REVIEW ARTICLE

Noninvasive mechanical ventilation in early acute respiratory distress syndrome

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ABSTRACT

Noninvasive ventilation (NIV) has a well-established role in the treatment of acute-on-chronic respiratory failure and cardiogenic pulmonary edema. Its role in acute hypoxemic respiratory failure has been increasingly investigated, but its impact on the management and outcome of the subset of patients with acute respiratory distress syndrome (ARDS) is still to be determined. ARDS could be a risk factor for NIV failure, and in these patients, delayed endotracheal intubation can lead to an increased mortality. On the other hand, in a subset of patients with ARDS, endotracheal intubation can be avoided when NIV is applied. This review summarizes the current practice of NIV use in patients with ARDS and underlines the importance of proper patient selection before an NIV trial as well as criteria that should be used to predict failure early enough. A brief overview of high-flow nasal cannula is also provided. The use of NIV in ARDS is still debated, and it is important to be aware of the potential limitations and pitfalls of this treatment, which, when properly applied, could reduce the incidence of endotracheal intubation.

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Introduction Invasive mechanical ventilation (IMV) is a life-saving procedure and remains the cornerstone of supportive therapies for patients with acute respiratory distress syndrome (ARDS).[1] However, while advances such as low-tidal-volume ventilation,[1] prone positioning,[2] and short-term use of neuromuscular blockade[3] may improve outcomes, IMV remains associated with the risk of ventilator-associated pneumonia,[4,5] complications from tracheal intubation and tracheostomy,[6,7] and ventilator-induced lung injury.[8] Consequently, strategies to avoid or delay IMV, such as noninvasive ventilation (NIV), have received attention in patients with ARDS.

In NIV, positive pressure is applied to the airways of the patient by means of an interface, such as a mask, with the aim of preventing alveolar derecruitment and to support the patient's respiratory muscles. NIV modes include the application of a single pressure, termed continuous positive airway pressure (CPAP), or 2 alternate pressure levels (as in pressure support ventilation), or biphasic positive airway pressure. NIV has become an established treatment modality for certain patient subgroups with respiratory failure, with strong evidence for its benefits in patients with acute exacerbations of chronic obstructive pulmonary disease[9-11] or cardiogenic pulmonary edema.[12]

Potential advantages of NIV in the management of patients with ARDS are mainly related to the avoidance of complications linked to oversedation, paralysis, and invasive ventilation.[13] However, the evidence supporting the use of NIV in patients with ARDS is sparse and based on clinical studies with relatively small sample sizes. Moreover, in most studies, patients treated with NIV were compared to patients treated with oxygen administration or to historical cohorts.[14,15] Therefore, the objective of this review was to critique the evidence regarding the current role of NIV in ARDS, to discuss the potential advantages and pitfalls, and to highlight the best practice regarding patient selection and technical aspects of NIV application.

Use of noninvasive ventilation in acute hypoxemic respiratory failure and acute respiratory distress syndrome: evidence and current practice

Acute hypoxemic respiratory failure The use of NIV in acute hypoxemic respiratory failure (AHRF) has increased over years,[16,17] together with the evidence

supporting its use, especially in specific populations of hypoxemic patients. Some studies focused on postsurgical hypoxemic respiratory failure,[14,16,18-20] either after solid organ transplantation, lung resection, or abdominal surgery. All of them found that in the case of AHRF, NIV could significantly reduce the intubation rate when compared with standard oxygen therapy and led to lower mortality rates. In a study by Antonelli et al,[20] NIV reduced the intubation rate also in the subgroup of patients with ARDS. Similarly, in 2013, Ferrer et al[15] treated patients affected by AHRF with NIV or high oxygen concentrations. The causes of AHRF were heterogeneous, from cardiogenic pulmonary edema to ARDS to thoracic trauma. NIV reduced the overall risk of intubation and increased the 90-day survival rates versus oxygen therapy alone. Interestingly, in this study, ARDS was a risk factor for intubation and for decreased 90-day survival rates in both groups. On the contrary, Delclaux et al[21] found that in patients with AHRF the use of CPAP led to a brief improvement in physiological parameters (the ratio of partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2]) but did not change the intubation rate nor survival in comparison with oxygen therapy. A systematic review of those studies found that NIV reduced the intubation rate, intensive care unit (ICU) and hospital length of stay, and ICU mortality in patients affected by AHRF, including both patients with and without ARDS.[9]

Acute respiratory distress syndrome All the cited studies involved a mixed population of hypoxemic patients. In 2007, Antonelli et al[22] conducted a prospective study to observe the use and outcome of NIV in patients with ARDS only. The study was multicentered and found that 31% of the patients could be considered suitable for a NIV trial. With this approach, the use of endotracheal tube intubation (ETI) could be avoided in 54% of the patients.[22] Subsequently, Agarwal et al[23] conducted the first meta-analysis specifically addressing the role of NIV in ARDS. They analyzed the results of the above randomized controlled trials (RCTs) by Antonelli et al,[20] Ferrer et al,[15] and Delclaux et al[21] only looking at the subgroups of patients with ARDS and did not find any advantage provided by NIV in terms of the intubation rate or survival. Later, the same authors conducted another meta-analysis that included not only RCTs but also observational trials[24] in order to increase the number of patients with ARDS involved in the analysis. Despite being an inconclusive study because of the large statistical heterogeneity of the trials included, this meta-analysis showed that NIV in ARDS was successful in 50% of the patients, a result very similar to that obtained in the prospective study conducted by Antonelli et al in 2001 and 2006.[22,25] A more recent meta-analysis including 6 RCTs clearly showed that NIV reduced the intubation rate when compared with standard oxygen therapy, but it did not have effects on ICU or in-hospital mortality.[26] These results were confirmed also by a small retrospective study on patients with ARDS treated by NIV.[27]

The recently published LUNG SAFE study[28] provided an overview of the worldwide use of NIV during ARDS. According to this study, almost 15% of the patients who developed ARDS on days 1 and 2 from ICU admission were treated with NIV as the first-line intervention for at least 24 hours. Among those, 65% were maintained with NIV, while the others were switched to IMV. Another study, which analyzed the NIV population of the LUNG SAFE study, found that NIV was attempted in 15% of the patients with ARDS, independently from the severity of the disease, but that patients with more severe ARDS had a lower rate of success (from 78% in mild to 53% in severe ARDS).[29] NIV use was also burdened with a higher mortality rate than IMV in patients with the most severe disease (PaO_2/FiO_2 <150 mm Hg). Moreover, it was associated with a lower rate of ARDS recognition by the treating physician, raising concern about the adequacy of the treatment in those patients.

In summary, the use of NIV gives an advantage in terms of the lower intubation rate when considering the overall hypoxemic population, while the diagnosis of ARDS increases the probability of NIV failure, and some evidence suggests a possible negative effect of NIV on survival of patients with more severe forms of ARDS. On the other hand, it seems quite attractive to avoid ETI in 50% of patients with ARDS who undergo a NIV trial. The question to be asked might then probably be: Can we correctly identify the 50% of patients with ARDS who would succeed in a NIV trial without harm and possibly avoid the complications related to ETI?

Patient selection and prediction of failure As summarized above, NIV failure is associated with an increased risk of death in patients with ARDS, particularly when endotracheal intubation is delayed. In fact, in some studies the failure of NIV and thus the need for delayed ETI are associated with a worse outcome than the one predicted from the baseline patient condition. Rana et al[30] found that patients with acute lung injury who needed intubation after a NIV trial had a mortality rate of 68% versus the 39% predicted by APACHE II. Carrillo et al[31] observed that a longer duration of NIV before intubation was associated with higher in-hospital mortality, but only in patients with de novo AHRF. Antonelli et al[22] reported a high mortality rate among patients who failed NIV (54%) and raised doubts that delaying a necessary intubation could worsen prognosis. In another study, patients who were intubated after 12 hours of NIV had a lower in-hospital mortality rate than those whose intubation was delayed for more than 12 hours, although in both groups, the mortality rate was extremely high.[32] Lastly, in the LUNG SAFE study,[28] patients with

TABLE 1 The HACOR score

Variable	Category	Assigned points
Heart rate, beats/min	≤120	0
	≥121	1
pH	≥7.35	0
	7.30–7.34	2
	7.25–7.29	3
	<7.25	4
Glasgow Coma Scale	15	0
	13–14	2
	11–12	5
	≤10	10
PaO_2/FiO_2 ratio, mm Hg	≥201	0
	176–200	2
	151–175	3
	126–150	4
	101–125	5
	≤100	6
Respiratory rate, breaths/min	≤30	0
	31–35	1
	36–40	2
	41–45	3
	≥46	4

Abbreviations: FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen

the most severe disease had a worse prognosis when treated with NIV than with IMV. For this reason, it is of paramount importance to select the cohort of patients in whom NIV is most likely to succeed, while monitoring closely for early signs of failure.

The first important element of stratification is based on the category of respiratory failure: "de novo" versus "acute on chronic" (ie, exacerbating an underlying cardiac or pulmonary condition).[16,31,33] NIV failure was associated with higher mortality only in the "de novo" respiratory failure group, while NIV success was associated with a better outcome only in "acute-on-chronic" patients. Even if these studies do not specifically involve patients with ARDS, they raise major concern about those patients who do not have an underlying chronic disease.

In clinical practice, 15%[29] to 31%[22] of patients with ARDS undergo a NIV trial. The contraindications to NIV are well known[22,34] and include severe hypoxemia or acidemia, inability to protect the airways, coma, upper airway obstruction, anatomical abnormalities (facial trauma), respiratory arrest/apnea, cardiac arrest, increased risk of aspiration/gastrointestinal bleeding, and multiple organ failure. Some studies include severe ARDS among the contraindications to NIV and advocate the use of NIV only in mild to moderate ARDS.[35,36]

When a patient is considered suitable for a NIV trial, it is critical to be aware of the factors that can predict the failure of the trial and to be able to rapidly institute IMV. The factors related to the patient include baseline severity of the patient condition, as assessed with the SAPS II, SOFA, or APACHE II scores. A SAPS II score exceeding 35,[25] 38,[22] or 45,[37] an average maximum SOFA score of 9,[31] or an APACHE II score exceeding 17[36,38] were associated with the need of endotracheal intubation. Other patient characteristics that were related to NIV failure included the presence of shock and metabolic acidosis[30,39] and ARDS itself. In fact, as already mentioned, in the studies that included patients who were hypoxemic for whichever cause, ARDS was listed as a cause of NIV failure.[25,31] In a very interesting study, Thille et al[40] compared non-ARDS AHRF versus ARDS. They were able to stratify the probability of NIV success based on ARDS severity and found that patients without ARDS and those with mild ARDS had almost the same intubation rate during NIV (31%–35%), while this rate almost doubled in moderate ARDS (62%). They also reported that it might not be worth attempting NIV in patients with severe ARDS, where the failure rate is 84%.

After the NIV trial has been started, a rapid improvement in the patient condition should be observed. Indeed, a factor often demonstrated to be associated with the outcome of NIV is the change of the PaO_2/FiO_2 ratio. Some cut-off values have been defined: a PaO_2/FiO_2 ratio of less than 146 mm Hg[25] or less than 175 mm Hg[22] after 1 hour of NIV predicts failure, or in general a decline or small improvement of the PaO_2/FiO_2 ratio.[30,31] The study by Thille et al[40] supports the use of NIV in patients with mild ARDS and suggests attempting it in those with moderate ARDS only if the PaO_2/FiO_2 ratio is higher than 150 mm Hg. These criteria for prediction of failure demand a close monitoring of patients with ARDS during NIV by expert personnel, who should be able to institute IMV as soon as needed. During NIV, adjunctive factors that were associated with failure were the worsening of chest X-ray results after 24 hours, not decrease of heart rate, and the decrease of bicarbonates after 1 hour.[31]

Recently, a new score has been developed and validated to easily predict the probability of NIV failure at the bedside.[32] The HACOR score assesses 5 parameters already demonstrated to be associated with a high rate of NIV failure (heart rate, acidosis, consciousness, oxygenation, and respiratory rate) and ranges from 0 to 25 points (**TABLE 1**). In a validation study, the score was significantly higher in the group that failed NIV at each time point tested (1, 12, 24, and 48 hours), and a cut-off value of 5 after 1 hour of NIV was found to have a high diagnostic accuracy for predicting NIV failure, making this score an easy and reproducible tool to evaluate the patient.

Lastly, an interesting French study evaluated the role of expired tidal volume (VTe) on NIV outcome.[41] The first finding was that, despite a NIV setting aimed at maintaining a VTe of 6 to 8 ml/kg, this was never obtained in patients with ARDS, whose median VTe was 9.8 ml/kg of

TABLE 2 Predictors of noninvasive ventilation failure

Predictor	Study[a]
Scores of severity (SAPS II, APACHE II, SOFA)	20,22,31,33,36,38,67
Age	20
PaO_2/FiO_2 ratio	20,22,30–32,36,38,68
ARDS severity	20,31,38,40
Metabolic acidosis/bicarbonates	30–32
Shock	30,38,40
Community-acquired pneumonia	20
Worsening chest X-ray results	31
Heart rate	31,32
Respiratory rate	32,67
Consciousness (low Glasgow Coma Scale score)	32,40
De novo respiratory failure	33
Cancer	40
Low positive end-expiratory pressure	40
High tidal volume	30,41

a see the References

predicted body weight (PBW), albeit VTe measurement in NIV might not be entirely accurate, owing to apparatus dead space and leaks. Still, "protective ventilation" is difficult to achieve in clinical practice during NIV. Secondarily, the authors stratified the patients according to ARDS severity (mild and moderate to severe, with a PaO_2/FiO_2 ratio of up to 200 mm Hg). In the second group, a VTe higher than 9.5 ml/kg PBW during the first 4 hours of NIV was an independent predictor of failure in a multivariate analysis, along with the SAPS II score. The reasons for this finding, according to the authors, could be twofold: a higher VTe is a marker of more severe disease or a higher VTe is a cause of ventilation-induced lung injury, further aggravating the lung injury. Another study looking at VTe[30] found a similar cut-off, where NIV failure occurred in patients with a VTe higher than 9 ml/kg PBW. All the factors associated with NIV failure are summarized in TABLE 2.

The above results underline the necessity of intensive monitoring of patients undergoing a NIV trial, or even the opportunity to develop a specific flow chart in each institution in order to appropriately select patients and timely stop NIV (an example is reported in FIGURE 1).[22,34,42]

Noninvasive ventilation in immunocompromised patients Survival of immunocompromised patients (ie, the ones affected by cancer, either solid or hematologic, and the ones who are pharmacologically immunosuppressed) has increased over the years, but still, patients with ARDS and cancer have a higher mortality than those without cancer.[43] Of these patients, 15% to 20% are admitted to ICU for complications, the majority of whom have respiratory failure of infectious origin. In these patients, endotracheal intubation was shown to carry an augmented risk of superinfection and death. Hence, the possibility to manage these patients without the need of ETI appears particularly appealing.[44] In 2001, Hilbert et al[45] showed that in a small group of immunocompromised patients, the use of NIV reduced the intubation rate, mortality, and serious complications. These data and those on AHRF following solid organ transplantation[20] led to the introduction of NIV as the first-line approach for AHRF management in immunocompromised patients in some local recommendations and guidelines.[16,46] Nevertheless, the need of an RCT was strongly advocated.[47] A multicenter RCT, published in 2015, aimed to confirm the previous findings, attempting to show an advantage in terms of survival.[48] It recruited 347 patients, stratified by the cause of immunosuppression. Surprisingly, no differences were found in a 28-day mortality rate between the NIV group and controls. Unfortunately, the study turned out to be underpowered, also because the mortality rate in the control group was lower than expected; moreover, high-flow nasal cannulas (HFNC) were used in both groups, thereby probably reducing the need for intubation. Moreover, the post hoc analysis of the study by Frat et al,[49] which involved immunocompromised patients randomly allocated to NIV, HFNC, and standard oxygen therapy, showed that the use of NIV was independently associated with an increased risk of ETI and mortality in these patients. In summary, these recent data do not allow us to make a recommendation about the use of NIV in immunocompromised patients, unless specific subgroups that could benefit from the treatment are identified. On the other hand, promising results have emerged from the studies on the use of HFNC, as detailed below.

How to apply noninvasive ventilation: interface, monitoring, and sedation Optimizing NIV settings and choosing an adequate interface is critical for NIV outcome. Indeed, poor compliance with the interface was described as an additional risk factor for NIV failure.[50] A very recent study by Patel et al[51] compared the application of NIV via face mask versus via helmet.[52] The study was prematurely interrupted due to evidence of superiority of the helmet interface (intubation rate of 18% vs 61%, along with more ventilator-free days, shorter ICU stay, and lower mortality).[51] The helmet seems to be better tolerated by patients, allowing for longer ventilation trials.[53] Moreover, the positive end-expiratory pressure applied in the study was significantly higher in the helmet versus the face-mask group, because of a lower leak. Even if some methodological concerns have been raised,[54] this study might suggest that the interface choice brings significant differences in terms of the effectiveness of ventilation, which could affect the outcome. It was suggested that unlike the face or nose mask, the helmet interface could reduce hospital mortality.[55]

Particular attention has to be paid to the appropriate setting of inspiratory flow and cycling-off time during helmet ventilation to reduce CO_2

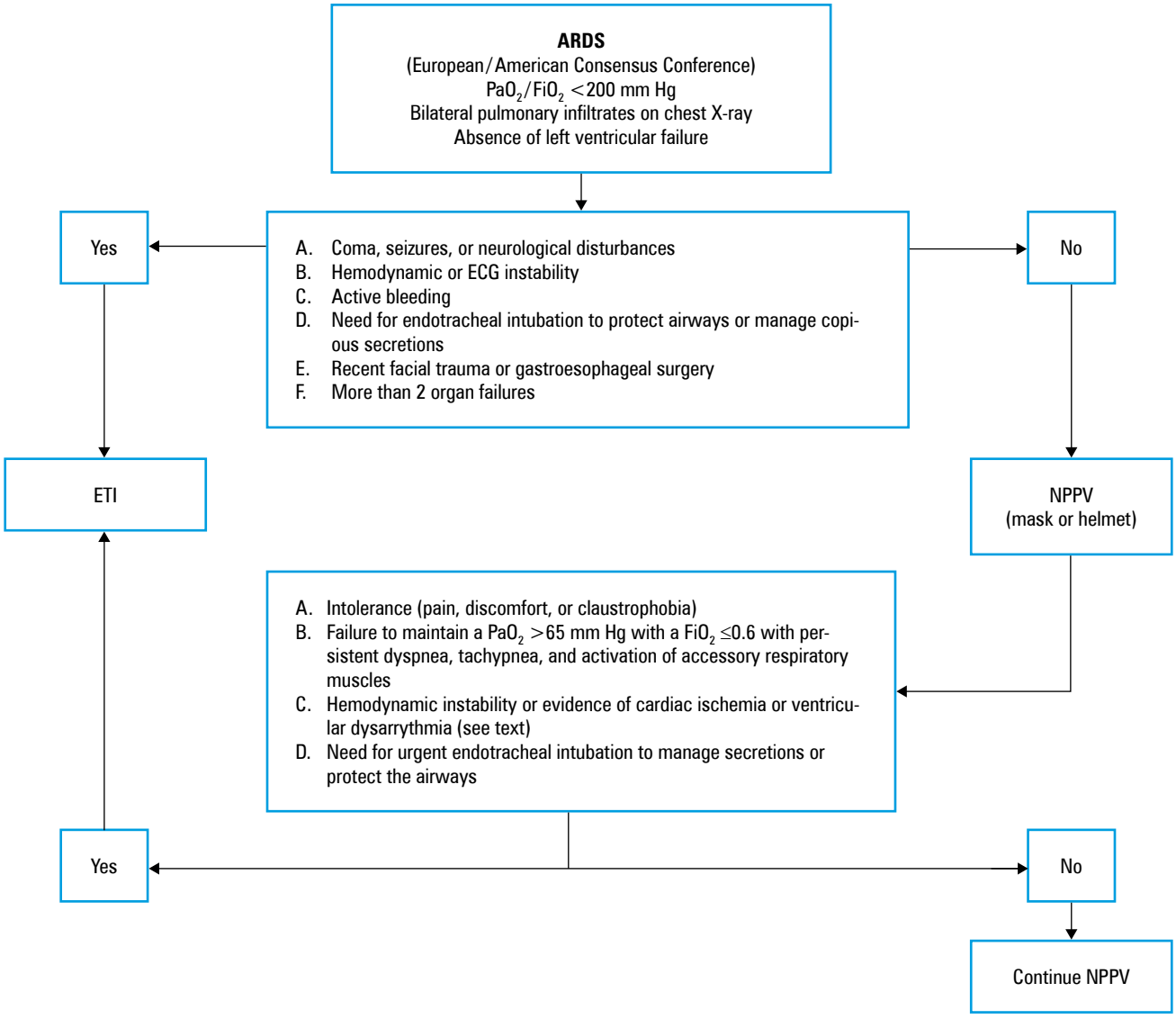

FIGURE 1 Example of a flow chart for noninvasive ventilation application (reproduced with permission from Antonelli et al[22]) Abbreviations: ARDS, acute respiratory distress syndrome; ECG, electrocardiogram; ETI, endotracheal intubation; NPPV, noninvasive positive pressure ventilation; others, see **TABLE 1**

rebreathing and improve the patient–ventilator interaction.[56,57] The helmet appears to be a very promising interface for delivering NIV in patients with ARDS. It can be used to deliver both continuous free-flow CPAP or pressure support. Helmet features can be optimized depending on the application: a larger, more compliant helmet for free-flow CPAP, and a smaller and less compliant for pressure support. The delivery of pressure support by helmet could appear somehow complicated, requiring several skills and adjustments.[58]

A recent editorial[59] advocated a very prudent approach to sedation use during NIV, because side effects could overcome benefits. In the case of a difficult patient–ventilator interaction, an approach based on the appropriate setting of the ventilator should be tried first. A sedated patient during NIV should be carefully monitored. In this setting, the use of dexmedetomidine could confer an advantage when compared to other drugs in terms of the efficacy and side effects.[60]

High-flow nasal cannula Even if HFNC was not primarily designed to deliver positive pressure ventilation, its use is becoming more popular among patients with AHRF. A recent review had nicely summarized the physiologic basis of the efficacy of this device, namely, the possibility to deliver high and stable FiO_2 levels, the effective humidification and warming of gases, the ability to create a low positive pressure which stabilizes the alveoli, and the reduction of anatomical dead space by CO_2 washing.[61] All these effects could result in a reduction of the work of breathing and improved alveolar ventilation.[62,63] Patient's comfort and improvement of dyspnea have been demonstrated,[64] and strong evidence in favor of HFNC came from a study by Frat et al.[65] This RCT, with the intubation rate as primary outcome, included patients affected by AHRF with a PaO_2/FiO_2 ratio of 300 mm Hg or less. The patients were randomized to receive either NIV or HFNC or standard oxygen therapy. While the primary outcome showed no differences among the 3 treatments, the secondary outcomes, that is, ICU and 90-day mortality, favored HFNC over both NIV and standard oxygen therapy. The results of the trial strongly encourage to consider the use of HFNC in patients with AHRF as the first-line

treatment, even if also in this case priority has to be given to not delaying intubation.[66]

Conclusions In addition to its well-known role in "acute-on-chronic" respiratory failure, the use of NIV in "de novo" ARDS has received a growing interest over the last decades. NIV might help avoid several complications related to IMV, but several concerns remain, such as the positive end-expiratory pressure applied is lower than during IMV and protective ventilation is hardly guaranteed.

This treatment should probably be limited to carefully selected patients with mild to moderate ARDS (failure is higher than 50% in severe ARDS) and applied in experienced centers with a close monitoring of blood gases and respiratory mechanics, since delayed intubation in the case of failure is detrimental to patients.

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