# Causes of Failure of Noninvasive Mechanical Ventilation

Stefano Nava MD and Piero Ceriana MD

**With selected patients noninvasive positive-pressure ventilation (NPPV) can obviate endotracheal intubation and thus avoid the airway trauma and infection associated with intubation. With patients who can cooperate, NPPV is the first-line treatment for mild-to-severe acute hypercapnic respiratory failure. NPPV is also used for hypercapnic ventilatory failure and to assist weaning from mechanical ventilation, by allowing earlier extubation. Some patients do not obtain adequate ventilation with NPPV and therefore require intubation. Also, some patients will initially benefit from NPPV (for one-to-several days) but will then deteriorate and require intubation. It is not always apparent which patients will initially benefit from NPPV, so researchers have been looking for variables that predict NPPV success/failure. The reported NPPV failure rate is 5–40%, so the necessary staff and equipment for prompt intubation should be readily available. Absolute contraindications to NPPV are: cardiac or respiratory arrest; nonrespiratory organ failure (eg, severe encephalopathy, severe gastrointestinal bleeding, hemodynamic instability with or without unstable cardiac angina); facial surgery or trauma; upper-airway obstruction; inability to protect the airway and/or high risk of aspiration; and inability to clear secretions. The NPPV training and experience of the clinician team partly determines whether the patient will succeed with NPPV or, instead, require intubation. Greater clinician-team NPPV experience and expertise are associated with a higher percentage of patients succeeding on NPPV and with NPPV success with sicker patients (than will succeed with a less-experienced clinician team). With patients suffering hypercapnic respiratory failure the best NPPV success/failure predictor is the degree of acidosis/acidemia (pH and $P_{aCO_2}$ at admission and after 1 hour on NPPV), whereas mental status and severity of illness are less reliable predictors. With patients suffering hypoxic respiratory failure the likelihood of NPPV success seems to be related to the underlying disease rather than to the degree of hypoxia. For example, the presence of acute respiratory distress syndrome or community-acquired pneumonia portends NPPV failure, as does lack of oxygenation improvement after an hour on NPPV. All the proposed NPPV success/failure predictors should be used cautiously and need further study. We predict that further study and team experience will improve the NPPV success rate and allow successful NPPV-treatment of sicker patients.** *Key Words: noninvasive mechanical ventilation, noninvasive positive pressure ventilation, hypoxemia, respiratory insufficiency, outcome, predictors, chronic obstructive pulmonary disease.* [Respir Care 2004;49(3):295–303. © 2004 Daedalus Enterprises]

## Introduction

The respiratory system includes a gas exchange membrane and a ventilatory pump: both these structures can

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fail and require temporary support with mechanical ventilation—a first-line treatment in respiratory failure, which is applied to decrease the work of breathing and reverse hypoxemia and respiratory acidosis.[1] Mechanical ventilation can be applied with positive or negative pressure, invasively or noninvasively (ie, with or without tracheal intubation). Over the last decade there has been increased scientific and clinical interest in noninvasive positive-pressure ventilation (NPPV), primarily because NPPV reduces and/or avoids certain risks and complications (eg, trauma, infections) of invasive mechanical ventilation.

The etiology of respiratory failure[2] can be roughly divided into (1) lung failure (eg, pneumonia, acute respiratory distress syndrome [ARDS], cardiogenic pulmonary edema) and (2) ventilatory pump failure (eg, decompensated chronic obstructive pulmonary disease [COPD], neuromuscular diseases, asthma). Mechanical ventilation aims to alleviate hypoxia by delivering oxygen and to alleviate ventilatory pump failure by applying positive pressure and thus acting as an accessory respiratory muscle, thus increasing alveolar ventilation. In many cases of hypoxic respiratory failure, positive end-expiratory pressure is applied to recruit alveoli and improve oxygenation,[3] whereas in hypercapnic ventilatory pump failure external positive end-expiratory pressure is applied to reduce the inspiratory load imposed by intrinsic positive end-expiratory pressure.[4]

Despite that basic difference in the rationale for application, NPPV has been widely applied for both types of respiratory failure, and the numerous clinical studies of NPPV published during the last decade have reported different results with NPPV.[5]

A third clinical application of NPPV is gaining increased attention. Two studies have suggested that NPPV can help a patient wean from mechanical ventilation, by allowing earlier extubation, and that this approach might be faster and more successful than conventional weaning.[6,7] NPPV-assisted weaning was recently employed with patients suffering persistent weaning failure, and NPPV was associated with better 60-day survival and fewer infectious complications.[8]

None of the studies published so far has reported a 100% success rate with NPPV. The NPPV failure rate may be fairly consistent for certain pathologies, and NPPV failure eventually requires intubation. Inability early to identify patients who will fail NPPV can cause inappropriate delay of intubation, which can cause clinical deterioration and increase morbidity and mortality. It is therefore very important to identify the variables that can help predict NPPV failure early and thus avoid delaying intubation in cases in which it will be necessary. To our knowledge, only one brief editorial[9] has assessed the predictors of NPPV success in hypercapnic respiratory failure, and to our knowledge there have been no systematic studies to analyze the causes of NPPV success and failure, for either hypercapnic or hypoxemic respiratory failure.

Our analysis of NPPV failure predictors was based on a MEDLINE search of reports published from 1985 to 2003. We used the search terms: noninvasive ventilation, noninvasive positive-pressure ventilation, hypoxemic respiratory failure, hypercapnic respiratory failure, success, failure, outcome, and predictors. We selected all reports in which the evaluation of failure criteria was one of the main study outcomes and/or in which the statistical analysis was performed either (1) to assess a statistical difference between success and failure or (2) to determine predictors of NPPV success or failure.

We identified 10 reports that met our criteria for hypercapnic respiratory failure[10–19] and 4 reports that met our criteria for hypoxemic respiratory failure.[20–23]

## Acute Hypercapnic Respiratory Failure

The recent international consensus conference on NPPV for acute respiratory failure (ARF)[24] stated that, "the addition of NPPV to standard medical treatment of patients with ARF may prevent the need for intubation and reduce the rate of complications and mortality in patients with hypercapnic respiratory failure." Moreover, NPPV can be applied earlier (than intubation) in the course of ventilatory failure and NPPV can be administered outside of the intensive care unit (ICU). A meta-analysis by Keenan et al[25] found that NPPV can reduce the need for endotracheal intubation and improve survival in this population. Unfortunately, a meta-analysis cannot determine the ideal setting in which to apply NPPV or which patients should receive NPPV.

Nonetheless, it should be emphasized that the positive results reported with NPPV were observed only in selected COPD patients, with the a priori exclusion of patients who needed endotracheal intubation early in the onset of respiratory failure. The NPPV failure rate in most of the important clinical trials has ranged from 5% to 40%,[26–28] because some patients, although initially eligible for a trial of NPPV, subsequently fail NPPV and need to be intubated. Hence it is important to identify early those patients who are likely to fail NPPV, to avoid delayed intubation of patients who will need intubation. This means that, wherever NPPV is carried out, the necessary staff and equipment for prompt intubation should be readily available. To minimize the incidence of failed NPPV physicians should know the clinical conditions that absolutely contraindicate NPPV:[10]

- Cardiac or respiratory arrest
- Nonrespiratory organ failure (eg, severe encephalopathy, severe gastrointestinal bleeding, hemodynamic instability with or without unstable cardiac angina)
- Facial surgery or trauma
- Upper-airway obstruction
- Inability to protect the airway and/or high risk of aspiration
- Inability to clear secretions

Several studies have indirectly suggested or directly investigated possible predictors of NPPV success/failure. The identification of NPPV success predictors is especially important outside the ICU, where initial intubation decisions are often made.

We identify 4 steps in determining whether a patient needs respiratory assistance and, if so, whether the patient should have NPPV or intubation:

1. Determine whether the patient needs ventilatory assistance: the clinical criteria include the presence of tachypnea, dyspnea, paradoxical abdominal motion, and accessory respiratory muscle activation, and the primary laboratory criterion is respiratory acidosis ($P_{aCO_2} > 55$ mm Hg and pH $< 7.35$).
2. Determine, based on the above-listed contraindications to NPPV, whether the patient is a candidate for NPPV or, instead, needs intubation.
3. If the patient is an NPPV candidate, choose the ventilation interface (nasal mask, face mask, or nasal pillows) and the ventilator settings. Once NPPV has been applied, closely surveil the patient's NPPV tolerance, comfort, and synchrony with the ventilator.
4. Closely monitor the variables that are currently recognized as predictors of NPPV success/failure.

In the remainder of this report we analyze predictors of NPPV success/failure.

## Arterial Blood Gases

Respiratory acidosis is probably one of the most valuable indicators of the severity of COPD decompensation, and all clinical studies report both pH and $P_{aCO_2}$ values sampled at baseline and after some time on NPPV (generally within a few hours of initiating NPPV).

Ambrosino et al[11] observed that, in a group of 47 patients with decompensated COPD, lower baseline pH and $P_{aCO_2}$ predicted NPPV failure: patients who were more acidemic before starting NPPV (pH 7.22 vs 7.28) subsequently failed NPPV. The pH values recorded 1 hour into the initial trial of NPPV also accurately identified patients who would succeed with NPPV. Furthermore, using a logistic regression analysis, baseline pH and pH after 1 hour of NPPV had strong predictive power, with high sensitivity (87% and 93%, respectively) and good specificity (54% and 82%, respectively).

Meduri et al[12] obtained similar results from a group of 158 patients with ARF from various causes. In a subgroup of 74 patients with hypercapnic ventilatory failure, NPPV failed with patients who had higher baseline $P_{aCO_2}$, whereas improvement of acidosis after a 2-hour NPPV trial predicted success with NPPV.

Plant et al[13] carried out a prospective, multicenter, randomized trial of NPPV versus standard medical treatment with 236 patients suffering COPD exacerbations and mild-to-moderate respiratory acidosis (pH 7.25–7.35). They observed that severe acidemia (pH $< 7.30$) at study entry was associated with NPPV failure and that improvement of pH after 4 hours of NPPV predicted NPPV success.

On the other hand, in a multicenter epidemiologic survey, Carlucci et al[14] found that pH at admission was significantly higher among NPPV responders (pH 7.36) than among nonresponders (pH 7.30), but that changes in arterial blood gas values after 1 day of NPPV could not discriminate NPPV responders (pH 7.37) from nonresponders (pH 7.34).

With a small group of 12 decompensated COPD patients treated with NPPV plus medical therapy, Soo Hoo et al[15] had a 50% NPPV success rate, and they found no difference in baseline pH or $P_{aCO_2}$ between NPPV responders and nonresponders. However, NPPV responders showed quicker correction of acidosis.

Anton et al[16] applied NPPV with 36 hypercapnic COPD patients and had a success rate of 77%. They devised a multiple-regression model to identify NPPV success-predictors, and they concluded that improvement of $P_{aCO_2}$ and pH after 1 hour of NPPV was highly predictive; they accurately predicted NPPV success/failure in about 95% of cases.

Most studies on NPPV success/failure prediction have addressed the issue of *early* NPPV failure, but Moretti et al[29] tried to analyze predictors of *late* NPPV failure, such as cases in which NPPV failed a few days after its initial application, despite initial improvement of clinical status and blood gas values on NPPV. Among 134 exacerbated COPD patients who received NPPV for $> 24$ hours, a subgroup of 31 patients did worse about 8 days after NPPV application. A thorough evaluation of patient characteristics at study entry and at the time of NPPV failure indicated that, among with other variables, lower pH at admission predicted late NPPV failure.

Table 1 summarizes the studies that considered baseline pH and pH changes after an NPPV trial.

## Severity of Disease

The most commonly used indexes of severity of illness are the Acute Physiology and Chronic Health Evaluation (APACHE)[30] and the Simplified Acute Physiology Score (SAPS II).[31] Another index, the Activities of Daily Living score,[17] is designed to measure the degree of functional limitation. The relationship between NPPV failure and the APACHE and SAPS scores has been studied, on the assumption that patients suffering from respiratory failure often have comorbidities (eg, malnutrition, cardiopathy, diabetes) and that respiratory failure is frequently associated with organ failure. During acute hypercapnic respiratory failure the ventilator works mainly as an accessory muscle, so the greater the degree of organ failure, the slower the recovery process and the less likely the success of NPPV.

Some researchers have found a positive correlation between severity of underlying disease and NPPV failure.

Table 1. Summary of Studies in Which Baseline pH or pH Change After an NPPV Trial Were Considered As Predictors of NPPV Success/Failure

| First Author | Baseline pH of NPPV Success Patients | Baseline pH of NPPV Failure Patients | p* | pH of NPPV Success Patients After NPPV Trial | pH of NPPV Failure Patients After NPPV Trial | p* |
|---|---|---|---|---|---|---|
| Soo Hoo[15] | 7.26 ± 0.06 | 7.26 ± 0.06 | NS | 7.33 ± 0.06 | 7.30 ± 0.06 | < 0.01 |
| Moretti[29] | 7.25 ± 0.07 | 7.22 ± 0.08 | NS | 7.30 ± 0.06 | 7.30 ± 0.06 | NS |
| Anton[16] | 7.27 ± 0.03 | 7.28 ± 0.4 | NS | 7.34 ± 0.4 | 7.28 ± 0.03 | < 0.01 |
| Ambrosino[11] | 7.28 ± 0.04 | 7.22 ± 0.08 | < 0.005 | 7.34 ± 0.04 | 7.25 ± 0.08 | < 0.005 |
| Plant[13]† | NA | NA | Yes | NA | NA | Yes |
| Carlucci[14] | 7.36 ± 0.09 | 7.30 ± 0.10 | < 0.01 | NA | NA | NA |
| Meduri[12] | 7.26 ± 0.06 | 7.27 ± 0.06 | NS | 7.33 ± 0.07 | 7.22 ± 0.05 | < 0.0001 |

NPPV = noninvasive positive-pressure ventilation.
*The p value represents the statistical difference between those who succeeded with NPPV and those who failed NPPV.
Values are mean ± SD.
†Data for separate groups were not reported. "Yes" means there was a statistically significant difference (via univariate analysis).
NS = not significant.
NA = not available.

Moretti et al[29] found that the presence of one or more complications at admission (eg, severe hyperglycemia) and marked functional disability were strong predictors of late NPPV failure.

Ambrosino et al[11] found a significantly greater severity of illness among patients who failed to improve with NPPV (mean APACHE II score 24 vs 18). Soo Hoo et al[15] also reported a difference in mean APACHE II score between those who failed (mean score 21) and those who improved (mean score 15) with NPPV. In the epidemiologic survey by Carlucci et al[14] a multiple-regression analysis showed that SAPS II score was an independent predictor of NPPV success/failure. In a randomized, prospective study in a general intensive care unit, Conti et al[18] treated 49 decompensated COPD patients (mean pH 7.2) with invasive (26 patients) or noninvasive (23 patients) ventilation after failure of medical treatment in the emergency department. The failure rate in the NPPV group was 52%, and patients who needed endotracheal intubation after a trial of NPPV had a significantly higher SAPS II score (mean score 39) than the patients who did not need intubation (mean score 35).

On the other hand, Anton et al[16] and Meduri et al[12] found no correlation between APACHE II score and NPPV failure. Similarly, Benhamou et al[32] found no link between SAPS II score and NPPV failure.

Table 2 summarizes the studies in which APACHE II, SAPS II, and Activities of Daily Living scores were considered as predictors of NPPV success/failure.

## Cooperation and Encephalopathy

Patient cooperation, tolerance, and absence of encephalopathy are necessary for NPPV to provide effective ventilation. During respiratory distress a tightly fitting mask may be poorly tolerated, and if the patient is not cooperative, the frequent patient movements and attempts to displace the mask or loosen the head straps will cause large air leaks and ineffective triggering. Furthermore, deteriorating mental status during NPPV can indicate worsening hypercarbia that will probably require intubation.

Some investigators have observed a positive correlation between baseline low mental status (scored according to Kelly and Matthay[33]) and NPPV failure.[11,16,18] The problem of NPPV tolerance and acceptance has been studied, using an arbitrary tolerance/acceptance score. Ambrosino et al,[11] Carlucci et al,[14] and Benhamou et al[32] found that poor clinical tolerance of NPPV was highly predictive of NPPV failure. Soo Hoo et al[15] observed that patients successfully treated with NPPV were able to tolerate the mask longer than patients who failed NPPV.

## Mixed Indexes

Other indexes have also been considered as possible predictors of NPPV success, but the statistical power of these indexes has not been systematically studied because of the difficulty of identifying objective classification systems. The amount of mask leak, mentioned by Soo Hoo et al[15] and Carlucci et al,[14] is closely related to the clinical team's skill in administering NPPV, the patient's facial anatomy, and the availability of proper equipment and supplies.

With respect to the ability to clear secretions, which is a very important variable, the determination of how well a patient is able to clear secretions can be highly subjective and thus differs among clinicians. One of the few studies that has addressed secretion clearance was by Carlucci et al.[14] They used a simple "yes or no" scoring system to evaluate patients' ability to mobilize secretions, and found

Table 2. Summary of Studies in Which Certain Clinical Scores Were Considered As Predictors of NPPV Success/Failure

| First Author | Baseline SAPS II Score of NPPV Success Patients | Baseline SAPS II Score of NPPV Failure Patients | Baseline APACHE II Score of NPPV Success Patients | Baseline APACHE II Score of NPPV Failure Patients | Baseline ADL Score of NPPV Success Patients | Baseline ADL Score of NPPV Failure Patients | p* |
|---|---|---|---|---|---|---|---|
| Carlucci[14] | $30 \pm 11$ | $45 \pm 27$ | — | — | — | — | $< 0.005$ |
| Moretti[29] | — | — | $22 \pm 4$ | $23 \pm 6$ | $2.1 \pm 0.8$ | $1.7 \pm 0.7$ | APACHE = NS ADL = 0.024 |
| Anton[16] | — | — | $19 \pm 2$ | $20 \pm 3$ | — | — | NS |
| Ambrosino[11] | — | — | $18 \pm 4$ | $24 \pm 4$ | — | — | $< 0.0001$ |
| Conti[18] | $35 \pm 2$ | $39 \pm 6$ | — | — | — | — | 0.04 |
| Soo Hoo[15] | — | — | $15 \pm 4$ | $21 \pm 4$ | — | — | 0.02 |
| Meduri[12] | — | — | $18 \pm 6$ | $20 \pm 4$ | — | — | NS |
| Benhamou[32] | $11 \pm 4$ | $12 \pm 4$ | — | — | — | — | NS |

SAPS = Simplified Acute Physiology Score.
APACHE = Acute Physiology and Chronic Health Evaluation.
ADL = Activities of Daily Living score.
*The p value represents the statistical difference between those who succeeded with NPPV and those who failed NPPV.
Values are mean ± SD.
— = not measured.

that more patients were able to effectively clear sputum in the successfully treated group.

## Training and Equipment

The success of NPPV depends largely on the patient's acceptance and compliance, and winning patient acceptance and compliance depends partly on the way the NPPV is applied by the clinician. Thus, the clinical team's training and experience is important. In 1992 Foglio et al[34] conducted a retrospective study and concluded that NPPV was not more effective than standard medical treatment alone in ARF due to decompensated COPD, but the same group later found opposite results,[35] and in an accompanying editorial Dr Brochard stated that, "it was possible that some learning effects explained part of the improvement in the success rate."[36] It is, we believe, probable that the accumulation of experience and expertise—among both clinicians and paramedical personnel—from the continued use of NPPV will modify clinical practice, that more severely ill patients will be treatable with NPPV, and that the NPPV success rate will improve.

Another issue, recently raised by Girault et al,[20] is that there might be an important difference between results reported in protocol-driven prospective clinical trials and results derived from routine clinical practice. Implementation of an NPPV protocol might influence the level of patient care and the staff's behavior, perhaps contributing to greater NPPV success. Girault et al[20] retrospectively analyzed all the patients treated with NPPV for various causes of respiratory failure (hypercapnic, hypoxemic, and weaning after extubation), during a 2-year period in a medical ICU. They reported a success rate of 62% with hypercapnic respiratory failure, 51% with hypoxemic respiratory failure, and 86% with patients weaning after extubation. Although the Girault et al study did not add any new information with respect to predictors of NPPV success/failure, it did confirm the feasibility and effectiveness of NPPV in the "real life" clinical scenario, outside of any protocol-driven trial.

Several studies have demonstrated that NPPV is not more demanding for the clinicians than is standard medical therapy or invasive ventilation. In a preliminary report Chevrolet et al[21] stated that NPPV is a time-consuming and difficult-to-apply procedure for nurses, but 10 years later Chevrolet et al concluded that, in experienced hands, NPPV does not appear to substantially increase the nursing work load.[37]

Very recently Carlucci et al[22] showed that the clinical practice of applying NPPV for COPD exacerbations may change such that, with greater staff training and experience, more severely ill patients may be treated with a lower risk of failure. The severity of the ARF episodes (defined by pH and APACHE II score at admission) that they saw in their institution worsened during the study period. Five years after the beginning of NPPV practice there had been a significant decrease in mean admission pH (Table 3). During 1992–1996 the mean admission pH was $7.25 \pm 0.07$. During 1997–1999 the mean admission pH was significantly lower: $7.20 \pm 0.08$ ($p < 0.0001$). In 1992–1996 the severity of acidosis (pH and $P_{aCO_2}$) and of illness (APACHE II score) were significantly worse among the patients who failed NPPV. In 1997–1999 NPPV failures and successes differed only in APACHE II scores ($p < 0.006$).

Table 3. Summary of the NPPV Study by Carlucci et al

| | 1992–1996 (n = 145) | | | 1997–1999 (n = 63) | | |
|---|---|---|---|---|---|---|
| | NPPV Success (n = 119) | NPPV Failure (n = 26) | p | NPPV Success (n = 53) | NPPV Failure (n = 10) | p |
| APACHE II score | 21 ± 6 | 25 ± 6 | 0.005 | 24 ± 5 | 29 ± 7 | 0.006 |
| pH at admission | 7.26 ± 0.07 | 7.21 ± 0.06 | 0.003 | 7.21 ± 0.08 | 7.18 ± 0.10 | 0.24 |
| pH after 1 h of NPPV | 7.31 ± 0.06 | 7.20 ± 0.09 | < 0.0001 | 7.30 ± 0.06 | 7.18 ± 0.08 | < 0.001 |
| Change in pH | 0.06 ± 0.03 | 0.01 ± 0.04 | < 0.0001 | 0.09 ± 0.04 | 0.002 ± 0.06 | < 0.0001 |
| $P_{aCO_2}$ at admission (mm Hg) | 83 ± 17 | 91 ± 14 | 0.03 | 88 ± 16 | 99 ± 22 | 0.06 |
| $P_{aCO_2}$ after 1 h of NPPV (mm Hg) | 75 ± 14 | 95 ± 18 | < 0.0001 | 77 ± 13 | 100 ± 22 | < 0.0001 |
| Change in $P_{aCO_2}$ | −8.3 ± 8 | 4.3 ± 6.2 | < 0.0001 | −9.7 ± 7.4 | 1.9 ± 9.3 | < 0.0001 |
| $P_{aO_2}$ at admission (mm Hg) | 55.1 ± 11 | 53.2 ± 11 | 0.43 | 52.9 ± 12.3 | 51.5 ± 13.6 | 0.74 |

NPPV = noninvasive positive-pressure ventilation.
APACHE = Acute Physiology and Chronic Health Evaluation.
Values are mean ± SD.
(Adapted from data in Reference 21).

Interestingly, NPPV failures during 1992–1996 had the same mean admission pH value as the patients who succeeded with NPPV during 1997–1999 (7.21 ± 0.06 vs 7.21 ± 0.08). The relative risk of failure among NPPV-treated patients, according to the severity of the respiratory failure at admission, was calculated for pH of 7.30 and 7.25. Compared with a patient who had a pH of 7.30 treated during 1997–1999, a patient with a pH of 7.25 had a 1.5-fold (95% confidence interval 1–3.8) higher risk of failure than if treated during 1997–1999, versus a 3.3-fold (95% confidence interval 2.2–5.1) higher risk if treated during 1992–1996 (p = 0.03). Increased confidence in NPPV technique may allow a clinical team to treat more severely ill patients outside the respiratory ICU and substantially reduce the cost of NPPV.

Equipment—in particular ventilators and monitoring systems—may also be important in determining NPPV success, since NPPV technology changed in the last decade and may have changed the type of patients treated, which relates to patient acceptance and tolerance and, therefore, the success of NPPV. Home-care ventilators are now equipped with software that compensates for air leaks and with new non-rebreathing devices and triggering systems, so the patient-ventilator interaction and carbon dioxide clearance may be better. The materials and shapes of NPPV face masks have also dramatically improved, which may improve tolerance and therefore permit treating more severely ill patients.

## Environment

The large majority of studies on NPPV have been performed in general ICUs,[26–28] respiratory ICUs,[11] and pneumology wards.[13,16] Only one study has been performed in

an emergency department.[22] No study has compared the outcomes of patients treated with NPPV in various settings, but such a study would be difficult, because the severity of respiratory impairment in the existing studies differed greatly. In fact, all the studies performed in general care wards concerned patients with mean pH > 7.29, whereas patients admitted to ICUs had more severe respiratory acidosis (pH < 7.29). A pH of 7.29 may reasonably be considered a cut-off point for deciding whether a patient should be admitted to an ICU for NPPV or, instead, can go to a general care ward. However, there is not sufficient worldwide experience with or evidence about NPPV on the wards to make a general recommendation. And other factors must be considered before admitting a patient to an ICU, including severity of illness, presence of comorbidity, prior quality of life, functional status, and central nervous system impairment.

## Acute Hypoxic Respiratory Failure

The large majority of NPPV studies have involved patients suffering acute hypercapnic respiratory failure, so there are few data about predictors of NPPV failure in "pure" hypoxemic respiratory failure. The definition and severity of an episode of hypoxemic respiratory failure revolve around the ratio of $P_{aO_2}$ to fraction of inspired oxygen ($P_{aO_2}/F_{IO_2}$), which includes various conditions and etiologies (eg, pneumonia, ARDS, cardiogenic pulmonary edema, pulmonary embolism) under the same "umbrella."

Most of the studies on "pure" hypoxemic respiratory failure have focused on a single pathology, such as cardiogenic pulmonary edema,[38] ARDS, acute lung injury,[39] or community-acquired pneumonia,[37,40] so it would be dif-

ficult to make a general recommendation on when NPPV should be avoided.

Antonelli et al[40] showed that application of the 2 different ventilatory techniques (invasive mechanical ventilation and NPPV) in hypoxemic respiratory failure resulted in similar short-term improvements in arterial blood gas values, but NPPV was associated with less serious complications and shorter ICU stay than conventional mechanical ventilation. Unfortunately, despite the fact that the 2 patient groups were apparently homogeneous, the study's small sample size disallowed subgroup analysis according to the underlying diseases, so the results may have been influenced by a subgroup that had a better response to NPPV. As a matter of fact, experience from other studies suggests (but does not prove) that for a similar $P_{aO_2}/F_{IO_2}$ the success or failure of NPPV depends predominantly on the underlying pathology, rather than on "simple" indexes.

Confalonieri et al[41] showed that in selected patients with ARF caused by severe community-acquired pneumonia NPPV (compared with medical treatment) was associated with significantly less need for intubation. But the subgroup analysis compels us to temper any optimism from that finding, because it showed that only hypercapnic patients really benefited from the treatment, whereas among nonhypercapnic patients the failure rate did not differ from that of the standard treatment. This was confirmed by Jolliet et al,[37] who, in an uncontrolled study with non-COPD patients suffering community-acquired pneumonia, found an even higher rate of NPPV failure than in the Confalonieri et al study (66% vs 38%).

We know that hypercapnic respiratory failure is a direct consequence of alveolar hypoventilation, whatever the cause of the respiratory pump's impairment. In that condition, the "artificial muscle" (the ventilator) takes on some or all of the work of breathing, giving time for the bronchodilator therapy to decrease airway obstruction and hyperinflation. On the other hand, hypoxemic respiratory failure can be the "end point" of several pathologies, each acting through different pathophysiological mechanisms (shunt, ventilation-perfusion mismatch, impairment of alveolar-capillary diffusion); the provision of adequate oxygenation is, therefore, the life-saving procedure. The addition of continuous positive airway pressure may be helpful, depending on the underlying pathologies, because it can increase functional residual capacity, improve respiratory mechanics (and therefore oxygenation), and, in certain instances such as cardiogenic pulmonary edema, decrease the left ventricular afterload. On the other hand, in most of those conditions the inspiratory aid given by the ventilator may theoretically not be needed if hypercapnia, as a direct sign of respiratory pump failure, is not present. Once satisfactory oxygenation is attained, the major determinant of the outcome is the response to medical therapy and the resolution of the underlying disease.

Domenighetti et al[42] recently published the first study of whether similar degrees of hypoxia ($P_{aO_2}/F_{IO_2}$) from 2 different causes (pneumonia and cardiogenic pulmonary edema) have different outcomes. They found that, despite initial $P_{aO_2}/F_{IO_2}$ improvements being similar in the first hour of treatment, the pneumonia patients' outcomes were much worse than that of the cardiogenic pulmonary edema patients. Pneumonia has a relatively slow onset, and time is also needed for conventional therapy to show its effects. The onset of cardiogenic pulmonary edema is very rapid, but its resolution is similarly quick if the appropriate medical therapy works. Providing good oxygenation and ventilatory assistance through an oxygen mask, NPPV, or invasive ventilation may therefore not be enough in terms of outcomes when an inflammatory disease is healing slowly. Interestingly, in the Domenighetti et al[42] study the only variable in the community-acquired pneumonia group, after 60 min of NPPV, that resulted in statistically significant difference between success and failure was respiratory rate, which tended to increase in the intubated patients and to significantly decrease in the successful NPPV patients.

The only study of NPPV success/failure predictors with patients in acute hypoxic respiratory failure was a multicenter, prospective trial by Antonelli et al, conducted in 8 ICUs in Europe and the United States, with 5,847 patients admitted over a 2-year period.[43] There were 354 patients treated with NPPV for hypoxemic respiratory failure of various causes (including pneumonia, pulmonary contusion, aspiration, ARDS, cardiogenic pulmonary edema, pulmonary fibrosis, pulmonary embolism) and who had a mean admission $P_{aO_2}/F_{IO_2}$ of $\leq$ 200 mm Hg. The overall NPPV failure rate was 30%, and the highest intubation rate was among patients with ARDS (51%) and community-acquired pneumonia (50%), whereas the lowest NPPV failure rate was among patients with cardiogenic pulmonary edema (10%) and pulmonary contusion (18%).

The multivariate analysis identified the following factors independently associated with NPPV failure:

- Age > 40 years
- SAPS II score $\geq$ 35
- Presence of ARDS and community-acquired pneumonia
- $P_{aO_2}/F_{IO_2}$ $\leq$ 146 mm Hg after 1 hour of NPPV

Antonelli et al found, contrary to previous reports regarding NPPV for hypercapnic respiratory failure, that the arterial blood gas values at study entry had no predictive value, and that most NPPV failures were related to the inability to correct gas exchange after 1 hour.[43] That may reflect that the individual response to NPPV strongly depends on the underlying pathology.

Table 4. Summary of NPPV Success/Failure Predictors

| Variable | Hypercapnic Respiratory Failure | Positive Studies (Total No. Studies) | Hypoxic Respiratory Failure | Positive Studies (Total No. Studies) |
|---|---|---|---|---|
| pH after 1 h of NPPV | Yes* | 5 (6) | No | ND |
| pH at admission | No | 3 (7) | No | ND |
| Severity of disease | Yes | 5 (8) | Yes | 1/1 |
| Cooperation | Yes | 3 (3) | No | ND |
| Age | No | ND | Yes | 1 (1) |
| $P_{aO_2}/F_{IO_2}$ | No | ND | Yes | 1 (1) |
| ARDS or CAP | No | ND | Yes | 1 (1) |

NPPV = noninvasive positive-pressure ventilation
*"Yes" indicates that the majority of the studies found that the variable in question had a statistically significant predictive power regarding NPPV success. "No" indicates that the majority of the studies found that the variable in question did not have a statistically significant predictive power regarding NPPV success or that the study did not specifically assess that variable (ND = no data)
$P_{aO_2}/F_{IO_2}$ = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen
ARDS = acute respiratory distress syndrome
CAP = community-acquired pneumonia.

## Conclusions

NPPV should be considered the first-line treatment for mild-to-severe acute hypercapnic respiratory failure, whereas in "pure" hypoxic respiratory failure the likelihood of success with NPPV seems to be related to the underlying disease rather than to the degree of hypoxia.

Table 4 summarizes the NPPV success/failure predictors. With hypercapnic respiratory failure, pH changes after 1 hour of NPPV is a strong predictor, whereas integrity of sensorium and overall illness severity seem to be less reliable predictors. Great care should be taken to identify patients at risk of late NPPV failure, since they have a bad prognosis.

With hypoxic respiratory failure the presence of ARDS or community-acquired pneumonia seems to be a high risk factor for NPPV failure, as is lack of oxygenation improvement after the initial NPPV attempt.

All the proposed NPPV success/failure predictors should be used cautiously and need further study to be validated. However, some of the cut-off limits that separate success from failure may depend on the NPPV training and experience of the clinicians administering the NPPV and on the environment and equipment available, which may modify the clinical approach.

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