Intensive Care Med (2006) 32:361–370
DOI 10.1007/s00134-005-0050-0

CLINICAL COMMENTARY

Stefano Nava
Paolo Navalesi
Giorgio Conti

Time of non-invasive ventilation

Received: 16 December 2005
Accepted: 16 December 2005
Published online: 14 February 2006

S. Nava · P. Navalesi (✉)
Fondazione S. Maugeri IRCCS, Pneumologia Riabilitativa e Terapia Intensiva Respiratoria,
Via Ferrata 8, 27100 Pavia, Italy
e-mail: pnavalesi@fsm.it
Tel.: +39-382-592-810
Fax: +39-382-592-075

G. Conti
Università Cattolica del Sacro Cuore, Istituto di Anestesia e Rianimazione,
Rome, Italy

Abstract Non-invasive ventilation (NIV) is a safe, versatile and effective technique that can avert side effects and complications associated with endotracheal intubation. The success of NIV relies on several factors, including the type and severity of acute respiratory failure, the underlying disease, the location of treatment, and the experience of the team. The time factor is also important. NIV is primarily used to avert the need for endotracheal intubation in patients with early-stage acute respiratory failure and post-extubation respiratory failure. It can also be used as an alternative to invasive ventilation at a more advanced stage of acute respiratory failure or to facilitate the process of weaning from mechanical ventilation. NIV has been used to prevent development of acute respiratory failure or post-extubation respiratory failure. The number of days of NIV and hours of daily use differ, depending on the severity and course of the acute respiratory failure and the timing of application. In this review article, we analyse, compare and discuss the results of studies in which NIV was applied at various times during the evolution of acute respiratory failure.

Keywords Non-invasive positive pressure ventilation · Respiratory failure · Chronic obstructive lung disease · Pneumonia · Cardiogenic pulmonary oedema · Endotracheal intubation · Weaning · Extubation failure

Introduction

Patients affected by acute respiratory failure (ARF) have been traditionally treated by endotracheal intubation and mechanical ventilation to correct life-threatening hypoxaemia and/or acute progressive respiratory acidosis, while reducing dyspnoea and inspiratory effort [1]. Although conventional invasive mechanical ventilation is a life-saving procedure, endotracheal intubation is the most important risk factor for nosocomial pneumonia [2] and may damage the tracheal mucosa [3]; furthermore, it increases patients' discomfort and need for sedatives.

Non-invasive ventilation (NIV) is nowadays widely recognised as a valid means to avoid intubation and its associated side effects and complications in patients with ARF [4, 5, 6]. NIV preserves airway defence mechanisms, speech, and swallowing; furthermore, NIV affords greater flexibility in applying and removing the ventilatory assistance [2].

The success of NIV depends on several factors, such as the type of ARF (hypoxaemic or hypercapnic), the underlying disease, the location of treatment, and the experience of the care team [4]. Time is also important, both in terms of the moment at which NIV is applied and its total duration (i.e. the number of days of NIV and the daily hours of use).

As summarised in Fig. 1, NIV may be used at different moments: (1) to prevent the occurrence of impending (but not established) acute or post-extubation failure, (2) at an early stage, when respiratory failure is already established, to avert the need for endotracheal intubation, and (3) as an alternative to invasive ventilation at a more ad-

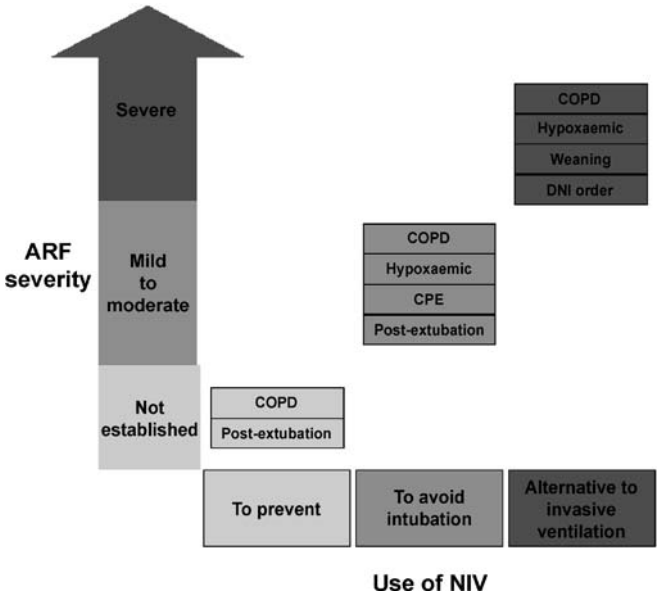


Fig. 1 Time of non-invasive ventilation (*NIV*) use with respect to severity of acute respiratory failure (*ARF*)

vanced stage of acute respiratory failure or to facilitate the process of weaning from mechanical ventilation. The duration and intensity of NIV strongly depend on the time it is instituted.

In this clinical commentary we summarise and discuss the results of the studies performed on both hypercapnic and hypoxaemic patients at different times. We analyse the results of studies dealing with intermittent positive pressure ventilation, excluding those in which continuous positive airway pressure alone or intermittent negative pressure ventilation was used.

NIV to prevent acute respiratory failure or post-extubation respiratory failure

Exacerbation of chronic obstructive pulmonary disease

Very few studies have so far assessed the efficacy of NIV at preventing the occurrence of acute respiratory failure, and all of those that did so included patients with a mild exacerbation of chronic obstructive pulmonary disease (COPD). Bardi et al. [7] randomised 30 patients, the large majority of whom had a pH > 7.35, to early NIV or medical therapy alone. No significant improvement in mortality, need for endotracheal intubation or time spent in hospital was found. In a similar population, Keenan et al. [8] reported no difference in any clinical outcome, but a significant reduction in dyspnoea with NIV, although mask ventilation was found to be very poorly tolerated.

In summary, according to these studies, anticipating the use of NIV in patients with an exacerbation of COPD to prevent, rather than to treat, respiratory distress and ventilatory failure is unhelpful and futile, and would therefore be an unnecessary waste of resources.

NIV to prevent extubation failure

Post-extubation failure is a major clinical problem in intensive care units (ICU) [9]. Extubation attempts may fail in as many as 23.5% of patients [10], and the in-hospital mortality of these patients may approach 30–40%. The cause of extubation failure and the time elapsed before re-intubation are independent predictors of outcome [11].

A few studies have evaluated the use of NIV as a means to prevent, rather than to treat, post-extubation respiratory failure. Jiang et al. [12] conducted a prospective study on 93 patients who were randomised to receive NIV or oxygen therapy after planned or unplanned extubation and found no difference in the re-intubation rate between the two groups. Epstein et al. [11] showed that there is a certain subset of patients whose clinical characteristics at the time of extubation may predict re-intubation. Based on this finding, two randomised trials were recently performed [13, 14] to assess whether NIV is effective in preventing the occurrence of post-extubation failure in patients at risk. Both of these two studies, which adopted similar criteria to define patients at risk and had comparable study designs, showed that the groups treated with NIV had a lower rate of re-intubation than did the groups in which standard therapy was used; furthermore, in one of the two studies [14] ICU mortality was also reduced in the subgroup of hypercapnic patients treated with NIV.

In conclusion, a promptly started use of NIV for at least 48 h in selected patients "at risk" may prevent post-extubation respiratory failure.

NIV to prevent endotracheal intubation and re-intubation

COPD exacerbation

The patients who benefit most from NIV are those with acute respiratory acidosis caused by an exacerbation of COPD [4]. When acute hypercapnic respiratory failure ensues, standard medical treatment may fail. The rate of failure of medical management ranges between 27% [15] and 74% [16]. Although pH is by far the most important determinant for deciding whether to institute NIV, other clinical indicators such as the severity of the dyspnoea, tachypnoea, and the use of accessory muscles are also considered in the selection of patients for NIV [4], which has the potential to prevent further clinical deterioration by increasing alveolar ventilation [17] and reducing inspiratory effort [18].

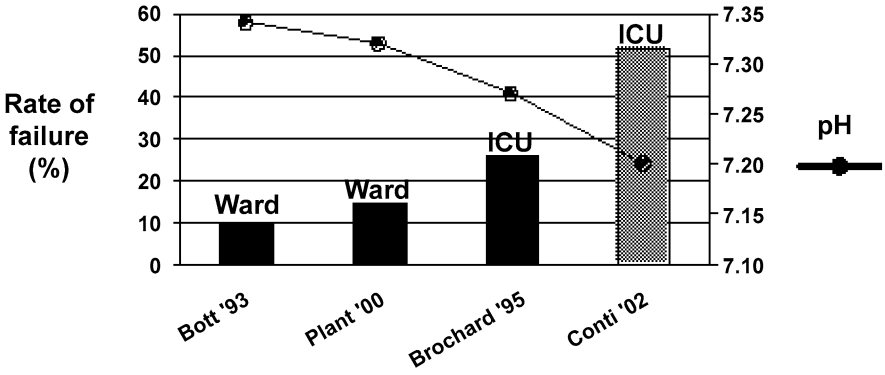


Fig. 2 The figure depicts the rate of NIV failure (*left axis*) and the corresponding average pH values (*right axis*) on study entry for four randomised controlled trials [5,6,9,53]. The three studies denoted by the *black bars* are those in which NIV was used to prevent endotracheal intubation in patients with mild to moderate acute respiratory failure, while the *light grey bar* indicates the study in which NIV was applied as an alternative to invasive mechanical ventilation in patients with more severe disease deemed to require ventilatory assistance. There is a clear inverse relationship between severity of respiratory acidosis and the rate of failure of NIV. The *labels* on the tops of the bars specify for each study the setting in which NIV was applied. See text for further explanation

In the last decade, several randomised controlled trials [15, 16, 19, 20, 21, 22, 23, 24] have shown that the addition of NIV to medical treatment relieves dyspnoea [15, 19], improves vital signs and gas exchange [15, 16, 19], prevents endotracheal intubation [15, 16, 20], reduces complications [16, 24], lowers mortality [15, 16] and shortens the time spent in hospital [16, 21, 22, 23]. Brochard et al. [16], however, found that the benefits of NIV over standard treatment vanished when only those patients in whom treatment failed and who required intubation were considered; in particular, after adjustment for intubation, there was no difference in mortality.

With few exceptions [15, 16], the above cited clinical trials were underpowered, so heavy use has been made in the last few years of systematic reviews and meta-analyses [6, 25, 26, 27, 28, 29]. By analysing pooled results from different trials, these studies confirmed that the addition of NIV to standard therapy decreases the need for endotracheal intubation [6, 25, 27, 28, 29], reduces complications [6, 29], lowers mortality rate [6, 25, 27, 28, 29], shortens the time spent in hospital [6, 28, 29] and reduces costs [26] in patients with acute hypercapnic respiratory failure secondary to an exacerbation of COPD.

Notwithstanding a general consensus on the value of NIV resulting from this large body of evidence [4, 30], some aspects still deserve consideration. For example, one randomised trial found that adding NIV to standard treatment in hypercapnic COPD patients admitted to a respiratory ward with very mild ARF did not produce further advantages; the success rate, however, was 100% for both NIV and standard treatment [31]. Moreover, a recent systematic review [28] concluded that, unlike patients with severe exacerbation and established acidosis, patients with extremely mild or no respiratory acidosis do not benefit from NIV. On the other hand, in a large multicenter trial including mildly to moderately acidotic COPD patients (initial pH ≤ 7.35 and ≥ 7.25) admitted to a medical ward, Plant et al. [15] found that the rate of failure was lower with NIV than with standard therapy alone; subgroup analysis showed that NIV improved the outcome of patients whose pH at enrolment was ≥ 7.30, while rate of failure and mortality did not differ between the two treatment groups among patients whose enrolment pH was < 7.30. These findings suggest that more severely ill patients need a higher dependency setting with a more favourable nurse:patient ratio and a higher level of monitoring [32]. As illustrated in Fig. 2, the more acidotic the patient is, the higher the likelihood of NIV failure. Although the need for intubation is reduced remarkably by NIV, it is not entirely abolished, so it is definitely advisable to manage patients with more severe ARF straightaway in the ICU, where endotracheal intubation can be rapidly performed if necessary, and move those patients who deteriorate or do not improve despite NIV to the ICU [33, 34, 35, 36].

In conclusion, considering the strong evidence of efficacy, the relatively few hours of daily use, and, compared with other applications, the fairly low rate of failure, the use of NIV to avoid intubation in COPD patients with mild to moderate ARF (i.e. pH < 7.35 and > 7.25) is strongly advisable and probably represents the best approach for those units that are willing to implement this technique.

Hypoxemic respiratory failure

Several clinical trials have evaluated NIV as a means to prevent intubation in patients with hypoxaemic ARF of varied aetiology [37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51]. The results have been controversial. Most of these studies enrolled patients with moderate ARF, in whom the indication for immediate endotracheal intubation was not mandatory.

Wysocki et al. [37] showed that, compared with standard therapy, NIV reduced the need for endotracheal intubation, shortened the duration of ICU stay and decreased

mortality rate only in the subgroup of patients with associated hypercapnia ($PaCO_2 > 45$ mmHg), but produced no advantage in purely hypoxaemic patients. In contrast, in a similar group of patients Martin et al. [38] found that NIV reduced the rate of intubation. More recently, Ferrer and co-workers [39] randomised a group of 105 patients with hypoxaemic ARF to receive either NIV or high O_2 concentration alone. NIV reduced the need for endotracheal intubation, the incidence of septic shock, the ICU mortality and the 90-day mortality.

One of the major confounders of these studies was the marked variability of the case mix; patients with different underlying disorders and pathophysiologic pathways were included under the same generic definition of having hypoxaemia [52]. Confalonieri et al. [40] evaluated NIV in patients with ARF ($PaO_2/FiO_2 < 250$) consequent to community-acquired pneumonia, including both patients with and without COPD. Compared to standard treatment alone, NIV produced a significant reduction in respiratory rate, need for endotracheal intubation and ICU stay. However a subgroup analysis showed that the benefits of NIV occurred only in the subgroup of COPD patients. Two subsequent observational studies [53, 54] suggested that NIV is not useful in avoiding intubation when hypoxaemic ARF is caused by community-acquired pneumonia in the absence of a pre-existing chronic pulmonary disorder.

Six trials compared NIV with continuous positive airway pressure (CPAP) delivered via a mask in patients with hypoxaemic ARF secondary to cardiogenic pulmonary oedema and found that NIV produces no further advantage vs CPAP [44, 47, 48, 49, 50, 51], although in one study NIV determined more rapid improvements in oxygenation and decreases in $PaCO_2$ [44]. Two trials [45, 46] assessed, with conflicting results, whether the addition of NIV to medical therapy could decrease the rate of intubation Subgroup analysis, performed in the study including the larger number of patients [46], suggested that only hypercapnic ($PaCO_2 > 45$ mmHg) patients benefited from NIV.

NIV may be used in the early treatment of ARF secondary to lung resection, a fatal complication in up to 80% of cases. Auriant et al. [43] showed that NIV is safe and effective in reducing the need for intubation and improving survival.

Early NIV application may be extremely helpful in immunocompromised patients, in whom intubation dramatically increases the risk of pneumonia, infections and ICU mortality [55]. Two trials evaluated NIV, as opposed to standard treatment alone, in immunocompromised patients characterised by a respiratory rate > 30 breaths/min and $PaO_2/FiO_2 < 200$. Antonelli et al. [41] compared NIV with standard therapy in solid organ transplant recipients with hypoxaemic ARF. Within the first hour of treatment, PaO_2/FiO_2 improved in 70% of patients in the NIV group and in only 25% of patients receiving medical therapy alone. NIV was associated with a significant reduction in the rate of intubation, complications, mortality and duration of ICU stay among survivors. In patients with immunosuppression secondary to haematological malignancies, transplantation or human immunodeficiency virus infection, Hilbert et al. [42] compared early NIV with standard treatment. All patients had fever, bilateral pulmonary infiltrates and hypoxemia. Fewer patients in the NIV group required intubation, had serious complications, or died in the ICU or in the hospital.

Acute respiratory failure is a complication that may ensue in patients with cancer [56, 57]. Intubation and invasive ventilation are strong predictors of mortality in critically ill cancer patients [58]. A retrospective cohort study suggested that NIV may improve the survival of patients with solid or haematological malignancies admitted to an ICU for ARF [59].

In conclusion, the outcome of NIV in patients with hypoxaemic ARF for whom endotracheal intubation is not yet mandatory depends primarily on the type and evolution of the underlying disorder. The high rate of failure of NIV in community-acquired pneumonia and acute respiratory distress syndrome suggests for these patients a cautious approach consisting in early treatment and avoidance of delay of needed intubation. A trial of NIV is advisable in immunosuppressed patients (in whom intubation is, per se, a strong predictor of mortality), after lung resection, and in patients with cardiogenic pulmonary oedema with associated hypercapnia.

NIV to prevent re-intubation

The use of NIV has been suggested in an attempt to avoid re-intubation in patients who show signs of "incipient" or even overt respiratory failure following extubation.

Hilbert and co-workers [60] demonstrated that NIV improved the outcome of patients with COPD and post-extubation hypercapnic respiratory failure by reducing the need for endotracheal intubation, the mean duration of ventilatory assistance and the duration of ICU stay when compared with conventional treatment of matched subjects.

In a more recent randomised, controlled trial [61] NIV was applied to patients who developed ARF within 48 h after extubation and compared with standard medical therapy. The patients were randomised to standard therapy alone or to NIV. The authors did not find any difference in re-intubation rate, hospital mortality rate, ICU stay and hospital stay, despite there being a trend to a shorter duration of hospital stay in the NIV group.

Very recently Esteban et al. [62] conducted a large multicentre, randomised trial to evaluate the effect of NIV on mortality in this clinical setting. Patients who had respiratory failure within the subsequent 48 h were randomly assigned to either NIV (114 patients) or standard medical therapy (107 patients). There was no difference between

the two groups in the need for re-intubation, while ICU mortality was higher in the NIV group (25% vs 14%; relative risk = 1.78); the median time from respiratory failure to re-intubation was longer in the NIV group, raising the suspicion that this delay in re-intubation may have influenced the negative results. The authors concluded that NIV does not prevent the need for re-intubation or reduce mortality in unselected patients who have respiratory failure after extubation. It is noteworthy that NIV was used as a "rescue" therapy in the patients who failed standard therapy and the rate of success was much higher than in the NIV group.

In summary, in spite of the early promising data from non-randomized studies, NIV does not prevent the need for re-intubation or reduce mortality in unselected patients with established post-extubation respiratory failure.

NIV as an alternative to invasive ventilation

Exacerbations of COPD

The early use of NIV in COPD patients with respiratory acidosis and impending respiratory muscle failure is effective in preventing further clinical deterioration and avoiding endotracheal intubation. Because of the abrupt onset of ARF, its rapid progression and/or delays in receiving medical evaluation and appropriate treatment, some patients may worsen so much that mechanical ventilation becomes mandatory. However, if endotracheal intubation in such patients is not strictly required because of gasping for air, unconsciousness or the need to protect the airway, NIV might still be advantageous compared with invasive ventilation.

There is only one randomised controlled trial that compared NIV with invasive ventilation in COPD patients with severe ARF in whom ventilatory support was deemed necessary [63]. Twenty-three and 26 patients were randomised to receive NIV and conventional invasive ventilation, respectively. The average pH on study entry was 7.20 for both groups, indicating that these patients had more severe ARF than those enrolled in the clinical trials in which NIV was used at an earlier stage (Fig. 2). In the NIV group, treatment failed in 12 patients (52%), who were thus intubated to receive invasive mechanical ventilation. The authors found no significant differences between the two groups in ICU and hospital mortality, overall complications, duration of mechanical ventilation and ICU stay. The patients in the NIV group had a lower rate of sepsis and septic shock and showed a trend toward a lower incidence of nosocomial pneumonia during their time in the ICU. In addition, at a 12-month follow-up, the rate of hospital re-admissions and the number of patients on long-term oxygen therapy were lower in the NIV group. Unfortunately, because of the relatively small number of patients included, this study was exposed to the risk of a type II error and, in addition, it was not possible to perform a post-hoc analysis to assess whether or not the patients in whom NIV failed were harmed by delayed intubation and invasive ventilation.

These results were confirmed by a subsequent case—control clinical trial including 64 consecutive COPD patients with severe ARF caused by exacerbation or community-acquired pneumonia [64]. Data from these patients were prospectively collected and compared with those from a tightly matched historical control group taken from a large database of COPD patients treated in the same ICU with conventional invasive ventilation during the previous 2 years. The average pH of the patients and controls on entry into the study was 7.18. NIV failed in 40 patients (62%), who were then intubated. The mortality rate, duration of mechanical ventilation, time spent in the ICU and duration of post-ICU hospitalisation were similar in the two groups; however, patients in the NIV group had fewer complications and showed a trend toward a lower probability of remaining on mechanical ventilation after 30 days. Apart from confirming the results obtained by Conti et al. [63], the large sample of patients and high rate of NIV failures allowed a subgroup analysis that showed that the outcomes of the 40 patients in whom NIV failed and of the 64 controls were no different, while the 24 patients in whom NIV was successful had better outcomes.

In both the aforementioned studies NIV was used in an ICU and the study protocols had predefined criteria for NIV failure which led in all cases to a prompt intubation, when required. Unlike the clinical trials in which NIV was used to avoid intubation and was then intermittently applied for relatively few hours [15, 16, 19, 20], in these two studies patients received almost continuous ventilatory support, at least for the first 24–48 h. This might account for the approximately 40% of patients in whom NIV failed because of mask intolerance and discomfort, as reported by Squadrone et al. [64].

In conclusion, as indicated in Fig. 2, in patients with COPD deemed severe enough to require ventilatory support, the use of NIV at a more advanced stage of ARF is more likely to fail. A NIV trial before proceeding to intubation and invasive ventilation does not, however, harm the patient and may be cautiously attempted, closely monitoring the patient in an ICU and avoiding excessive delay of the required intubation.

Hypoxaemic respiratory failure

To our knowledge, only one randomised trial has so far evaluated the use of NIV in hypoxaemic patients considered sufficiently ill to require mandatory ventilatory assistance. Antonelli et al. [65] compared NIV with conventional ventilation through an endotracheal tube in selected patients with hypoxaemic ARF secondary to

cardiogenic pulmonary oedema, acute lung injury/acute respiratory distress syndrome or pneumonia who failed to improve despite aggressive medical therapy and met predefined criteria for mechanical ventilation. Sixty-four consecutive patients were enrolled (32 in each arm). After 1 h of mechanical ventilation, the PaO_2/FiO_2 ratio had improved in both groups. Ten (31%) patients in the NIV group required intubation. Patients randomised to conventional ventilation more frequently developed serious complications (66% vs 38%) and, in particular, infections secondary to endotracheal intubation (i.e. pneumonia and/or sinusitis). Among survivors, the duration of mechanical ventilation and ICU stay was shorter for patients randomised to NIV. It should, however, be kept in mind that this single study was conducted in selected patients in one well-experienced centre.

In summary, in our opinion, the use of NIV as an alternative to invasive ventilation in severely hypoxaemic patients (i.e. $PaO_2/FiO_2 < 200$) is not generally advisable and should be limited to haemodynamically stable patients who can be closely monitored in an ICU by highly skilled staff.

NIV to wean patients off the ventilator

In the majority of cases withdrawal of mechanical ventilation and extubation are possible immediately after resolution of the underlying problems responsible for ARF. However, there is a group of ventilated patients who require more gradual and longer withdrawal of mechanical ventilation.

NIV is theoretically able to counteract several physiological mechanisms associated with weaning failure or difficulties. In ventilator-dependent COPD patients NIV has been shown to be as effective as invasive ventilation in reducing inspiratory effort and improving arterial blood gases [66]. In fact, following some uncontrolled clinical studies in which NIV was used as a bridge to weaning [67, 68, 69, 70, 71], the first randomised controlled study of this strategy was performed [72] in severely ill COPD patients ventilated through an endotracheal tube. Patients who failed the T-piece trial were randomised to either extubation, with immediate application of NIV, or to continued weaning with the endotracheal tube in place. Overall, this study showed that the likelihood of weaning success is increased, while the duration of mechanical ventilation and ICU stay are decreased, when NIV is used as a weaning technique.

A second randomised controlled study in a single ICU [73] was conducted on patients with chronic respiratory disorders intubated for an episode of acute respiratory failure. Thirty-three patients were randomised to receive "traditional" weaning or NIV. This study also found a shorter duration of invasive mechanical ventilation in the groups weaned non-invasively, although no differences were found in ICU stay, hospital stay or 3-month survival between the two groups.

In a third recent randomised controlled trial [74], patients who failed spontaneous breathing trials on three consecutive days were randomised to be extubated and receive NIV or to remain intubated and continue a conventional weaning protocol. Most of the patients (about 80%) were affected by hypercapnic respiratory failure. The duration of conventional mechanical ventilation, the time spent in the ICU and the duration of hospitalisation were significantly lower in the NIV group. Patients treated with NIV also had lower rates of nosocomial pneumonia and septic shock and better ICU and 90-day survival.

Further studies are clearly needed to assess the benefits of NIV in weaning in other forms of respiratory failure, such as acute respiratory distress syndrome, post-surgical complications or cardiac impairment.

In conclusion, NIV may be safely and successfully used in ICU to shorten the process of liberation from mechanical ventilation in stable patients recovering from an episode of hypercapnic ARF who had previously failed a weaning trial.

NIV in patients with a 'do not intubate' order

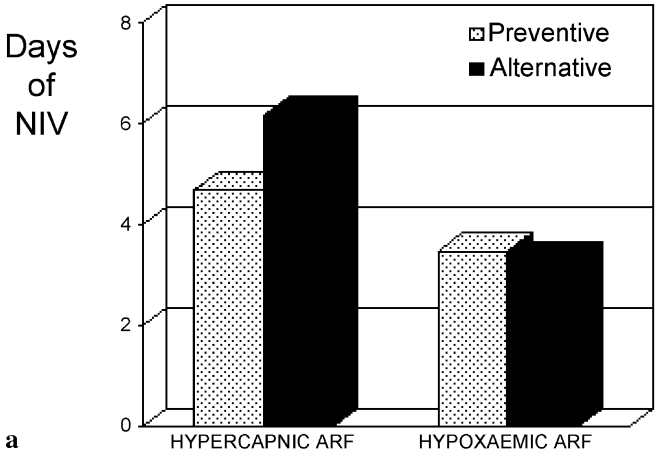
NIV has been used as an alternative to invasive ventilation in patients with a 'do not intubate' order [75]. In a recent study [76], NIV was applied to treat episodes of ARF in 114 patients with 'do not intubate' orders. About half of the patients survived and were discharged from the ICU. The underlying disease was an important determinant of survival; the outcome of patients with congestive heart failure was significantly better than that of patients with COPD, pneumonia, or cancer. Similar results have been recently obtained by Schettino et al. [77]. In another study [78], NIV was used in 37 hypercapnic COPD patients with 'do not intubate' orders and their outcomes were compared with those of a group of COPD patients in whom instructions on intubation had not been given. As opposed to the patients in the latter group, most of the patients with 'do not intubate' orders died or developed another life-threatening event within 1 year. It should be noted, however, that patients in the former group were older, more dyspnoeic, and had more co-morbidities and spent more time in hospital in the year preceding the study.

In summary, the use of NIV to provide ventilatory assistance to patients with 'do not intubate' order is appealing, although robust evidence from randomized controlled trials is so far lacking.

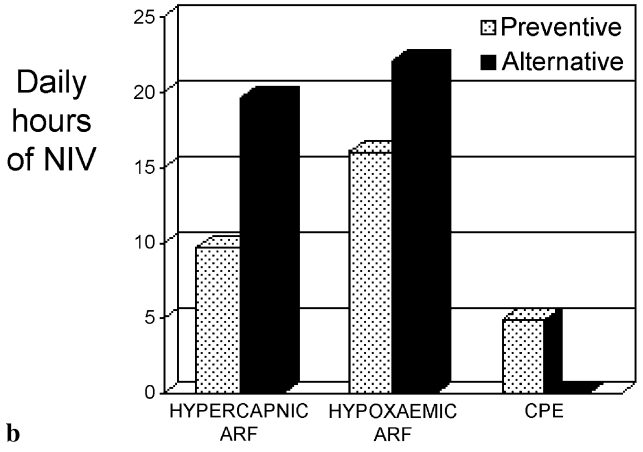
Overall duration and intensity of NIV application

As opposed to invasive mechanical ventilation, discontinuing and resuming ventilator support with NIV is not

cumbersome and can be carried out several times a day. To prevent intubation and re-intubation NIV is commonly applied intermittently for a variable number of hours, depending on various factors, such as the severity of the ARF and the patient's tolerance. It is worth noting that 3–4 days of NIV (Fig. 3A) for less than 12 h/day (Fig. 3B) are usually sufficient to reverse ARF; in patients with cardiogenic pulmonary oedema NIV is commonly required for less than 6 h (Fig. 3B).



a



b

Fig. 3 Days of NIV use (**A**) and hours of daily application (**B**) in patients with mild to moderate (*grey bars*) and severe (*black bars*) already established hypercapnic and hypoxaemic acute respiratory failure (*ARF*). Pertinent information was obtained when available from the published report, or directly by communication from the authors. Patients with cardiogenic pulmonary oedema (*CPE*) are not included in panel **A** because NIV was applied for less than 1 day in all cases, while they are grouped separately in panel **B**. See text for further explanation. References considered: preventive NIV in hypercapnic ARF: [15, 16, 9, 20, 21]; preventive NIV in hypoxaemic ARF: [37, 38, 39, 40, 41, 42, 43, 61]; cardiogenic pulmonary oedema: [44, 45, 46, 48, 49, 50, 51]; alternative in hypercapnic ARF: [63, 64, 72, 73, 74]; alternative in hypoxaemic ARF: [65]

Not surprisingly, the total duration of mechanical ventilation (Fig. 3A) and the mean hours of daily application (Fig. 3B) are longer when NIV is applied as an alternative to endotracheal intubation or in the weaning process. This may help to explain the higher rate of NIV failure due to discomfort and intolerance observed when NIV is used as an alternative to invasive ventilation [64].

Time is also a critical factor when assessing the success or failure of NIV, because it is important not to unduly delay the decision to intubate a patient. Most of the studies evaluating predictors of NIV outcome suggest that patients who do not improve within a few hours should be considered for intubation. Changes in arterial blood gases (i.e. pH for hypercapnic respiratory failure and PaO_2/FiO_2 for hypoxic respiratory failure) have been considered the best predictors, although respiratory rate has also been found to be a good predictor of response to NIV [79, 80]. Despite prompt improvement soon after the institution of NIV, this treatment may fail in some patients later on. In a recent observational study of 134 patients with COPD exacerbations who underwent NIV, a subgroup of 31 patients (characterised by lower pH values and a higher rate of co-morbid conditions) deteriorated some days after the institution of NIV [81].

Conclusions

After a "pioneering era", NIV is nowadays a therapeutic strategy which belongs to the real world of clinical practice. NIV should primarily be used for the early treatment of established episodes of ARF, in order to avoid further deterioration and intubation, and eventually to shorten the duration of invasive mechanical ventilation in COPD patients.. A skilled team may also advantageously use NIV in the ICU as an alternative to invasive ventilation in patients with more advanced ARF episodes of different aetiologies [82]. Instituting this strategy at a more advanced stage does, however, imply the use of many consecutive hours of NIV, increasing the risk of side effects leading to patient discomfort.

Knowledge of NIV-specific features and choice of the right patient in the appropriate setting are key factors for the success of NIV. Considering and understanding the implications of the time at which NIV is applied may help to increase the efficacy and reduce the drawbacks of this valuable technique.

References

1. Tobin MJ (2001) Advances in mechanical ventilation. New Engl J Med 344:1986–1996
2. Meduri GU (1998) Noninvasive ventilation. In: Marini J, Slutsky A (eds) Physiological basis of ventilatory support: a series on lung biology in health and disease. Dekker, New York, pp 921–998
3. Burns HP, Dayal VS, Scott A, van Nostrand AW, Bryce DP (1979) Laryngotracheal trauma: observations on its pathogenesis and its prevention following prolonged orotracheal intubation in the adult. Laryngoscope Aug 89:1316–25
4. International Consensus Conferences in Intensive Care Medicine (2000) Noninvasive positive pressure ventilation in acute respiratory failure. Intensive Care Med 27:166–178
5. Girou E, Brun-Buisson C, Taille S, Lemaire F, Brochard L (2003) Secular trends in nosocomial infections and mortality associated with noninvasive ventilation in patients with exacerbation of COPD and pulmonary edema. JAMA 290:2985–2991
6. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS (2003) Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. Br Med J 326:185
7. Bardi G, Pierotello R, Desideri M, Valdisserri L, Bottai M, Palla A (2000) Nasal ventilation in COPD exacerbations: early and late results of a prospective, controlled study. Eur Respir J 15:98–104
8. Keenan SP, Powers CE, McCormack DG (2005) Noninvasive positive-pressure ventilation in patients with milder chronic obstructive pulmonary disease exacerbations: a randomized controlled trial. Respir Care 50:610–616
9. Epstein SK (2004) Putting it all together to predict extubation outcome. Intensive Care Med 30:1255–1257
10. Epstein SK, Ciubataru RL, Wong JB (1997) Effect of failed extubation on the outcome of mechanical ventilation. Chest 112:186–192
11. Epstein SK, Ciubotaru RL (1998) Independent effects of etiology of failure and time of reintubation on outcome for patients failing extubation. Am.J Respir Crit Care Med 158:489–493
12. Jiang JS, Kao SJ, Wang SN (1999) Effect of early application of biphasic positive airway pressure on the outcome of extubation in ventilator weaning. Respirology 4:161–165
13. Nava S, Gregoretti C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, Beltrame F, Navalesi P (2005) Noninvasive ventilation to prevent respiratory failure after extubation in high risk patients Crit Care Med 33:2465–2470
14. Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A (2005) Early non-invasive ventilation averts extubation failure in patients at risk. A randomized trial. Am J Respir Crit Care Med ; e-pub ahead of print on October 13, 2005 as DOI 10.1164/rccm.200505–718OC
15. Plant PK, Owen JL, Elliot MW (2000) A multicentre randomised controlled trial of the early use of non-invasive ventilation in acute exacerbation of chronic obstructive pulmonary disease on general respiratory wards. Lancet 335:1931–1935
16. Brochard L, Mancebo J, Wysochi M, Lofaso F, Conti G, Rauss A, Simonneau G, Benito S, Gasparetto A, Lemaire F, Isabey D, Harf A (1995) Noninvasive ventilation for acute exacerbation of chronic obstructive pulmonary disease. N Engl J Med 333:817–822
17. Diaz O, Iglesia R, Ferrer M, Zavala E, Santos C, Wagner PD, Roca J, Rodriguez-Roisin R (1997) Effects of noninvasive ventilation on pulmonary gas exchange and hemodynamics during acute hypercapnic exacerbations of chronic obstructive pulmonary disease. Am.J Respir Crit Care Med 156:1840–1845
18. Appendini L, Patessio A, Zanaboni S, Carone M, Gukov B, Donner CF, Rossi A (1994) Physiologic effects of positive end-expiratory pressure and mask pressure support during exacerbations of chronic obstructive pulmonary disease. Am. J Respir Crit Care Med 149:1069–1076
19. Bott J, Carrol MP, Conway JH, Keity SEJ, Ward EM, Brown AM, Paul A, Elliot MW, Godfrey RC, Wedzicha JA (1993) Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet 341:1555–1557
20. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS (1995) Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 151:1799–1806
21. Celikel T, Sungur M, Cayhan B, Karakurt S (1998) Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. Chest 114:1636–1642
22. Avdeev SN, Tretyakov AV, Grigoryants RA, Kutsenko MA, Chuchalin AG (1998) Noninvasive positive airway pressure ventilation: role in treating acute respiratory failure caused by chronic obstructive pulmonary disease [in Russian]. Anesteziologita Reanimatologia 3:45–51
23. Dikensoy O, Ikidag B, Filiiz A, Bayram N (2002) Comparison of non-invasive ventilation and standard medical therapy in acute hypercapnic respiratory failure: a randomised controlled trial at a tertiary health centre in SE Turkey. Int J Clin Pract 56:85–88
24. Thys F, Roeseler J, Reynaert M, Liistro G, Rodenstein DO (2002) Noninvasive ventilation for acute respiratory failure: a prospective randomised placebo-controlled trial. Eur Respir J 20:545–555
25. Keenan SP, Kernerman PD, Cook DJ, Martin CM, McCormack D, Sibbald WJ (2002) Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: A meta-analysis. Crit Care Med 25:1685–1692
26. Keenan SP, Gregor J, Sibbald WJ, Cook D, Gafni A (2000) Noninvasive positive pressure ventilation in the setting of severe, acute exacerbation of chronic obstructive pulmonary disease: more effective and less expensive. Crit Care Med 28:2094–2112
27. Peter JV, Moran JL, Phillips-Hughes J, Warn D (2002) Noninvasive ventilation in acute respiratory failure – a meta-analysis update. Crit Care Med 30:555–562
28. Keenan SP, Sinuff T, Cook DJ, Hill N (2003) When is the addition of noninvasive positive pressure ventilation effective in acute exacerbations of COPD? A systematic review. Ann Intern Med 138:861–870
29. Ram FSF, Picot J, Lightowler J, Wedzicha JA (2004) Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease (Cochrane Review). In: The Cochrane Library, Issue 3. Wiley, Chichester, UK
30. British Thoracic Society Standards of Care Committee (2002) Non-invasive ventilation in acute respiratory failure. Thorax 57:192–211
31. Barbè F, Togores B, Rubi M Pons S, Maimo A, Agusti AG (1996) Noninvasive ventilatory support does not facilitate recovery from acute respiratory failure in chronic obstructive pulmonary disease. Eur Respir J 9:1240–1245

32. Elliott MW, Confalonieri M, Nava S (2002) Where to perform noninvasive ventilation? Eur Respir J 19:1159–1166
33. Ambrosino N, Foglio K, Rubini F, Clini E, Nava S, Vitacca M (1995) Noninvasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. Thorax 50:755–757
34. Soo Hoo GW, Santiago S, Williams AJ (1994) Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: determinants of success and failure. Crit Care Med 22:1253–1261
35. Anton A, Guell R, Gomez J, Serrano J, Castellano A, Carrasco JL, Sanchis J (2000) Predicting the result of noninvasive ventilation in severe acute exacerbations of patients with chronic airflow limitation. Chest 117:828–833
36. Carlucci A, Richard JC, Wysochy M, Lepage E, Brochard L (2001) Noninvasive versus conventional mechanical ventilation. An epidemiology survey. Am J Respir Crit Care Med 63:874–880
37. Wysocki M, Tric L, Wolff MA, Millet H, Herman B (1995) Noninvasive pressure support ventilation in patients with acute respiratory failure. A randomized comparison with conventional therapy. Chest 107:761–768
38. Martin TJ, Hovis JD, Costantino JP, Bierman MI, Donahoe MP, Rogers RM, Kreit JW,Sciurba FC, Stiller RA, Sanders MH (2000) A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. Am J Respir Crit Care Med 161:807–813
39. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A (2003) Noninvasive ventilation in severe hypoxemic respiratory failure: a randomised clinical trial Am J Respir Crit Care Med 168:1438–1444
40. Confalonieri M, Della Porta R, Potena A, Carbone G, Gregoretti C, Gandola L, Tolley EA, Meduri GU (1999) Acute respiratory failure in patients with severe community-acquired pneumonia: a prospective randomized evaluation of noninvasive ventilation. Am. J Respir Crit Care Med 160:1585–1591
41. Antonelli M, Conti G, Bufi M, Costa MG, Lappa A, Rocco M, Gasparetto A, Meduri GU (2000) Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. JAMA 12 283:235–241
42. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, Reiffers J, Cardinaud JP (2001) Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 344:481–487
43. Auriant I, Jallot A, Herve P, Cerrina J, Le Roy Ladurie F, Fournier JL, Lescot B, Parquin F (2001) Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. Am J Respir Crit Care Med 164:1231–1235
44. Mehta S, Jay GD, Woolard RH, Hipona RA, Connolly EM, Cimini DM, Drinkwine JH, Hill NS (1997) Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. Crit Care Med 25:620–628
45. Masip J, Betbese AJ, Paez J, Vecilla F, Canizares R, Padro J, Paz MA, de Otero J, Ballus J (2000) Non-invasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: a randomised trial. Lancet 356:26–32
46. Nava S, Carbone G, Dibattista N, Bellone A, Baiardi P, Cosentini R, Marenco M, Giostra F, Borasi G, Groff P (2003) Noninvasive ventilation in cardiogenic pulmonary edema: a multicenter, randomized trial. Am J Respir Crit Care Med 2003 168:1432–1437
47. Crane SD, Elliott MW, Gilligan P, Richards K, Gray AJ (2004) Randomised controlled comparison of continuous positive airways pressure, bilevel non-invasive ventilation, and standard treatment in emergency department patients with acute cardiogenic pulmonary oedema. Emerg Med J 21:155–161
48. Park M, Sangean MC, Volpe M.S., Feltrim M, Nozawa E, Leite PF, Amato M, Lorenzi-Filho G (2004) Randomized, prospective trial of oxygen, continuous positive airway pressure, and bilevel positive airway pressure by face mask in acute cardiogenic pulmonary edema. Crit Care Med 32:2407–2415
49. Cross AM, Cameron P, Kierce M, Ragg M, Kelly AM (2003) Non-invasive ventilation in acute respiratory failure: a randomised comparison of continuous positive airway pressure and bi-level positive airway pressure. Emerg Med J 20:531–534
50. Bellone A, Monari A, Cortellaro F, Vettorello M, Arlati S, Coen D (2004) Myocardial infarction rate in acute pulmonary edema: noninvasive pressure support ventilation versus continuous airway pressure. Crit Care Med 32:1860–1865
51. Bellone A, Vettorello M, Monari A, Cortellaro F, Coen D (2005) Noninvasive pressure support vs. continuous positive airway pressure in acute hypercapnic pulmonary edema. Intensive Care Med 31:807–811
52. Nava S, Carlucci A (2002) Non-invasive pressure support ventilation in acute hypoxemic respiratory failure: common strategy for different pathologies? Intensive Care Med 28:1205–1207
53. Jolliet P, Abajo B, Pasquina P, Chevrolet JC (2001) Noninvasive pressure support ventilation in severe community acquired pneumonia. Intensive Care Med 27:812–821
54. Domenighetti G, Gayer R, Gentilini R (2002) Noninvasive pressure support ventilation in non-COPD patients with acute cardiogenic pulmonary edema and severe community-acquired pneumonia: acute effects and outcome. Intensive Care Med 28:1226–1232
55. Girou E, Schortgen F, Delclaux C, Brun-Buisson C, Blot F, Lefort Y, Lemaire F, Brochard L (2000) Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. JAMA 284 (18):2361–2367
56. Blot F, Guiget M, Nitenberg G, Laeclercq B, Gachot B, Escudier B (1997) Prognostic factors for neutropenic patients in an ICU: respective roles of underlying malignancies and acute organ failure. Eur J Cancer 33:1031–1037
57. Nava S, Cuomo AM (2004) Acute respiratory failure in the cancer patient: the role of non-invasive mechanical ventilation. Crit Revi Oncol Hematol 51:91–103
58. Rubenfeld GD, Crawford SW (1996) Withdrawing life support from mechanically ventilated recipients of bone marrow transplant: a case for evidence-based guidelines. Ann Intern Med 125:625–633
59. Azoulay E, Alberti C, Bornstain C, Leleu G, Moreau D, Recher C, Chevret S, Le Gall JR, Brochard L, Schlemmer B (2001) Improved survival in cancer patients requiring mechanical ventilatory support: impact of noninvasive mechanical ventilatory support. Crit Care Med 29:519–525

60. Hilbert G, Gruson D, Portel L, Gbikpi-Benissan G, Cardinaud JP (1998) Non-invasive pressure support ventilation in COPD patients with postextubation hypercapnic respiratory insufficiency. Eur Respir J 11:1349–1353
61. Keenan SP, Powers C, McCormack DG, Block G (2002) Noninvasive positive-pressure ventilation for post-extubation respiratory distress. JAMA 287:3238–3244
62. Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguia C, Gonzales M, Epstein SK, Hill N, Alia l, Nava S, Soares MA, D'Emapire G, Anzueto A (2004) Non-invasive positive pressure ventilation for respiratory failure after extubation. New Engl J Med 350:2452–2460
63. Conti G, Antonelli M, Navalesi P, Rocco M, Bufi M, Spadetta G, Meduri GU (2002) Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. Intensive Care Med 28:1701–1707
64. Squadrone E, Frigerio P, Fogliati C, Gregoretti C, Conti C, Antonelli M, Costa R, Baiardi P, Navalesi P (2004) Noninvasive vs invasive ventilation in COPD patients with severe acute respiratory failure deemed to require ventilatory assistance. Intensive Care Med 30:1303–1310
65. Antonelli M, Conti G, Rocco M, Bufi M, De Blasi RA, Vivino G, Gasparetto A, Meduri GU (1998) A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. New Engl J Med 339:429–435
66. Vitacca M, Ambrosino N, Clini E, Porta R, Rampulla C, Lanini B, Nava S (2001) Physiological response to pressure support ventilation delivered before and after extubation in patients not capable of totally spontaneous autonomous breathing. Am J Respir Crit Care Med 164:638–641
67. Udwadia ZF, Santis GK, Steven MH, Simonds AK (1992) Nasal ventilation to facilitate weaning in patients with chronic respiratory insufficiency. Thorax 47:715–718
68. Goodenberger DM, Couser J, May JJ (1992) Successful discontinuation of ventilation via tracheostomy by substitution of nasal positive pressure ventilation. Chest 102:1277–1279
69. Restrick LJ, Scott AD, Ward EM, Feneck RO, Cornwell WE, Wedzicha JA (1993) Nasal intermittent positive-pressure ventilation in weaning intubated patients with chronic respiratory disease from assisted intermittent, positive-pressure ventilation. Respir Med 87:199–204
70. Gregoretti C, Beltrame F, Lucangelo U, Burbi L, Conti G, Turello M, Gregori D (1998) Physiologic evaluation of non-invasive pressure support ventilation in trauma patients with acute respiratory failure. Intensive Care Med 24:785–790
71. Kilger E, Briegel J, Haller M, Frey L, Schelling G, Stoll C, Pichler B, Peter K (1999) Effects of noninvasive positive pressure ventilatory support in non-COPD patients with acute respiratory insufficiency after early extubation. Intensive Care Med 25:1374–1380
72. Nava S, Ambrosino N, Clini E, Prato M, Orlando G, Vitacca M, Brigada P, Fracchia C, Rubini F (1998) Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. Ann Intern Med 128:721–728
73. Girault C, Daudenthun I, Chevron V, Tamion F, Leroy J, Bonmarchand G (1999) Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure. A prospective, randomized controlled study. Am J Respir Crit Care Med 160:86–92
74. Ferrer M, Esquinas A, Arancibia F, Bauer TT, Gonzalez G, Carrillo A (2003) Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. Am J Respir Crit Care Med 168:70–76
75. Meduri GU, Fox RC, Abou-Shala N, Leeper KV, Wunderink RG (1994). Noninvasive mechanical ventilation via face mask in patients with acute respiratory failure who refused endotracheal intubation. Crit Care Med 22:1584–1590
76. Levy M, Tanios MA, Nelson D, Short K, Senechia A, Vespia J, Hill NS (2004) Outcomes of patients with do-not-intubate orders treated with noninvasive ventilation. Crit Care Med 32:2002–2007
77. Schettino G, Altobelli N, Kacmarek RM (2005) Noninvasive positive pressure ventilation reverses acute respiratory failure in selected "do-not-intubate" patients. Crit Care Med 33:1976–1982
78. Chu CM, Chan VL, Wong IW, Leung WS, Lin AW, Cheung KF (2004) Noninvasive ventilation in patients with acute hypercapnic exacerbation of chronic obstructive pulmonary disease who refused endotracheal intubation. Crit Care Med 32:372–377
79. Plant PK, Owen JL, Elliott MW (2001) Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. Thorax 56:708–712
80. Confalonieri M, Garuti G, Cattaruzza MS, Osborn JF, Antonelli M, Conti G, Kodric M, Resta O, Marchese S, Gregoretti C, Rossi A (2005) A chart of failure risk for non-invasive ventilation in patients with COPD exacerbation. Eur Respir J 25:348–355
81. Moretti M, Cilione C, Tampieri A, Fracchia C, Marchioni S, Nava S (2000) Incidence and causes of non-invasive mechanical ventilation failure after an initial (> 48 h) successful attempt. Thorax 55:819–825
82. Carlucci A, Delmastro M, Rubini F, Fracchia C, Nava S (2003) Changes in the practice of non-invasive ventilation in treating COPD patients over 8 years. Intensive Care Med 29:419–425