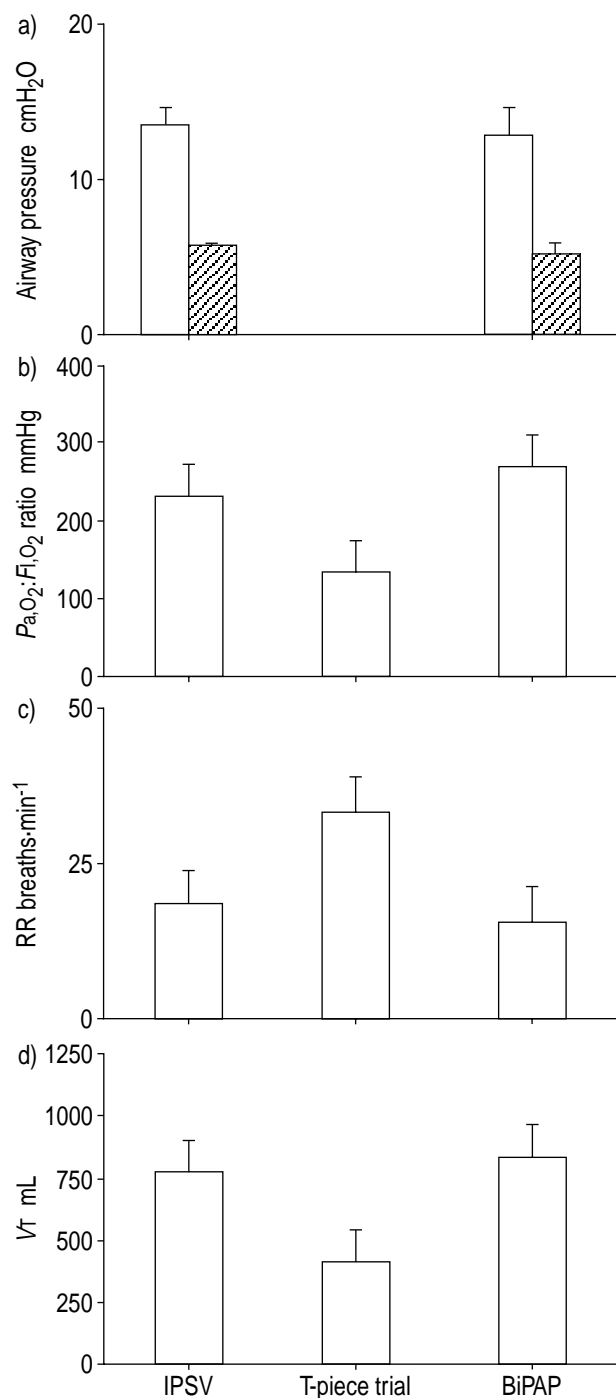


Fig. 2.—a) Inspiratory airway pressure (IPAP: □), expiratory airway pressure (EPAP: ▨), b) the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ($P_{a,O_2}:F_{I,O_2}$), c) the respiratory rate (RR) and d) the tidal volume (V_T) in 22 patients with post-traumatic hypoxaemic respiratory failure during invasive pressure support ventilation (IPSV), a T-piece trial and face mask bilevel of positive airway pressure (BiPAP). For similar level of EPAP and IPAP, values obtained with BiPAP were comparable to those obtained during invasive mechanical ventilation. Adapted from [21].

found a reduction in the mortality rate which was 30% (95% CI: 19–40%) in the control group and 19% (95% CI: 13–26%) in the NIMV group. The

absolute risk reduction was 15% (95% CI: 10–20%) and 13 patients needed to receive NIMV for saving one.

Six of the 13 studies included a total of 283 patients exclusively with CPO [1, 2, 28, 30, 34, 35]. Endotracheal intubation was required in 48 of the 142 patients (32% (19–45%)) assigned to a conventional treatment and in 32 of the 141 patients (23% (17–30%)) assigned to NIMV. Only four studies [1, 28, 30, 34] found a reduction in the rate of endotracheal intubation with NIMV with an absolute risk reduction of 28% (95% CI: 20–37%) and a number of patient to-treat-to-avoid one tracheal intubation which was 4. A reduction in the mortality rate was found in five studies with a small absolute risk reduction of 7% (95% CI: 0–15%).

The remaining seven studies were performed in patients with HRF nonexclusively from CPO and included 437 patients [5, 14, 27, 29, 31–33]. All the studies found a reduction in the rate of endotracheal intubation with NIMV. Endotracheal intubation was required in 138 of the 216 patients (68% (57–79%)) assigned to a conventional treatment and in 75 of the 221 patients (35% (22–47%)) assigned to NIMV. The absolute risk reduction for endotracheal intubation was 33% (95% CI: 31–35%) and the number of patient to-treat-to-avoid one endotracheal intubation was six. The mortality rate was 45% (95% CI: 32–57%) in the control group and 20% (95% CI: 10–30%) in the NIMV group, an absolute risk reduction of 23% (95% CI: 21–25%) with five patients to treat with NIMV for saving one.

Indeed, such analysis should be considered very cautiously, mainly because of possible heterogeneity among the studies. For example in patients with CPO, a reduction in the intubation rate was observed only in studies comparing CPAP with no ventilatory support [1, 28, 30], while no or small benefit may be observed from recent studies [2, 34, 35]. Heterogeneity was also observed between the remaining studies [5, 14, 27, 29, 31–33]. In the study of ANTONELLI *et al.* [5], all the patients treated conventionally were endotracheally intubated (*i.e.* the intubation rate was 100%). Obviously, the 31% intubation rate in the NIMV group gave a large absolute risk reduction of 69% with NIMV. Intermediate values (table 1) were reported from MARTIN *et al.* [29] and low values from WYSOCKI *et al.* [31]. A recent study [32] was designed to compare CPAP to standard oxygen therapy in patients with hypoxaemic nonhypercapnic acute respiratory insufficiency (acute lung injury: n=102, cardiac disease: n=21). After 1 h of treatment, subjective responses to treatment and median $P_{a,O_2}:F_{I,O_2}$ ratios were greater with CPAP (203 *versus* 151; p=0.02) but CPAP failed to reduce the endotracheal intubation rate (34 *versus* 39% in the standard therapy group; p=0.53), hospital mortality (31 *versus* 30%, p=0.89), or median ICU length of stay (6.5 *versus* 6.0 days; p=0.43).

Finally, two recent randomized controlled studies in immunosuppressed patients [14, 33] found a large reduction in endotracheal intubation and mortality rates with NIMV (table 1).

Table 1. – Randomized controlled studies comparing noninvasive mechanical ventilation to a conventional approach in patients with hypoxaemic respiratory failure

First author (Ref no.)	aetiology	Mode	Number of patients				Endotracheal intubation				Mortality									
			NIMV		Controls		NIMV n (%)		Controls n (%)		NIMV n (%)		Controls n (%)		RR %		ARR %		NTT n	
			n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
RASANEN [30]	CPO	CPAP	20	6 (30)	20	50	30	3.3	3 (15)	4 (20)	25	5	20.0							
BERSTEN [1]	CPO	CPAP	19	0 (0)	20	100	35	2.9	2 (11)	4 (20)	47	9	10.6							
LIN [28]	CPO	CPAP	50	8 (16)	50	56	20	5.0	2 (4)	3 (6)	33	2	50.0							
SHARON [35]	CPO	BIPAP	20	16 (80)	20	*	*	*	2 (10)	0 (0)	*	*	*							
MASIP [34]	CPO	BIPAP	19	1 (5)	18	84	28	3.6	0 (0)	2 (18)	100	11	9.0							
DELCLAUX [32]	Miscellaneous	CPAP	62	21 (34)	61	14	5	18.3	19 (31)	19 (31)	*	*	*							
WYSOCKI [31]	Miscellaneous	BIPAP	21	13 (62)	20	12	8	12.4	7 (33)	10 (50)	33	17	6.0							
METHA [2]	CPO	BIPAP	13	1 (8)	14	*	*	*	1 (8)	2 (14)	46	7	15.2							
ANTONELLI [5]	Miscellaneous	BIPAP	32	10 (31)	32	69	69	1.5	9 (28)	15 (47)	40	19	5.3							
CONFALONERI [27]	CAP	BIPAP	28	6 (21)	28	65	39	2.5	7 (25)	6 (21)	*	*	*							
MARTIN [29]	Miscellaneous	BIPAP	32	9 (28)	29	52	30	3.3	5 (16)	10 (34)	55	19	5.3							
ANTONELLI [14]	Organ transplant	BIPAP	20	4 (20)	20	71	50	2.0	4 (20)	10 (50)	60	30	3.3							
HILBERT [33]	Immunosuppressed	BIPAP	26	12 (46)	26	40	31	3.3	13 (50)	21 (81)	38	31	3.3							

NIMV: noninvasive mechanical ventilation; HRF: hypoxaemic respiratory failure; CPO: cardiogenic pulmonary oedema; CAP: community acquired pneumonia; CPAP: continuous positive airway pressure; BIPAP: bilevel positive airway pressure; RR: relative risk; ARR: absolute risk reduction; NTT: number of patients to treat. *: the treatment effect is in the other side, i.e. conventional treatment improves the outcome.

Cardiogenic pulmonary oedema

In patients with CPO, the work of breathing is increased from reduced lung compliance and increased airway resistances. The reduction in lung compliance correlates with derangement in pulmonary gas exchange. The large negative swings in pleural pressure generated by respiratory muscles increase left ventricular (LV) transmural pressure and afterload.

Reduction in cardiac output compromises oxygen delivery to the respiratory muscles and may create a vicious circle. The most important haemodynamic effect of NIMV, with or without EPAP, is to reduce venous return. On the normal ventricle (responding to preload changes), a reduction in venous return may lead to a decrease in LV preload and cardiac output. On failing LV, the reduction in preload may be beneficial on LV output. Finally, during positive pressure ventilation, part of the airway pressure is transmitted to the LV and thoracic aorta which can reduce LV afterload. The efficacy of mask CPAP in patients with CPO was proven by three randomized studies [1, 28, 30]. RASANEN *et al.* [30] randomly assigned 40 patients with CPO (19 with acute myocardial infarction) to either ambient airway pressure or 10 cmH₂O CPAP while *Fi*O₂ was kept constant at 28–30%. By contrast with the control group, patients receiving CPAP rapidly and significantly improved *Pa*aO₂ (fig. 3) and simultaneously decreased the respiratory rate and the *Pa*aCO₂. Furthermore, CPAP resulted in rapid and significant improvement in heart rate and in blood pressure (fig. 3). During the study period, 12 patients in the control group and six in the CPAP group required intubation (p=0.07). Reasons for intubation included hypoxaemia (four patients), carbon dioxide (CO₂) retention (one patient), and need for cardiac resuscitation (one patient). BERSTEN *et al.* [1] randomized 39 patients with CPO to receive oxygen (O₂) supplementation alone or with face mask CPAP (10 cmH₂O). The respiratory rate was unchanged from 32±6 to 33±9 breaths·min⁻¹ in patients receiving O₂ alone while it decreased significantly from 35±8 to 27±6 breaths·min⁻¹ in those receiving 30 min of CPAP. The *Pa*aCO₂ decreased slightly from 64±17 to 62±14 mmHg in those receiving O₂ alone while significantly from 58±8 to 46±4 mmHg in those receiving CPAP. By contrast with patients treated by O₂ alone, those receiving CPAP also had a greater and significant increase in arterial pH (from 7.18±0.08 to 7.28±0.06) and in *Pa*aO₂:*Fi*O₂ ratio (from 138±32 to 206±126). After 24 h, however, there were no significant differences between the two treatment groups in any of these respiratory indexes. Seven (35%) of the patients who received O₂ alone but none who received CPAP required intubation and MV (p=0.005). However, the inpatient mortality rate and the length of the hospital stay were not different between patients receiving O₂ alone or CPAP. In the report of LIN *et al.* [28], 100 patients with CPO were randomized to receive either O₂ alone or face mask CPAP. Patients had similar physiological characteristics at study entry. When compared to conventional treatment, CPAP was associated with a significant improvement in stroke

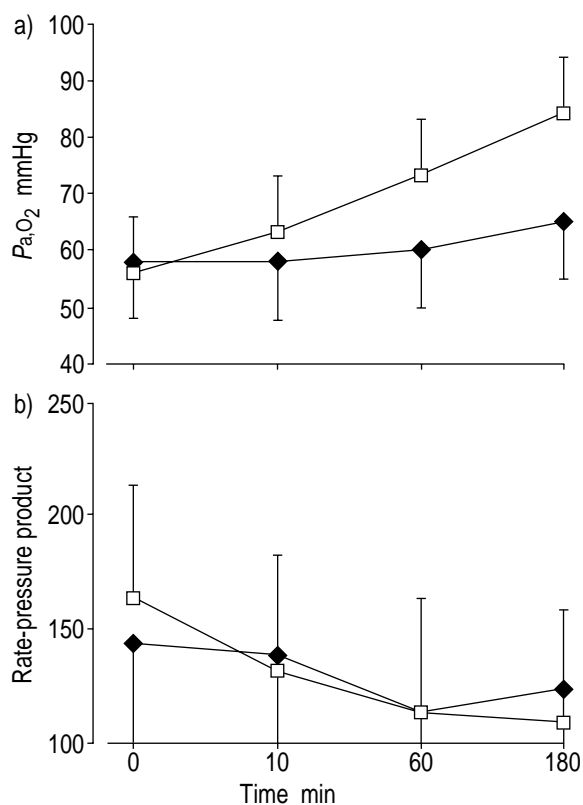


Fig. 3. – By contrast with the control group ($n=20$; ◆), patients receiving 10 cmH₂O of continuous positive airway pressure ($n=20$; □) rapidly and significantly improved the a) partial pressure of arterial oxygen (P_{a,O_2}) and b) the rate-pressure product. Adapted from RASANEN *et al.* [30].

volume index, heart rate, P_{a,O_2} , intrapulmonary shunt (Q_s/Q_t), and with a lower rate of endotracheal intubation (ETI) (16% versus 36%, $p<0.01$).

BIPAP ventilation has also been proposed in patients with CPO. RUSTERHOLTZ *et al.* [11] applied EPAP 5 cmH₂O and IPAP 20 cmH₂O by facial mask to 26 consecutive patients with CPO, and noted that only five failed and required endotracheal intubation. Patients who failed had significantly lower P_{a,CO_2} (32 ± 2 versus 54 ± 15 mmHg) and higher creatine-kinase values related to acute myocardial infarction (four of five in the failure group versus two of 21 in the success group). The use of NIMV in an uncontrolled cohort of patients with CPO has been reported in other recent studies with a high success rate [36]. Subgroup analysis in a recent randomized study [14], found that the four patients with CPO assigned to NIMV avoided intubation and survived, while the five assigned to conventional treatment required intubation and died ($p=0.04$). By contrast, a recent randomized controlled study including 27 patients with CPO assigned to receive medical treatment plus CPAP or plus BIPAP was terminated after interim analysis due to an excess rate of acute myocardial infarction in patients receiving BIPAP [2]. Among the 14 patients receiving BIPAP, 10 had acute myocardial infarction (AMI) (71%) by contrast with four among the 13 receiving CPAP (31%) ($p=0.06$). The delay between the

onset of myocardial infarction and the beginning of ventilation was not clear, and creatinine kinase concentrations before ventilation was higher in patients receiving BIPAP, however, these results strongly suggest that CPO from myocardial infarction is probably not an indication for NIMV. *A contrario*, CPO from other and rapidly reversible causes may be a good indication for NIMV. The latter study [2] also raised the respective role of CPAP and of BIPAP in patients with HRF from CPO [12]. While BIPAP may be more efficient than CPAP, several aspects such as comfort, tolerance, the ease of use of some simplified CPAP systems should be taken in consideration. Controversies on the use of NIMV in patients with CPO have also been highlighted by two recent randomized controlled studies [34, 35]. The first one [35] compared 20 patients treated with NIMV and 20 patients receiving high-dose intravenous isosorbide-dinitrate and found a 80% rate of endotracheal intubation in the NIMV group by contrast with 20% in the isosorbide-dinitrate group ($p=0.0004$). Two patients died in the NIMV group by contrast with zero in the isosorbide-dinitrate group and the combined end-point (death, need for mechanical ventilation or myocardial infarction) was more frequently observed in the NIMV group. It should be stressed that patients were intubated during the first hour of treatment, suggesting that patients in the NIMV received ventilatory support for a very short period of time. More importantly, the medical treatment in the two groups were different since patients in the NIMV group received only low doses of isosorbide-dinitrate. Conversely, the study from MASIP *et al.* [34] compared two groups of patients with CPO receiving comparable medical treatment and found that those receiving NIMV in addition to the medical treatment were less frequently endotracheally intubated.

In summary, in patients with HRF from CPO, the role of NIMV is highly debated. This may be related to the populations selected from the available studies (hypercapnic versus nonhypercapnic patients, patients with or without myocardial infarction), to the treatment in the controlled group (with or without CPAP) and to the comparability in the medical management.

Postoperative respiratory failure

Thoracic and upper abdominal surgery are associated with a marked and prolonged postoperative reduction in functional reserve (or residual) capacity (FRC), P_{a,O_2} , and forced vital capacity (FVC) which can be reversed by applying NIMV. PENNOCK *et al.* [25] first reported on the use of nasal BiPAP in 22 postsurgical patients who developed HRF. Initial ventilatory settings were EPAP (5 cmH₂O) and IPAP (10 cmH₂O). After 1 h on BIPAP, there was a significant improvement in gas exchange and a reduction in respiratory rate. NIMV lasted 2 h–6 days and only four of the 22 patients required intubation. These investigators later expanded their experience to a total of 97 postoperative patients, with an 80% NIMV success rate [37]. In the initial report from WYSOCKI *et al.* [26], seven out of 17 patients had HRF following surgery,

four were successfully ventilated with NIMV and three failed and required endotracheal intubation. In a prospective study, 19 patients with HRF following lung resection were randomized to receive either nasal BIPAP or standard medical treatment [38]. Patients randomized to NIMV had a significant increase in P_{a,O_2} (fig. 4) without increase of the dead space to tidal volume ratio or worsening of pleural air leaks. From available literature, NIMV can be successfully applied to treat patients with postoperative HRF. However, randomized controlled trials are still required to confirm the beneficial effect of NIMV in this kind of patient.

Trauma

Pulmonary disorders are common in traumatized patients. These disorders lead to reduced FRC, compliance, and subsequent restrictive defects resulting in impaired gas exchange. Although mask CPAP has

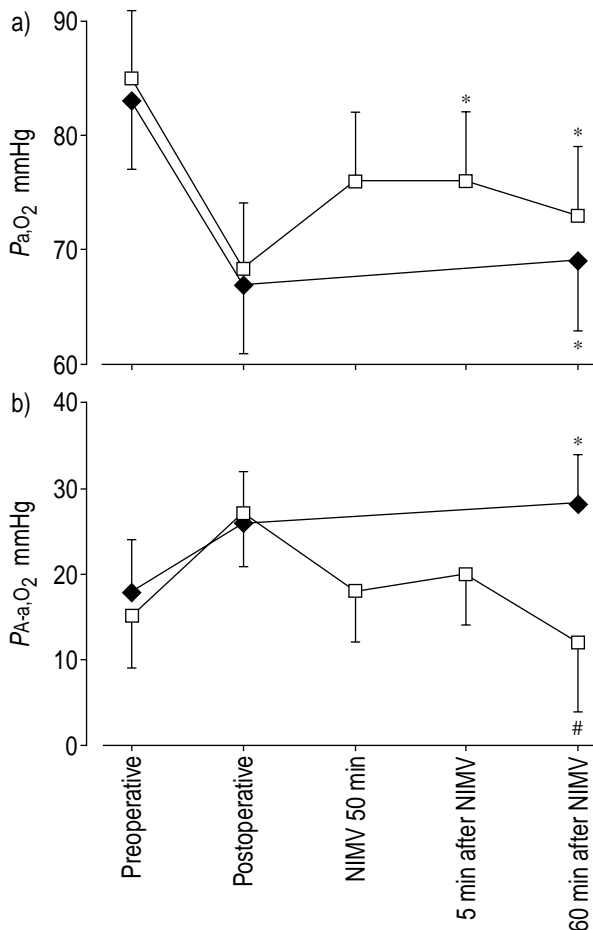


Fig. 4.—Patients with hypoxaemic respiratory failure ($n=19$) following lung resection were randomized to receive either nasal noninvasive mechanical ventilation (NIMV; $n=10$) or standard medical treatment ($n=9$). Patients randomized to NIMV had a significant increase in a) the partial pressure of arterial oxygen (P_{a,O_2}) and a significant and sustained decrease in b) the alveolar-arterial pressure difference for oxygen (P_{A-a,O_2}) in the postoperative period. *: $p<0.05$ within the group from baseline; #: $p<0.05$ between groups. Adapted from [38].

been proposed previously to treat "traumatic wet lung" with several investigators describing successful application of mask CPAP, physiological data in this patient population are not available [39]. In a recent study, 22 trauma patients, switched from invasive ventilation to face mask NIMV at similar levels of EPAP (5.8 ± 2.5 and 5.2 ± 2.2 cmH_2O) and of IPAP (13.0 ± 5.0 versus 12.8 ± 1.7 cmH_2O) had a similar improvement in gas exchange and respiratory pattern [21] (fig. 2). The median duration of NIMV was 47 h (range 6–144). All patients tolerated NIMV, but nine patients (40.9%) required re-intubation. Six of them died after 36 ± 13 days while still on MV. In a recent randomized controlled study [5] of patients with HRF requiring MV, four of the 32 (12%) patients assigned to NIMV had trauma with pulmonary contusion or atelectasis. NIMV was associated with a rapid and significant improvement in the $P_{a,O_2}:F_{I,O_2}$ ratio and all four patients avoided intubation and survived. Four of the 32 (12%) patients assigned to the conventional ventilation group also had post-trauma HRF and were by study design endotracheally intubated and one died. In summary, NIMV is probably useful in some trauma patients but large randomized controlled studies specifically designed for post-traumatic HRF are lacking to confirm such opinion.

Severe community-acquired pneumonia

Mortality of community-acquired pneumonia (CAP) requiring ICU admission ranges 22–54%. Nearly 58–87% of patients with severe CAP develop HRF and require MV. Few studies have reported the use of NIMV in patients with HRF from CAP and results are conflicting. Among 30 patients with HRF and receiving nasal NIMV, BENHAMOU *et al.* [15] found no difference in response rate (60% success) in patients with or without pneumonia. A similar, but smaller, experience was reported by PENNOCK *et al.* [25]. In the report of MEDURI *et al.* [4], NIMV improved gas exchange in >75% and avoided intubation in 62% of the 41 patients with CAP (14 with and 27 without COPD). By contrast in a retrospective analysis of 25 patients with HRF treated with NIMV, CONIA *et al.* [40] found that all the patients with pneumonia failed and required endotracheal intubation. CONFALONIERI *et al.* [27], in a recent multicentre, prospective, randomized trial compared the efficacy of face mask NIMV with standard medical treatment, in patients with severe CAP and HRF. Fifty-six consecutive patients were enrolled (28 in each treatment group) and the two groups were very similar at study entry. The use of NIMV was well tolerated, safe, and associated with a significant reduction in respiratory rate, need for endotracheal intubation (21 versus 50%; $p=0.03$), and duration of ICU stay (1.8 ± 0.7 days versus 6 ± 1.8 days; $p=0.04$). Subgroup analysis however, revealed that the beneficial effects of NIMV were mainly observed in patients with COPD. In summary, the usefulness of NIMV in patients with HRF from CAP is hard to establish. Conflicting results from available literature can be related to differences in patients severity and in coexisting

underlying disease such as COPD. In the authors opinion, NIMV could be useful to avoid endotracheal intubation in CAP of mild severity, in CAP occurring in patients with COPD and when tracheal secretions can be removed easily.

Transplant and immunocompromised patients

Data on the application of NIMV to transplanted patients with HRF are scarce. A randomized trial compared face mask NIMV to standard treatment as a modality to avoid endotracheal intubation in 40 solid organ transplant recipients with HRF [14]. Within the first hour of treatment, 14 (70%) patients in the NIMV group, and five (25%) in the standard treatment group improved their $P_{a,O_2} : F_{I,O_2}$ ratio. Over time, a sustained improvement in $P_{a,O_2} : F_{I,O_2}$ ratio was noted in 12 (60%) patients in the NIMV group, and in five (25%) in the standard treatment group ($p=0.03$). The use of noninvasive ventilation was associated with a significant reduction in the rate of endotracheal intubation (20% versus 70%; $p=0.002$), rate of fatal complications (20% versus 50%; $p=0.05$), length of stay in the ICU of survivors (5.5 ± 3 days versus 9 ± 4 ; $p=0.03$) and ICU mortality (20% versus 50%; $p=0.05$).

In immunosuppressed patients a very recent randomized trial evaluated NIMV as a means to avoid intubation and associated complications in immunocompromised patients admitted to the ICU for hypoxaemic ARF ($P_{a,O_2} : F_{I,O_2} < 200$), fever and lung infiltrates [33]. Fifty-two patients were enrolled in this study (30 patients with haematological malignancies and neutropenia, 18 who received immunosuppression to prevent rejection after solid organ transplantation and four with acquired immune deficiency syndrome) and were randomized to receive conventional treatment (O_2 plus aggressive medical therapy) or NIMV plus conventional treatment. NIMV was administered intermittently with a face mask in BIPAP. The two groups were comparable at the inclusion. NIV significantly reduced the rate of intubation (46% versus 77%, $p=0.003$) and serious complications (50% versus 81%, $p=0.02$). Both ICU (38% versus 69%, $p=0.03$) and hospital mortality (50% versus 81%, $p=0.02$) were significantly reduced. The authors concluded that the early intermittent application of NIV ameliorates the prognosis of immunocompromised patients admitted to the ICU. In this prospective randomized study on immunocompromised patients treated with NIMV, authors obtained impressive results in the subgroup of patients with haematological malignancies and neutropenia, suggesting an extended clinical application of NIMV to these conditions.

In patients with cystic fibrosis who are heavily colonized with *Pseudomonas aeruginosa*, endotracheal intubation with conventional ventilation is frequently associated with dissemination of the pulmonary infection and development of septic shock. Then the avoidance of endotracheal intubation seems crucial. Several reports have described the successful implementation of NIMV as a bridge to transplantation in patients with cystic fibrosis [41]. In one study, duration of intubation and ICU stay after transplantation

were much shorter in cystic fibrosis patients supported preoperatively with NIMV [41]. In their report on NIMV compared to conventional treatment in solid organ transplantation, ANTONELLI *et al.* [14] reported that one of the four lung recipients, who had cystic fibrosis, received NIMV as a bridge for transplantation. In the post-transplant period the patient developed HRF and was randomized to the NIMV treatment group, endotracheal intubation was avoided and the patient was finally discharged alive from the hospital. In the authors opinion, active transplant programmes should consider NIMV in the treatment of patients with HRF who have no contraindications and who can be monitored safely in the appropriate environment. Because of the consequences of endotracheal intubation, NIMV may probably be of great beneficial effect in such immunocompromised patients.

Acute respiratory distress syndrome

Few studies have applied NIMV in patients with ARDS, the older used CPAP while the more recent used some form of BIPAP. COVELLI *et al.* [42] evaluated the application of face mask CPAP in 33 patients with severe ARDS of varied aetiologies. Most of the applied EPAP did not exceed 5 cmH₂O. In seven patients who required an EPAP level >10 cmH₂O, the shunt fraction decreased from 44 ± 4 – 28 ± 4 . Significant improvements in the $P_{a,O_2} : F_{I,O_2}$ was obtained within 1 h of therapy. Five patients required intubation. The recent uncontrolled study from ROCKER *et al.* [43] reported the use of face mask NIMV during twelve episodes of acute lung injury/ARDS occurring in 10 patients. Intubation was avoided in 66% of the episodes, and ICU survival was 70%. Two controlled randomized studies comparing NIMV with a conventional approach in patients with HRF, included some patients with ARDS [5, 14]. Fifteen out of 40 patients had an ARDS in the first one [14] and 16 out of 64 in the second study [5]. The rate of intubation was 40% for patients randomized to NIMV and the mortality rate was 35%. These results should be intercepted cautiously and invite a prudent approach towards NIMV in ARDS, and to limit the application of NIMV to haemodynamically stable patients who can be closely monitored and where endotracheal intubation is promptly available.

Technological and logistic aspects

Technological and logistical aspects concerning NIMV in patients with HRF are not different than for patients with other forms of ARF [44]. However, in HRF some specific aspects should be pointed out because of the life threatening situation associated with hypoxaemia.

The mask

The mask, a critical part of NIMV, has been neglected for many years and still has not been extensively

evaluated while a major cause of NIMV failure seems related to the mask (intolerance, impossibility to fit the mask, facial deformity, *etc.*). In a recent cohort of 158 patients noninvasively ventilated, 52 patients were unable to be ventilated with NIMV. Of these 52 patients, nine (17%) failed because of intolerance to the mask and because of a mask that fit poorly. Several types of mask and patient-ventilator interfaces have been proposed for NIMV [45–47], but nasal and facial masks are the most frequently used. In patients with HRF, leaks by the mouth may be more critical than for hypercapnic patients and in a group of nine patients receiving NIMV, CARREY *et al.* [8] demonstrated that the nasal masks were no longer able to reduce the electric diaphragmatic activity when the mouth was opened. These aspects suggest that in patients breathing mouth opened (as it is frequently observed in HRF), a facial mask may be safer and more efficient than a nasal mask. Conversely, in keeping with the report of PUTENSEN *et al.* [48], in the authors experience the nasal mask seems better tolerated than the facial mask and should be proposed as soon as possible. Recently a full face mask was compared to a nasal and a nasobuccal mask in a group of nine patients receiving NIMV [49]. Leaks, discomfort and dyspnoea were significantly lower using this mask, and despite a high internal volume (1500 mL), gas exchanges were improved (as well as with other masks) by maintaining an EPAP level of 5 cmH₂O and by the presence of two orifices at the upper part of the mask. However, to the best of the authors knowledge and so far, this mask has not been investigated further and is not markedly available.

The ventilatory modality

In patients with HRF and noninvasively ventilated, the modalities which were most frequently used are those generating positive airway pressures. The physiological effects of ventilatory modalities used with NIMV have been investigated exclusively in COPD patients. In these patients GIRAULT *et al.* [50], compared volume-controlled ventilation and pressure-controlled ventilation and found that the inspiratory work of breathing was significantly reduced with both modalities but more importantly with volume-controlled ventilation (-69%) than with pressure-support ventilation (-55%, $p < 0.05$). Gas exchanges were similarly improved with both modalities but in keeping with a previous study [51] the respiratory comfort assessed by a visual analogue scale was better in pressure-support mode (81±25 mm) than in volume-controlled mode (57±30 mm, $p < 0.01$). From these results [50, 51] it seems possible to suggest pressure-support mode as a first line modality except in the most severe patients or in case of uncompleted resolution, situation in which a trial in volume-controlled mode could be proposed. Finally, except for the studies on CPAP in patients with CPO, pressure-support ventilation was used in the five randomized studies on NIMV in HRF [5, 14, 27, 29, 31]. Based on the above mentioned studies, although it is not possible to firmly recommend one ventilatory modality over another, it is

clearly possible to state that pressure-support modes may be the most frequently used to date. A new mode of ventilation, proportional assist ventilation (PAV), has been recently investigated in patients receiving NIMV [7]. In PAV, the pressure generated by the ventilator is continuously and breath-by-breath in proportion with the patient's respiratory effort [52, 53]. Using noninvasive PAV in 11 patients with HRF, WARD *et al.* [7] demonstrated that respiratory rate and the dyspnoea score were significantly reduced after 1 h of NIMV.

The exhalation device

This is an important technological issue that has been recently discussed [54–56]. Some ventilators designed for home NIMV are using a single inspiration-expiration circuit with a connector which permits venting of expiratory gas towards the atmosphere between the mask and the circuit. However, using such a system, a significant rebreathing has been demonstrated [54–56] which can be relevant clinically in patients with high minute ventilation as it may be observed in those with HRF. Therefore in patients having HRF, it is warmly recommended to use a non-rebreathing valve and a separate circuit for expiration. The exhalation device must also be low-resistive to not induce a significant expiratory effort as demonstrated with some home-ventilators [57].

The ventilator

The ventilators used by MEDURI *et al.* [26] and by WYSOCKI *et al.* [31] in the earlier studies [23, 24] were ICU ventilators while those used by PENNOCK *et al.* [25, 37] were portable and specifically designed. Both ICU and specific ventilators have advantages and limitations while recent ventilators tried to overcome such limitations; ICU ventilators by inserting in their software a noninvasive modality to realize NIMV easily, specified ventilators by being more complex and able to monitor the patient more closely. Among specific ventilators, six pressure-controlled ventilators were recently evaluated in an artificial lung model [57]. Of these ventilators five had been developed for home NIMV and one specifically for NIMV in acute care setting [6, 58]. Major differences between the ventilators were noted such as the minimal EPAP imposed by the ventilator (which were two- to four-fold higher in some home-ventilators) but also in the flow acceleration generated (which were two- to four-fold lower in some home-ventilators) and in the expiratory work imposed on the lung model (which were two- to four-fold higher in some home-ventilators). Because these differences may have clinical impacts the authors suggested that ventilators designed for NIMV in the acute care setting should have a minimal time to generate pressure support and a minimal expiratory resistance [57]. In addition, the same group demonstrated that most of CPAP ventilators had significant delay to return to the pressure assigned or were unable to maintain the pressure assigned when a leak

was created in the circuit. Because leaks are frequently observed in NIMV, the ability of the ventilators to maintain the level of airway pressure in presence of leaks is an important issue. Most of conventional ventilators are usually able to increase inspiratory flow to maintain the level of airway pressure in presence of leaks but this may not be the case for all specific ventilators. This issue could be crucial in patients with HRF and considering the risk of hypoxaemia, NIMV should be recommended only in the ICU setting (with extensive monitoring) and therefore using ICU ventilators.

Limits and causes of failure

Publications on NIMV are mostly focused on feasibility, indications or efficacy of NIMV and few are available on limits and on causes of failure. To the best of the authors knowledge, specific studies on predictive factors of NIMV failure were performed in COPD patients with acute exacerbation only. Soo Hoo *et al.* [59] designed a study to assess predictors of nasal NIMV failure in 14 acute exacerbation occurring in 10 COPD patients. The seven successful episodes were compared with the seven unsuccessful episodes and patients who failed were found to have a slower correction of their respiratory acidosis and greater severity of illness than successfully treated patients. The authors noted that unsuccessfully treated patients were oedentulous, had pneumonia or excess secretions, and had pursed-lip breathing, factors that prevented adequate mouth seal and contributed to a greater mouth leak than in successfully treated patients (314 ± 107 versus 100 ± 70 mL; $p < 0.01$). A second, not extensively published study [60], included a cohort of 51 COPD patients with an acute exacerbation among which 53% were successfully ventilated with NIMV while 47% failed and required endotracheal intubation. Multivariate analysis showed that the most encephalopathic patients (OR (Odd Ratio)=4, $p=0.001$), those >65 yrs (OR=4, $p=0.04$) and those presenting with a blood urea nitrogen ≥ 10 $\text{mM} \cdot \text{L}^{-1}$ (OR=3, $p=0.01$) failed to be ventilated with NIMV. Excluding the previous two specific studies [59, 60], a comparison between patients who failed and those successfully ventilated has been reported in several published studies, most of them were in COPD patients but five studies included a population of patients with mixed hypoxic-hypercapnic respiratory disorders. The first one [23] found that by contrast with patients who succeed, those who failed with NIMV did not improve pH and P_{a,CO_2} within 1–6 h of NIMV. The second [26] compared eight patients successfully ventilated to nine who failed and noted that the pre-NIMV P_{a,CO_2} was lower and the pH higher in patients who failed. The authors also found that day 1 P_{a,O_2} (off NIMV) was not improved in patients who ultimately required endotracheal intubation. In the BENHAMOU *et al.* [15] study on terminally ill patients only an initial agitation could predict NIMV failure. In a comparable population, MEDURI *et al.* [16] found that the pH after 1 h on NIMV was not improved and significantly lower in

patients who failed. This was also the case in a more recent study [61] in which 43 patients successfully ventilated were compared with 15 who failed. Finally, in the French multicentre study [62], only the Simplified Acute Physiological Score (SAPS) and tolerance to NIMV were independently associated with the success or the failure of the method.

From a practical point of view, these studies suggest that severe comorbid conditions, agitation or severe encephalopathy, nonimprovement in gas exchange with NIMV, excess secretions and mouth leaks may be limiting factors for NIMV. The method should also be avoided in patients with haemodynamic instability and in those who require an ET to protect the airways (coma, impaired swallowing, *etc.*). Patients with severe hypoxaemia ($P_{a,O_2} : F_{I,O_2} \leq 60$), morbid obesity ($>200\%$ of ideal body weight) or with unstable angina or acute myocardial infarction should be closely managed only by experienced personnel. Criteria for NIMV discontinuation and endotracheal intubation must be thoroughly considered in order to avoid dangerous delays (table 2).

Conclusions

Undoubtedly, noninvasive mechanical ventilation may play a significant role in hypoxaemic respiratory failure patients, by avoiding endotracheal intubation and subsequent side-effects, as well as by reducing the length of intensive care unit stay and ultimately the overall morbidity and mortality. However, by contrast with chronic obstructive pulmonary disease patients with acute exacerbation who constitute a relatively homogeneous group of patients, those with hypoxaemic respiratory failure constitute a much more heterogeneous group. Consequently further studies and/or statistical power are required to confirm the beneficial effects of noninvasive mechanical ventilation in patients with hypoxaemic respiratory failure. Interestingly, studies concerning specific patients such as those with hypoxaemic respiratory failure following solid organ transplant [14] or in immunosuppressed patients [33] were able to demonstrate the beneficial effects of noninvasive mechanical ventilation. Indeed, a lot of issues need to be clarified such as the selection of patients as well as the technological and organizational

Table 2. – Criteria for noninvasive mechanical ventilation discontinuation

Need for urgent endotracheal intubation
Cardiac or respiratory arrest
Coma
Inability to clear tracheal secretions
Protection of the airways
Inability to improve gas exchanges and dyspnoea
Haemodynamic instability or evidence of cardiac ischaemia or ventricular dysarrhythmia
Mask intolerance (discomfort or claustrophobia)
Inability to improve mental status, within 30 min after the application of noninvasive mechanical ventilation, in agitated hypoxaemic patients

aspects for safely delivering noninvasive mechanical ventilation in patients with hypoxaemic respiratory failure.

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