

Gil Gonçalves¹, Haitham Saeed², Mohamed E Abdelrahim², Hadeer S Harb², Yasmin M Madney², Kevin Eng³, Habib MR Karim⁴, Mohamad El-Khatib⁵, Bushra Mina⁶, Szymon Skoczyński⁷, Irena Sarc⁸, Vânia Caldeira⁹, Sara M Cabral¹, Bruno Cabrita¹⁰, Miguel Guia¹¹, Jun Duan¹², Igor Barjaktarevic³, Giuseppe Fiorentino¹³, Edoardo Piervincenzi¹⁴, Güniz Köksal¹⁵, Sibel O Sarin¹⁶, Peter J Papadakos¹⁷, Benan Bayrakci¹⁸, Vijay Hadda¹⁹, Gerhard Laier-Groeneveld²⁰, Karen EA Burns²¹, Raffaele Scala²², Andres C Alcaraz²³, Antonio M Esquinas²³

¹Pulmonology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

²Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt

³Division of Pulmonary and Critical Care, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, United States

⁴Department of Anesthesiology and Critical Care, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India

⁵Department of Anesthesiology, American University of Beirut-Medical Center, Beirut, Lebanon

⁶Department of Medicine, Division of Pulmonary and Critical Care Medicine, Northwell Health, Lenox Hill Hospital, New York, United States

⁷Department of Pulmonology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

⁸Noninvasive Ventilation Department, University Clinic for Pulmonary and Allergic Diseases, Golnik, Slovenia

⁹Pulmonology Department, Santa Marta Hospital, Lisbon, Portugal

¹⁰Pulmonology Department, Pedro Hispano Hospital, Matosinhos, Portugal

¹¹Pulmonology Department, Hospital Professor Doutor Fernando Fonseca, Amadora, Portugal

¹²Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Chongqing Medical University, Chongqing, China

¹³Respiratory Unit, AO Ospedali dei Colli Monaldi, Naples, Italy

¹⁴Department of Anaesthesiology and Intensive Care Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

¹⁵Department of Anaesthesiology and Reanimation, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey

¹⁶Internal Medicine, Istanbul Umraniye Research Hospital, Istanbul, Turkey

¹⁷Department of Anesthesiology, University of Rochester, Rochester, United States

¹⁸Pediatric Intensive Care Department, Hacettepe University, Ankara, Turkey

¹⁹Department of Pulmonary, Critical Care & Sleep Medicine, All India Institute of Medical Sciences, New Delhi, India

²⁰Pneumology, Clinical and Home Ventilatory Support and Sleep, Schellstrasse, Bochum, Germany

²¹Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada

²²Pulmonology and Respiratory Intensive Care Unit, S Donato Hospital, Arezzo, Italy

²³Intensive Care and Noninvasive Ventilatory Unit, Hospital Morales Meseguer, Murcia, Spain

Non-invasive ventilation in patients with an altered level of consciousness. A clinical review and practical insights

Abstract

Non-invasive ventilation has gained an increasingly pivotal role in the treatment of acute hypoxemic and/or hypercapnic respiratory failure and offers multiple advantages over invasive mechanical ventilation. Some of these advantages include the preservation of airway defense mechanisms, a reduced need for sedation, and an avoidance of complications related to endotracheal intubation.

Despite its advantages, non-invasive ventilation has some contraindications that include, among them, severe encephalopathy. In this review article, the rationale, evidence, and drawbacks of the use of noninvasive ventilation in the context of hypercapnic and non-hypercapnic patients with an altered level of consciousness are analyzed.

Key words: non-invasive ventilation, altered consciousness, encephalopathy, coma

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Address for correspondence: Gil Gonçalves, Pulmonology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; e-mail: bgilgoncalves@gmail.com

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Introduction

The utility of non-invasive ventilation (NIV) has been fully proven and well documented in several categories of patients with acute respiratory failure (ARF) [1–3]. Recent ERS/ATS and ISCCM guidelines reported a high level of evidence in favor of the use of NIV in acute acidic hypercapnic respiratory failure due to a COPD exacerbation, in acute pulmonary edema, in immunosuppressed hosts, and as a facilitating tool for transitioning from invasive ventilation to spontaneous breathing [4, 5].

By preventing endotracheal intubation (ETI), NIV confers many advantages over invasive mechanical ventilation (IMV). NIV is more comfortable and does not require the use of sedation in most cases [6]. It also allows patients to continue oral nutrition. The non-invasive interface allows positive pressure to be delivered while keeping the airway patent, thus preserving natural defense mechanisms. As such, NIV reduces morbidity and mortality by avoiding many complications associated with IMV including nosocomial ventilator-associated pneumonia, sepsis, and additional infectious sequelae [7].

Although NIV is an effective treatment, there are important limitations and contraindications to its use. In 2001, the International Consensus Conference on NIV [8] recommended against its use in the setting of cardiac or respiratory arrest, hemodynamic instability, unstable cardiac arrhythmias, severe encephalopathy (Glasgow coma scale < 10), severe upper gastrointestinal bleeding, facial surgery or trauma, upper airway obstruction, and in patients who are at high risk for aspiration who are unable to protect their airway or to cooperate or clear respiratory secretions.

Most studies use the Glasgow coma scale (GCS) or the Kelly-Matthay score (KMS) to assess the level of consciousness. Although GCS is the tool which has been mostly used in the clinical setting, this 15-point scoring system in which a lower score corresponds to a lower level of consciousness was originally developed to assess and monitor changes in the level of consciousness after head trauma [9]. The 6-level KMS is a tool specifically designed to evaluate neurological alterations in patients ventilated in the intensive care unit (ICU) [10]. With the KMS, a higher score corresponds to a lower level of consciousness.

In this article, we reviewed the rationale, evidence, and pitfalls regarding use of NIV in hypercapnic and non-hypercapnic ARF in patients with an altered level of consciousness.

Material and methods

We performed a search in the PubMed National Library with the keywords “non-invasive ventilation”, “hypercapnic”, “hypoxemic”, “altered consciousness”, “encephalopathy”, and “coma”. Articles were selected according to their relevance to the topic of this review. Backward reference searching from selected articles was also performed. In addition, other articles were reviewed and included based on the authors’ judgment of their relevance. Studies were limited to the English language.

Rationale for NIV use in patients with hypercapnic ARF encephalopathy

The pathophysiology of hypercapnic encephalopathy may be explained by the acidosis of cerebrospinal fluid and brain interstitial tissue. Acute respiratory acidosis has a greater impact on cerebrospinal fluid pH than metabolic acidosis does because CO₂ crosses the blood-brain barrier easily and quickly due to its high liposolubility. Accordingly, symptoms of hypercapnic encephalopathy (i.e. cognitive defects, delirium, and coma) correlate more strongly with changes in cerebrospinal pH than with those in arterial pH and/or PaCO₂ [11]. Although several pulmonary and extrapulmonary factors are involved as well, it is safe to assume that by normalizing arterial pH by diminishing arterial PaCO₂, cerebrospinal pH can be normalized as well.

The rationale for using NIV in hypercapnic encephalopathy is based on the reduction in PaCO₂ levels and its advantages over IMV. Firstly, its efficacy on respiratory muscles, improvement in gas exchange, and in in-hospital mortality in patients with respiratory acidosis due to acute exacerbations of COPD with the use of NIV is comparable to that of IMV [11, 12].

Secondly, the absence of ETI and other invasive devices reduces the risk of ventilator-associated pneumonia [13].

Thirdly, the risk of gastric distension and aspiration is probably overestimated due to the physiological barriers of the upper (resting pressure between 60–139 cm H₂O) [14] and lower sphincters (resting pressure between 14–41 cm H₂O) [15]; it is uncommon to use NIV pressures higher than 30 cm H₂O, thus minimizing this risk.

Fourthly, NIV has an important role as a form of salvage therapy in frail patients with end-stage chronic respiratory failure and do-not-intubate orders, especially in cases of hypercapnic coma [16].

Finally, NIV has been shown to reduce the length of ICU and hospital stays and can lead to more effective resource utilization [17]. These important quality metrics translate into improved patient outcomes and reduced financial burden [11].

Current evidence for the use of NIV in hypercapnic ARF encephalopathy

We reviewed the published literature examining the use of NIV in patients with hypercapnic encephalopathy. Most reports showed an improvement in the GCS score within a few hours after NIV initiation (Figure 1, Table 1).

Corrado *et al.* [18] were the first to evaluate patients with hypercapnic coma of various etiologies treated with NIV (iron lung). In their study, the mean arterial pH was 7.13 ± 0.3 and PaCO_2 was 112 ± 21 mm Hg. Of the 150 patients analyzed, treatment was successful in 70%, ranging from 0% in patients with a GCS of 3 to 85% with a GCS of 8. Five patients had aspiration complications, but all were successfully treated without intubation. Through multivariate analysis, a GCS of ≤ 6 and age ≥ 70 years were the only variables associated with NIV failure.

In a study by Briones *et al.* [19], the effectiveness of positive pressure NIV compared to IMV

was assessed in two cohorts of twelve patients each with similar baseline characteristics (GCS < 8 , arterial pH < 7.25 , APACHE II scores). Both groups presented to the Emergency Department with severe hypercapnia secondary to an acute exacerbation of COPD. NIV was considered successful when the following parameters were met: respiratory rate of < 24 breaths/min, heart rate of < 90 beats/min, improvement in consciousness level (GCS 15/15), and compensated arterial pH with adequate oxygen saturation at room air or with the use of a low percentage of inspired oxygen ($\text{FiO}_2 < 31\%$). The authors identified a lower 30 day mortality (16.7% vs 33.3% , $p = 0.01$), fewer days on mechanical ventilation (3.6 ± 1.1 vs 5.6 ± 1.2 , $p = 0.006$), and a shorter hospital stay (6.5 ± 1.9 vs 11.1 ± 4.7 days, $p = 0.001$) in the NIV (vs IMV) group, but no differences in survival at 6 months (80% vs 71.4% , $p = 0.80$). This study noted that improvements in PaCO_2 , pH, and GCS measured at 3 hours after NIV initiation were predictive of continued success of NIV therapy. Important differences, measured and unmeasured, may have existed between the cohorts and may in part explain the observed differences in outcomes.

Diaz *et al.* [20] prospectively examined patients with hypercapnic coma (GCS ≤ 8) secondary

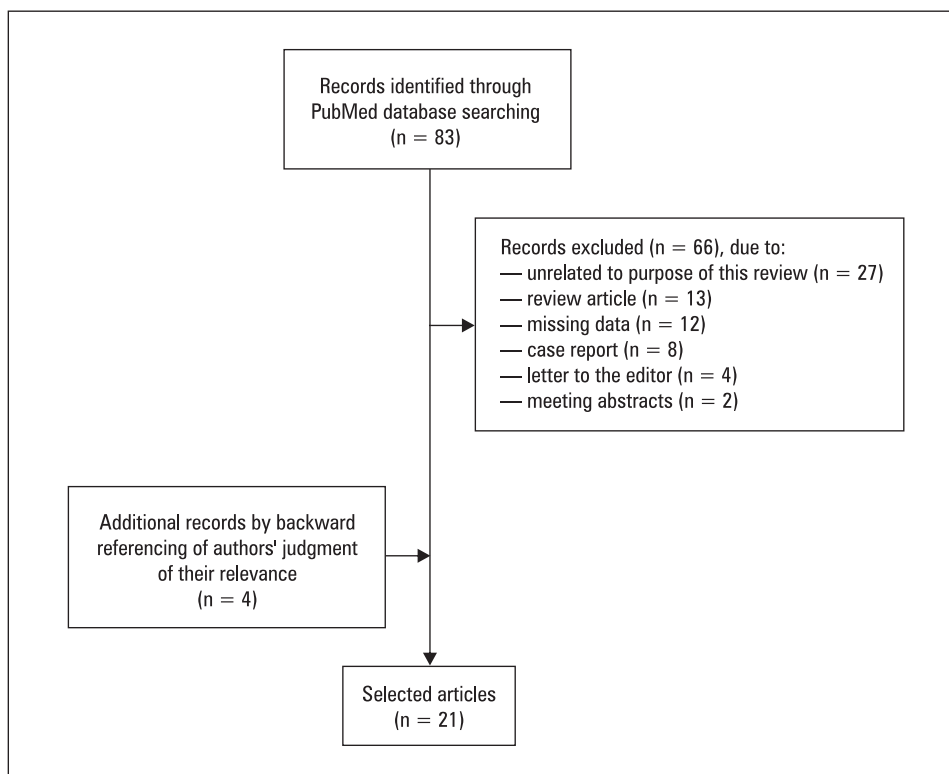


Figure 1. Flowchart of the study selection process for using non-invasive ventilation in hypercapnic acute respiratory failure encephalopathy

Table 1. Current evidence for using NIV in hypercapnic ARF encephalopathy

Author, year	Patients and aim of the study	Level of consciousness	Type of study	Results	Limitations
Lemyze 2019 [16]	86 DNI patients, NIV in hypercapnic coma vs NIV in hypercapnic ARF without coma	Comatose group with KMS ≥ 5	Prospective observational case-control study	70% survived to hospital discharge and half survived 6 months, with similar outcomes to controls	Selection bias could not be ruled out
Corrado 1996 [18]	150 patients, evaluate NIV (iron lung) success in hypercapnic coma	All GCS 3–8	Retrospective, uncontrolled study	NIV failure in 30%. GCS ≤ 6 had negative prognostic value	Retrospective study, limited availability of iron lung
Briones 2008 [19]	24 patients, NIV vs IMV in hypercapnic coma	All GCS < 8	Prospective interventional study	Less days on mechanical ventilation, days of stay and 30-day mortality	Small group of patients
Diaz 2005 [20]	958 patients, determine NIV success in hypercapnic coma vs NIV while awake	All GCS ≤ 8	Prospective, open, noncontrolled study	No increase in failure or mortality relative to non-comatose patients	Observational design, lack of control subjects
Scala 2007 [21]	40 patients, NIV vs IMV in hypercapnic encephalopathy	All KMS ≥ 3	Prospective matched case-control study	Shorter duration of mechanical ventilation and lower rate of complications. Mortality similar in both groups	Case-control design and lack of randomization
Zhu 2007 [22]	68 patients, evaluate the effectiveness and safety of NIV for severe hypercapnic encephalopathy	GCS < 10 vs GCS ≥ 10	Prospective case-control study	Similar results in hospital mortality and NIV success vs control group	Different levels of pressure support and NIV time between groups
Stefan 2015 [24]	2577 patients, compare outcomes of acute exacerbation of COPD, NIV vs IMV	GCS in NIV group of 15 (IQR 14–15)	Retrospective, multicenter cohort of prospectively collected data	Lower GCS was predictive of NIV failure	Patients received ventilatory support for an exacerbation of COPD and not necessarily hypercapnic acidotic exacerbation
Confalonieri 2005 [25]	1033 patients, assess the risk of NIV failure in acute exacerbations of COPD	GCS 13.2 ± 2.3	Prospective study	GCS ≤ 14 was predictive of NIV failure; main factor influencing the outcome was the pH value	Absent
Fan 2014 [26]	261 patients, measure cough strength and outcomes in acute exacerbations of COPD on NIV	GCS 14.8 ± 0.5 in NIV success vs GCS 13.8 ± 2.5 in NIV failure	Prospective observational study	APACHE II, semi-quantitative cough strength score and total proteins were the only predictors of NIV failure	Accuracy of cough measurements based on the clinicians' experience
Wang 2017 [27]	164 patients, compare NIV and IMV combined with a non-invasive strategy for clearing secretions in hypercapnic encephalopathy	All KMS ≥ 3	Prospective cohort study	2 hours of NIV with clearance of secretions significantly improved KMS and arterial blood gases. Hospital mortality lower in the NIV group	Not a randomized controlled trial, single-center study, hospital setting between groups differed, did not include an additional group with NIV alone

Table 1. Current evidence for using NIV in hypercapnic ARF encephalopathy [cont.]

Scala 2010 [28]	30 patients, early fiberoptic bronchoscopy during NIV vs IMV-based strategy in hypercapnic encephalopathy	KMS 2–4	Prospective matched case-control study	Higher complication rates in the IMV group. Similar hospital mortality, hospital lengths of stay, and duration of ventilation in the two groups	NIV application with the concomitant use of fiberoptic bronchoscopy to remove secretions should be reserved for centers where all staff members have sufficient experience
Contou 2013 [51]	242 patients admitted for hypercapnic ARF, assess the rate of NIV failure	Included RASS < 0	Observational cohort study	Altered levels of consciousness at admission had no influence on outcome	Retrospective, single unit, longstanding experience in NIV practice
Briones 2013 [52]	22 patients, BiPAP S/T vs AVAPS mode	All GCS < 10	Prospective interventional match-controlled study	Rapid improvement in arterial blood gases and GCS in both groups	Small number of patients
Scala 2005 [53]	153 patients requiring NIV divided into 4 groups, according to level of consciousness	Groups: KMS 1, KMS 2, KMS 3 and KMS > 3	5-year case-control study with a prospective data collection	Significant improvement in arterial blood gases and KMS in all groups after 1 to 2 hours. NIV failure and 90-day mortality significantly increased with worse KMS	No randomization
Jatoi 2019 [54]	78 patients, predict NIV success in post-TB sequelae	GCS 8.4 ± 2.1 in nonresponders vs GCS 9.4 ± 1.8 in responders	Single center, prospective, cohort study	Lower GCS was a significant independent predictor of NIV failure	Single unit, no IMV group control, absence of long-term mortality or morbidity
Scarpazza 2013 [55]	78 patients, assess NIV success in hypercapnic ARF	GCS 7.2 ± 1.5 in non-responsive patients vs GCS 9.7 ± 2.9 in responsive patients	Single center, prospective, cohort study	Lower GCS was a significant independent predictor of NIV failure	Single unit, no IMV group control
van Gemert 2015 [56]	50 COPD patients, assess risk factors in transition from NIV to IMV	GCS 9–15	Retrospective cohort study	Lower GCS at presentation is associated with the transition from NIV to IMV in COPD patients with hypercapnic ARF	Retrospective study, small sample size
Ucgun 2006 [57]	151 patients, identify factors affecting mortality and intubation in COPD patients	GCS 14.1 ± 1.4 in nonintubated vs GCS 10.8 ± 3.4 in intubated	Single center, prospective study	Lower GCS was associated with intubation	Small sample size, low rate of NIV applications, inclusion of pneumonia and heart failure leading to acute exacerbation of COPD
Kida 2012 [58]	42 patients, identify predictors of NIV success in elderly	GCS 8.9 ± 2.4 in survivors vs 4.0 ± 1.7 in non-survivors	Single center, retrospective study	GCS < 9 was associated with higher mortality	Retrospective study, small sample size

ARF — acute respiratory failure; AVAPS — average volume-assured pressure support; BiPAP — bilevel positive airway pressure; COPD — chronic obstructive pulmonary disease; DNI — do not intubate order; GCS — Glasgow coma scale; ICU — intensive care unit; IMV — invasive mechanical ventilation; IQR — interquartile range; KMS — Kelly-Matthay score; NIV — non-invasive ventilation; RASS — Richmond Agitation-Sedation Scale; TB — tuberculosis

to respiratory failure of various causes and treated with NIV. At the beginning of ventilatory therapy, arterial pH was 7.13 ± 0.06 and PaCO_2 was 99 ± 19 mm Hg. Improvements in pH, GCS, PaCO_2 , and $\text{PaO}_2/\text{FiO}_2$ within the first hour of NIV correlated with NIV success. A high rate of response to NIV was achieved in comatose patients with cardiogenic pulmonary edema, COPD, and obesity. Subjects with acute respiratory distress syndrome (ARDS) and pneumonia had a higher probability of not responding to NIV. These findings support that NIV success may be related to the type and nature of the underlying disease.

Scala *et al.* [21] conducted a prospective matched case-control study comparing 40 patients with neurological impairment (KMS ≥ 3) secondary to an acute exacerbation of COPD treated with NIV or IMV. In this study, the mean arterial pH and PaCO_2 in NIV patients was 7.22 ± 0.02 and 88 ± 15 mm Hg. In the control group, these same parameters were 7.22 ± 0.05 and 90 ± 10 mm Hg. They noted that consciousness improved from a mean of 3.4 ± 0.6 to 2.1 ± 0.8 points in NIV patients after 2 hours of treatment, and to 1.6 ± 1.0 at 24 hours. Compared to the IMV group, the NIV group showed a shorter duration of mechanical ventilation and a lower complication rate due to fewer cases of nosocomial pneumonia and sepsis despite similar (25%) in-hospital mortality rates between groups.

In a case control study, Zhu *et al.* [22] compared a group of 22 exacerbated COPD patients with GCS < 10 with a control group of 21 subjects with GCS ≥ 10 . They noted similar rates of hospital mortality (14% vs 14%, $p > 0.05$) and NIV success (73% vs 68%, $p > 0.05$). However, pressure support, NIV time, and hospital length of stay were significantly higher in patients with GCS < 10 .

These studies conclusively demonstrated that many of the consensus-based “absolute” contraindications to NIV should be viewed as “relative”, although an increase in failure rates can be expected in the most severe forms of hypercapnic encephalopathy. Additionally, severe complications from NIV are rare. However, most published series have been submitted by teams with extensive experience in ventilatory support, and it is difficult to know whether these results can be extrapolated to other groups with less expertise.

Current evidence against the use of NIV in hypercapnic ARF encephalopathy

By contrast, there is also evidence that NIV can be harmful in certain settings. Some studies

demonstrate high rates of NIV failure in patients with low consciousness levels. In these particular patients who initially receive NIV and then experience NIV failure, there is a subsequent need for them to be intubated in order to undergo IMV, which results in them being more likely to die in the hospital [23, 24]. One possible reason for the increased mortality can be due to an inappropriate initial selection of NIV candidates and/or delay in ETI.

In a study by Confalonieri *et al.*, the risk of NIV failure in a large unselected population admitted to different hospital units with expertise in NIV was assessed. The authors used this data and built two risk charts for NIV failure; one at admission and the other after 2 hours. NIV failure occurred in 236 patients (22.9%); among those, 142 died (13.7%). Risk factors for NIV failure included APACHE II score ≥ 29 , GCS ≤ 14 , pH < 7.25 , and respiratory rate ≥ 30 breaths/minute. At admission, in a patient with pH < 7.25 , APACHE II ≥ 29 and GCS ≤ 11 , the chart shows a predicted risk of failure $> 70\%$. This risk increases to 90% if the same parameters are kept after 2 hours [25].

In addition, there is data that suggest additional harm in patients with excessive secretions. Most COPD exacerbations are triggered by pulmonary infections, and exacerbations are usually associated with copious secretions. A previous study has reported that COPD patients with low cough strength were more likely to experience NIV failure (up to 80%) [26]. In selected scenarios, a reduction in NIV failure may be achieved by initiating early suction of secretions with bronchoscopy performed during NIV by an expert team [27, 28]. In a matched case-control study by Scala *et al.* [28], bronchoscopy was performed 18.5 ± 6.9 minutes after NIV initiation and lasted 7.8 ± 3.1 minutes with the removal of 23 ± 18 mL of respiratory secretions. In these patients, although both KMS and cough efficiency significantly improved after two hours, NIV still failed in 3 of 15 patients (20%). Compared to the IMV group, hospital mortality, hospital length of stay, and duration of ventilation were similar to patients in the NIV group.

Finally, a lack of cooperation in agitated patients may limit NIV success [29]. Continuous infusion of a single sedative and analgesic titrated to obtain a “conscious sedation” may decrease patient discomfort and improve gas exchange, with no significant effects on respiratory drive or hemodynamic status [30]. However, larger and more controlled trials are needed to clarify the indications of sedation during NIV.

Rationale for NIV use in patients with hypoxemic ARF and an altered level of consciousness

In this section, we will consider non-hypercapnic patients with an altered level of consciousness who have symptoms related to impaired mental function that appeared as a result of hypoxia and sepsis. Hypoxemic non-hypercapnic patients with an altered level of consciousness refers to a syndrome marked by cerebral dysfunction caused by brain hypoxia and ischemia due to hypoxemic ARF. Similarly, septic encephalopathy is an impaired mental status syndrome with a clinical presentation ranging from clouded thinking/consciousness to deep coma as can be seen in patients with systemic inflammation. Pathophysiologic hallmarks are thought to comprise diffuse neuroinflammation, vascular dysfunction, and neurotransmitter imbalances leading to direct cellular neuronal damage, impaired autoregulation, and excitotoxicity [31].

The goal of using NIV is to improve oxygenation, to decrease dyspnea and the work of breathing, and to avoid intubation [32]. It is believed to be beneficial because it recruits collapsed alveoli, increases the functional residual capacity, and decreases intrapulmonary shunt which, as a result, improves respiratory mechanics and gas exchange [33].

Hypoxemic ARF is usually defined as significant hypoxemia ($\text{PaO}_2/\text{FiO}_2 \leq 200$ mm Hg) and tachypnea in a patient not diagnosed with COPD [4]. Thus, hypoxemic ARF represents the final result of a large number of different underlying pathologies [34]. Given the variety of the pathophysiology that leads to severe hypoxemia, drawing reasonable conclusions regarding the use of NIV for hypoxemia is associated with significant challenges.

The Berlin definition for ARDS is as follows: mild when $\text{PaO}_2/\text{FiO}_2$ is > 200 and < 300 mm Hg; moderate when $\text{PaO}_2/\text{FiO}_2$ is > 100 and ≤ 200 mm Hg; and as severe when $\text{PaO}_2/\text{FiO}_2 \leq 100$ mm Hg. Positive end-expiratory pressure (PEEP), which can be delivered through NIV, can markedly affect $\text{PaO}_2/\text{FiO}_2$. Therefore, a minimum level of PEEP (5 cm H_2O) was added to the definition [35].

In the LUNG SAFE Study, 2813 patients with ARDS were managed with NIV or IMV irrespective of the severity category. In this study, NIV failure occurred in 37.5% of patients with ARDS and in almost half of patients with moderate and severe ARDS. NIV was associated with a worse adjusted ICU mortality than IMV in patients with a $\text{PaO}_2/\text{FiO}_2 < 150$ mm Hg. However, there was no difference in hospital mortality [36].

Additionally, a new concept of patient self-inflicted lung injury can arise as spontaneous vigorous effort in non-intubated patients has been shown to worsen lung injury in moderate to severe ARDS. Higher EPAP through NIV can reduce the amount of atelectasis in the lung, decrease force generated by spontaneous effort, and often improves gas exchange. However, even in volume-controlled NIV mode, spontaneous effort can deteriorate lung injury by increasing local lung stress and overdistension [37].

As such, the use of NIV in patients with severe hypoxemic ARF is controversial [6, 38]. Most of the published literature has focused on common hypoxemic clinical conditions such as acute pulmonary edema and pneumonia [39]. Other investigations have focused on the use of NIV in severely hypoxemic patients due to ARDS [36, 40].

Current evidence for the use of NIV in hypoxemic ARF in patients with an altered level of consciousness

We reviewed published studies designed to assess the use of NIV as a first-line intervention in hypoxemic ARF to avoid ETI. However, the majority of studies excluded patients with altered levels of consciousness. Studies on altered mental status due to primitive neurological diseases (e.g. stroke) or metabolic/toxic causes were not included (Figure 2, Table 2).

Only one study compared NIV efficacy in hypoxemic ARF in patients with an altered level of consciousness (GCS 9–14) versus patients with full awareness [41]. Patients were divided into two groups according to the presence (66 patients) or absence (82 patients) of encephalopathy. Patients with encephalopathy were older (median of 72 vs 78 years, $p = 0.02$), had a higher APACHE II score (18 vs 19, $p = 0.02$), and received a higher level of IPAP. With the caveat of being a retrospective study with important baseline imbalances, there were no significant differences between groups in rates of NIV failure (24% vs 30%, $p = 0.4$) and in in-hospital mortality (13% vs 16%, $p = 0.3$).

Data from other studies must be cautiously taken into account as they did not exclude patients from their studies based simply on a certain level of awareness. Changes to the level of consciousness were not primary or secondary endpoints.

In a randomized clinical trial, Ferrer *et al.* [42] compared the efficacy of NIV versus the Venturi mask with FiO_2 of 50% based on survival

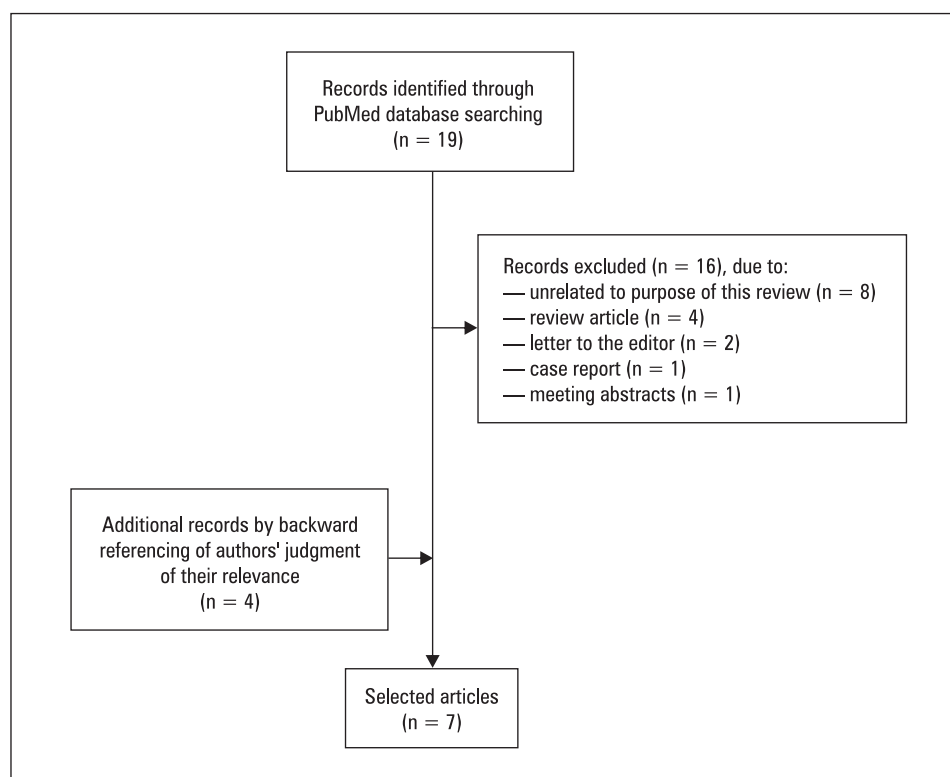


Figure 2. Flowchart of the study selection process for using non-invasive ventilation in hypoxemic acute respiratory failure in patients with an altered level of consciousness

and avoidance of ETI in 105 patients with GCS 12–15 and hypoxemic ARF. After multivariate analysis, NIV was independently associated with a decreased risk of ETI (OR 0.20, $p = 0.003$) and 90-day mortality (OR 0.39, $p = 0.017$).

In a study enrolling cardiogenic pulmonary edema patients with hypoxemic ARF who had a mildly altered level of consciousness (GCS 8–15), CPAP significantly improved 48-hour mortality (7% vs 24%, $p = 0.017$) and reduced the need for intubation (9% vs 30%, $p = 0.001$). However, there was no improvement in in-hospital mortality compared to that of standard medical care [43].

Patel *et al.* conducted a study of ARDS patients with GCS 8–15 randomized to treatment with NIV delivered by helmet or face mask. Patients in the helmet (vs face mask) group showed a lower need for ETI (18.2% vs 61.5%, $p < 0.001$) and an improved survival rate at 90 days from randomization (34.1% vs 56.4%, $p = 0.02$) [44]. That being said, the helmet group had significantly higher EPAP and lower pressure support results compared to the face mask group which may have influenced the final results.

Hilbert *et al.* published a study comparing the use of NIV to standard treatment with sup-

plemental oxygen to treat immunosuppressed patients with hypoxemic ARF, including those with mildly altered levels of consciousness (GCS 9–15). This study showed that NIV can obviate the need for ETI in this population (46% vs 77%, $p = 0.03$) and diminish in-hospital mortality rates (50% vs 81%, $p = 0.02$) [45].

In summary, the current literature is insufficient to address the efficacy of NIV compared to other treatments in patients with hypoxemic non-hypercapnic ARF who also have an altered level of consciousness.

Current evidence against the use of NIV in hypoxemic ARF in patients with an altered level of consciousness

Delayed intubation in patients undergoing trials of NIV can lead to increased mortality [46, 47]. A previous study has reported a useful score (HACOR score) to predict NIV failure in patients with *de novo* hypoxemic ARF [48]. In this score, consciousness accounts for the highest weight among all risk factors for NIV failure. Patients with higher HACOR scores were more likely to experience NIV failure. Regarding consciousness, one assigns a HACOR score of 0 for GCS 15, 2 for

Table 2. Current evidence for using NIV in hypoxemic ARF in patients with an altered level of consciousness

Author, year	Patients and aim of the study	Level of consciousness	Type of study	Results	Limitations
Kogo 2018 [41]	148 patients, NIV efficacy in mildly altered consciousness	GCS 9–14 vs GCS 15	Retrospective study	No significant differences in NIV failure and in-hospital mortality	Retrospective study
Ferrer 2003 [42]	105 with severe ARF, NIV vs oxygen	GCS 12–15	Prospective, randomized controlled. Compares oxygen with NIV	NIV improves oxygenation, mortality, and decreases intubation rates	Difficulty for a correct blinding, relative heterogeneity of patients
L'Her 2004 [43]	89 patients with cardiogenic pulmonary edema, CPAP vs standard treatment	GCS 8–15	Prospective, randomized, concealed, and unblinded study	Reduction in early 48 h-mortality and ETI	Blinding impossible
Patel 2016 [44]	83 patients with ARDS, helmet vs face mask	GCS 8–15	Single-center randomized clinical trial	Reduction of intubation rates and 90-day mortality with helmet NIV	Blinding impossible
Hilbert 2001 [45]	52 immunosuppressed patients, NIV vs standard treatment	GCS <15	Prospective, randomized trial	Reduction in ETI, serious complications and mortality	Blinding impossible, single unit
Duan 2017 [48]	358 patients in the validation cohort, develop a scale to predict NIV failure in hypoxemic ARF	GCS in NIV success 14.8 ± 0.6 vs 14.3 ± 1.6 in the NIV failure group	Prospective observational study	NIV failure was associated with lower GCS	Observational study
Thille 2013 [49]	113 patients, assess rates and predictive factors of NIV failure	GCS in NIV success 14.9 ± 0.5 vs 14.6 ± 1.2 in the NIV failure group	Observational cohort study	NIV failure was associated with lower GCS	Single unit with long-standing experience in the use of NIV

ARDS — acute respiratory distress syndrome; ARF — acute respiratory failure; CPAP — continuous positive airway pressure; ETI — endotracheal intubation; GCS — Glasgow coma scale; NIV — non-invasive ventilation

GCS 13–14, 5 for GCS 11–12, and 10 for GCS \leq 10. In this study, in patients with a HACOR score > 5 , the risk for NIV failure reached up to 80%. Thus, the use of NIV in patients with low levels of consciousness must be done cautiously, especially in those with GCS \leq 10.

In an observational cohort study, Thille *et al.* [49] assessed the rates and predictive factors of NIV failure in patients admitted to the ICU for hypoxemic ARF. Among 113 patients receiving NIV, 82 had ARDS and 31 had non-ARDS. Intubation rates significantly differed between ARDS and non-ARDS patients (61% vs 35%, $p = 0.015$) according to the clinical severity of ARDS. NIV failure was associated with active cancer, shock, moderate/severe ARDS, lower EPAP at NIV initiation, and lower GCS ($p = 0.018$).

In fact, the latest ERS/ATS clinical practice guidelines for NIV do not offer a recommendation about NIV use for *de novo* hypoxemic ARF [4]. This is justified, firstly, by the fact that as soon as NIV is ceased, the positive effects previously

gained in terms of alveolar recruitment and oxygenation are lost. Secondly, during NIV, tidal volume results from the pressures given by the ventilator coupled with the respiratory muscle pressure generated by the patient's respiratory drive. Due to this mechanism, tidal volume is often high and may trigger ventilator-induced lung injury which contrasts with the intended lung protective ventilation strategies (low tidal volume of 6 mL/kg of predicted body weight) [32]. Finally, in a randomized controlled trial, the use of high-flow nasal cannula therapy has shown benefit in patient survival when compared with NIV and standard oxygen therapy in the treatment of hypoxemic ARF [50].

Conclusion

The overall analysis of the studies reviewed support the use of NIV as an adjunctive therapy in patients with hypercapnic encephalopathy because it decreases complication rates, the

Table 3. Advantages and disadvantages for using NIV over IMV in hypercapnic ARF encephalopathy

Advantages	Disadvantages
Less complication rates	Benefits decrease with lower levels of consciousness
Less cost	Benefits more significant in acute pulmonary edema, COPD, and obesity rather than ARDS or pneumonia
Less hospital and ICU length of stay	
Less mortality	

ARDS — acute respiratory distress syndrome; COPD — chronic obstructive pulmonary disease; ICU — intensive care unit

Table 4. Advantages and disadvantages for using NIV over IMV in hypoxemic ARF in patients with an altered level of consciousness

Advantages	Disadvantages
Less complication rates	NIV failure associated with active cancer, shock, moderate/severe ARDS Lower EPAP at NIV initiation and lower GCS
Less cost	Higher risk of NIV failure when GCS \leq 10

ARDS — acute respiratory distress syndrome; EPAP — expiratory positive airway pressure; GCS — Glasgow coma scale; NIV — non-invasive ventilation

need for ETI, hospital length of stay, and mortality rate when compared to IMV. Patients with hypercapnic ARF and impaired consciousness can be treated with NIV, however, these results appear to be more relevant to specific patient populations including those with acute pulmonary edema, COPD, and obesity rather than conditions such as ARDS or pneumonia. Close monitoring is also mandatory as improvements in blood gas percentages within the first hours correlate with NIV success (Table 3).

Data regarding NIV effectiveness in hypoxemic ARF patients with an altered level of consciousness are more controversial given the heterogeneity of the studies identified and the fact that many studies excluded patients with alterations in mental status. Based on the examined studies, there is no evidence to either support or reject the routine use of NIV in patients with hypoxemic altered levels of consciousness due to ARF. However, NIV failure seems to increase with declining levels of consciousness. A multicenter, randomized, and controlled study trial is needed to clarify whether a benefit of NIV exists compared to other supportive treatments with regard to clinically important outcomes such as intubation rate, mortality, hospital/ICU length of stay, and other patient-centered outcome measures (Table 4).

In all cases, increased clinical experience in administering NIV, patient tolerance, and selection of the most appropriate interfaces are important considerations. The clinical status of

the patient must be carefully monitored during NIV application. Clinicians must ensure that the use of NIV does not delay the need for ETI in patients who are deteriorating during NIV treatment. Proper patient monitoring is critical to ensure safe NIV initiation and titration. Skills in NIV application and limiting its use to highly monitored clinical settings are critical factors to consider to ensure optimal use of NIV and patient safety.

Conflict of interest

None declared.

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