Non-invasive Ventilation: How, when, for whom, and what outcome?

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Introduction

Restricting the benefit of clinical research to randomized clinical trials would be a mistake in the field of non-invasive ventilation (NIV). Observational studies, physiological studies, and matched paired case-control studies have put together an enormous body evidence demonstrating the benefits of NIV and the working mechanisms of this technique. The randomized controlled trials have confirmed the evidence and helped to more formally indicate when NIV should be a first line treatment. Randomized controlled trials, however, are non-blinded, are highly selective regarding the inclusion of patients, and do not represent the real life. Additional studies conducted out of the context of clinical trials are of utmost importance to ensure that the results of these trials can be observed in real life.

In this chapter, the main studies focusing on the efficacy of NIV in acute respiratory failure will be reviewed. Articles published in non-English language and meta-analysis will not be considered. When data are available, the discussion will address the type of ventilatory modality.

Non-invasive Ventilation in Acute Exacerbation of Chronic Respiratory Failure (Table 1)

The studies including acute on chronic respiratory failure most frequently concern patients with chronic obstructive pulmonary disease (COPD). Definitions for chronic diseases, however, are sometimes imprecise.

Patients with hypercapnic forms of acute respiratory failure are most likely to benefit from NIV. The pathophysiology of most episodes of acute decompensation of chronic respiratory failure was demonstrated in a physiological study [1], and involves the inability of respiratory muscles to generate adequate alveolar ventilation in the presence of severe abnormalities in respiratory mechanics (intrinsic positive end-expiratory pressure [PEEP], high inspiratory resistances). Therefore, despite massive stimulation of the respiratory centres and large negative intrathoracic pressure swings generated by the respiratory muscles, these patients generate small tidal volumes at the mouth, which are inadequately compensated for by an increase in breathing rate [1]. This rapid shallow breathing has limited efficiency for removing CO_2 and is associated with a potential risk of respiratory

Table 1. Main studies of the efficacy of non-invasive ventilation (NIV) in patients with chronic obstructive pulmonary disease (COPD)

Author, year [ref] Number of pts	Population/ Location	Type of study	Conclusions for NIV
Brochard, 1990 [1] n = 26	COPD/ICU	Case control study	Reduction of ETI, length of stay
Vitacca, 1993 [7] n = 29	COPD/ICU . RCT PSV vs ACV . Cohort (35)		The two modalities had better results than conventional treatment
Bott, 1993 [6] n = 60	COPD/ward	**RCT**	Improvement of ABG, dyspnea Reduction of ETI criteria Reduction in mortality (after excluding 4 patients who did not receive NIV)
Kramer, 1995 [8] n = 31	Mixed 74 % of COPD/ICU	RCT	Improvement of ABG, dyspnea Reduction of ETI (67 % to 9 % in COPD)
Brochard, 1995 [9] n = 84	COPD/ICU	RCT	Improvement of ABG Reduction of ETI (74 % to 26 %), of complications, LOS Reduction in mortality
Barbé, 1996 [21] n= 24	COPD/ emergency ward	RCT	No benefit of NIV ***Note:*** *no patient required ETI*
Angus, 1996 [10] n = 17	COPD NIV vs doxapram	RCT	Improvement in ABG
Celikel, 1998 [11] n = 30	COPD	RCT	Improvement of ABG Reduction of criteria for ETI, of LOS
Confalonieri, 1999 [40] n = 56	Community-acquired pneumonia – 41% of COPD/ICU	RCT	Improvement of ABG Reduction of ETI (50 % to 21 %), of complications, of ICU stay Improvement in 2 month survival for COPD (38% vs 89 %)
Plant, 2000 [12] n = 236	COPD / ward	RCT	Improvement of ABG Reduction of criteria for ETI Reduction in mortality
Girou, 2000 [45] n = 100	COPD and cardiogenic pulmonary edema/ICU	Case / control study	Reduction in complications (infections) and in mortality

Table 1. *Continued*

Author, year [ref] Number of pts	Population/ Location	Type of study	Conclusions for NIV
Conti, 2002 [15] n = 49	COPD admitted to the ICU (late NIV) need for ventilation:	RCT	Reduction of ETI (48 % vs 100%) Similar ICU outcome Fewer long-term readmissions (65 % vs 100 %)
Long-term follow-up			
Vitacca, 1996 [16] n = 57	COPD	NonR CT	Better survival at one year follow-up (30% vs 63%)
Confalonieri, 1996 [18] n = 48	COPD	Casecontrol study	Better survival at one year follow-up (50 % vs 71 %)
Bardi, 2000 [17] n = 30	COPD	NonR CT	Better survival at one year follow-up
Post-extubation			
Hilbert, 1998 [55] n = 60	COPD with post extubation respiratory distress	Case-control study	Reduction in ETI
Nava, 1998 [59] n = 50	Deliberate shortening of MV after 48 hours	RCT	Improvement of weaning success Reduction of LOS, of complications Reduction in mortality
Girault, 1999 [60] n = 33	Deliberate shortening of MV after 4–5 days	RCT	Feasibility No change in outcome Longer duration of ventilation with NIV
Carlucci, 2002 [58]	COPD with post extubation respiratory distress	RCT	Lower ETI rate (6 vs 25%) Reduction of LOS and mortality (9 vs 35%)

MV: mechanical ventilation; *ETI*: endotracheal intubation; *RCT*: randomized controlled trial; non *RCT*: non-randomized controlled trial; *LOS*: length of stay; *ICU*: Intensive care unit ; *PSV*: pressure support ventilation; *ACV*: Assist-control ventilation; *ABG*: Arterial blood gases

muscle fatigue. During these episodes, severe gas exchange deterioration accompanies a worsening of the clinical condition, with dyspnea, right ventricular failure, and encephalopathy. This vicious circle can be stopped by NIV, which allows the patient to take deeper breaths with less effort [1, 2]. NIV with two levels of pressure (pressure support [PSV] and PEEP) delivers a positive inspiratory pressure in synchrony with the patient's inspiratory effort, while maintaining a lower level of pressure during expiration allows to counterbalance the effects of dynamic hyperinflation, which result in a positive residual alveolar pressure at the end of expiration.

Several studies have demonstrated that NIV reverses the clinical abnormalities related to hypoxemia, hypercapnia, and acidosis [1, 3].

Clinical Trials Evaluating Need of Intubation And Outcome

Acute exacerbation of COPD is a frequent reason for hospital and ICU admission, and the efficacy of NIV in this situation has been extensively studied. A recent international consensus conference recommended that NIV be considered as a first-line treatment in these patients [4] and the British Thoracic Society Guidelines recommend that every hospital should be able to deliver NIV on a 24 hour-a-day basis in this indication [5]. In 1990, a case-control study had first demonstrated that NIV could markedly reduce the need for endotracheal intubation [1]. Subsequently, several prospective randomized trials confirmed that NIV reduces the need for endotracheal intubation and the rate of complications, shortens length of stay, and improves survival in patients with COPD [6-11]. A major reduction in the need for endotracheal intubation was found by Kramer et al. [8]. In this study, 74% of patients had COPD and the reduction in intubation rate in this group was from 67 to 9%. Two studies, conducted in the United Kingdom, showed the efficacy of NIV out of the ICU [6, 12]. In the largest study in the ICU, in which 85 patients with COPD were randomized to treatment with or without facemask PSV [9], the endotracheal intubation rate was 74% in the controls with standard medical treatment as compared to only 26% in the NIV group. This reduction was associated with fewer complications during the ICU stay, a reduced length of hospital stay, and, more importantly, a significant reduction in mortality rate (from 29 to 9%). The overall decrease in mortality was ascribable to reductions in the need for endotracheal intubation and in various ICU-related complications. A prospective, multicenter randomized trial conducted in the UK by Plant et al. compared standard therapy alone (control group) with NIV in 236 COPD patients admitted to general respiratory wards for acute respiratory failure [12]. The failure rate (reaching criteria for ETI) was higher in the control group (27% vs. 15%), and NIV was associated with a lower in-hospital mortality rate. Because of admission policy in the UK, all patients who failed NIV were not transferred to an ICU and for this reason the results may not be extrapolated to all kinds of medical institution. The authors stressed the fact that for the most severe patients (pH <7.30 on admission) the benefit of delivering NIV out of the ICU became marginal, with a high mortality rate. These patients would probably have benefited from an early ICU admission for timing NIV delivery.

These studies indicate that early NIV to prevent further deterioration must become an important part of the first-line therapy of acute exacerbation of COPD [13].

A very low pH, marked alteration in mental status when NIV is started, and presence of comorbidities or a high severity score characterize patients who experience NIV failure [14]. Several of these factors seem to indicate that a late delivery of NIV in the course of the exacerbation reduces the likelihood of success. Every effort should be made to deliver NIV early and close monitoring is, therefore, in order when NIV is started late. In addition, a recently published randomized controlled trial indicates that the efficacy of NIV is diminished when this therapy is applied lately in the course of the exacerbation. Indeed, Conti et al. showed a reduction of intubation from 100 to 52%, which was associated with only marginal short-term benefits. NIV was applied to patients with COPD who had stayed a mean of 14 hours in the emergency ward before being admitted to the ICU at the time they needed intubation [15]. Interestingly, there were still significant long-term benefits associated with the use of NIV such as a decrease in the readmission rate.

Clinical trials Evaluating Long-term Survival

Three studies have suggested that the use of NIV is associated with a better one-year survival compared to a standard ICU therapy [16, 17] or compared to invasive mechanical ventilation [18].

Clinical Trials Evaluating Location of Application of NIV

The two studies by Bott et al. and by Plant et al. were performed in the respiratory ward, with a training period of 8 hours over the three months preceding the study for the latter study [6, 12]. During the study, one hour per month on average was deemed necessary in each center to maintain the level of expertise of the personnel. One study was performed in the emergency ward but patients included had a very low severity [21]. In another study in the emergency ward, some patients with COPD were included [22]. The results of this study suggested that NIV could have inappropriately delayed endotracheal intubation. However, the small samples in this study, some imbalance between groups, and the lack of precise description of NIV settings make it difficult to draw conclusion from this study.

The feasibility of treating patients with COPD out of the ICU has been demonstrated, but applicability of the results need to take into account the need for training personnel.

Other management strategies associated with NIV

1. Negative pressure ventilation: This technique is only available in very few centers in the world. Its efficacy for treatment of acute exacerbations of COPD

seems to be superior in terms of outcome than a traditional approach with invasive mechanical ventilation [19], and may be similar to face mask NIV [20].
2. Helium-oxygen mixture: The use of a helium-oxygen mixture seems very promising during NIV in patients with COPD [23, 24]. Several randomized controlled trials are in progress to test the hypothesis that this gas mixture could increase the success rate of this technique.

Non-invasive Ventilation in Cardiogenic Pulmonary Edema (Table 2)

Studies mixed patients with different etiologies for cardiac failure. The results may differ, however, in case of ischemic heart failure

Continuous positive airway pressure (CPAP) raises intrathoracic pressure, decreases shunting, and improves arterial oxygenation and dyspnea in these patients [25]. Interestingly, CPAP can lessen the work of breathing substantially and improve cardiovascular function by decreasing the left ventricular afterload in non-preload-dependent patients [26]. Pressure support plus PEEP induces similar pathophysiological benefits.

Most patients with cardiogenic pulmonary edema improve rapidly under medical therapy. A few, however, develop acute asphyxic respiratory distress and require ventilatory support until the medical treatment starts to work. This may be particularly common in elderly patients with heart disease and in patients with concomitant chronic lung disease [27]. Several NIV modalities have been tried successfully, the goal being to avoid endotracheal intubation.

Clinical Trials Comparing CPAP or Pressure Support Plus PEEP

Randomized trials comparing either CPAP or pressure support plus PEEP to standard medical therapy found closely similar results with the two techniques in terms of improvement in arterial blood gases and breathing rate. Both CPAP and pressure support plus PEEP significantly reduced the endotracheal intubation rate rate [25, 28-30]. Two studies, however, indicate a need for caution. One compared pressure support plus PEEP and CPAP [31]. Acute myocardial infarction was more common in the pressure support plus PEEP group than in the CPAP group and it remains unclear whether this should be ascribed to a randomization bias or to a deleterious effect of pressure support plus PEEP itself. A higher rate of acute myocardial infarction was not found in the NIV arm of a randomized controlled trial with pressure support and PEEP, nor in the observational studies [32, 33]. The second study compared intravenous bolus therapy of high-dose nitrates, to conventional medical therapy (a different medical therapy) and pressure support plus PEEP. The first of these two treatments was far more effective clinically than NIV and resulted in a better outcome [34]. These two studies draw attention to the vulnerability of patients with cardiogenic pulmonary edema, particularly those with ischemic heart disease. They indicate that both appropriate drug therapy and

Table 2. Main studies of the efficacy of non-invasive ventilation (NIV) in patients with cardiogenic pulmonary edema

Author, year [ref] Number of patients	Mode of ventilation	Type of study	Conclusions for NIV
Rasanen, 1985 [28] n = 40	CPAP	RCT	Improvement in physiological parameters in "treatment failure" Reduction of ETI (65% vs 35%, p = 0.06)
Bersten, 1991 [29] n = 39	CPAP	RCT	Improvement in physiological parameters Reduction of ETI (35 % to 0%) and ICU stay
Lin, 1995 [25] n = 100	CPAP	Case control study	Improvement in physiological parameters Reduction in "treatment failure criteria" and ETI
Mehta, 1997 [31] n = 27	CPAP vs PSV + PEEP	RCT	Larger improvement in physiological parameters with PSV Higher rate of AMI with PSV (71% vs 38%)
Rustherholtz, 1999 [32] n = 26	PSV + PEEP	Cohort	Low failure rate (21 %). Success in hypercapnic patients. Failure for AMI patients
Hoffmann, 1999 [33] n = 29	PSV + PEEP	Cohort	Low failure rate (1/29)
Masip, 2000 [30] n = 40	PSV + PEEP	RCT	Improvement in physiological parameters Reduction of ETI (5% vs 33 %) and ICU stay
Sharon, 2000 [34] n = 40	PSV + PEEP Vs High doses of nitrates	RCT	More ETI and complications with NIV (85% vs 25% of failure) *Note*: medical therapy was different

MV: mechanical ventilation; *ETI*: endotracheal intubation; *RCT*: randomized controlled trial; non *RCT*: non-randomized controlled trial; *LOS*: length of stay; *ICU*: Intensive care unit ; *PSV*: pressure support ventilation; *ACV*: Assist-control ventilation; *ABG*: Arterial blood gases; *PEEP*: positive end-expiratory pressure; *CPAP*: continuous positive airway pressure; *AMI*: acute myocardial infarction.

close monitoring are in order when using any form of NIV, especially in patients with ischemic heart disease.

Ventilatory support seems to be a useful adjunct to medical treatment in case of asphyxic pulmonary edema, but caution is needed in case of ischemic heart failure when using NIV.

Non-invasive Ventilation in Hypoxemic Respiratory Failure (Table 3)

The studies include very different etiologies causing hypoxemic respiratory failure.

Clinical Trials Evaluating CPAP

A recent investigation evaluated whether facemask CPAP produced physiologic benefits and reduced the need for endotracheal intubation in patients with acute lung injury (ALI) [35]. Despite an early favorable physiological response to CPAP in terms of comfort and oxygenation, no differences were found in the need for endotracheal intubation, in-hospital mortality, or length of ICU stay. In addition, the use of CPAP was associated with more complications, including stress ulcer bleeding and cardiac arrest at the time of endotracheal intubation. These results suggest that CPAP alone cannot be recommended to avoid endotracheal intubation in patients with ALI. Its use should be limited to a short initial period of time if no other method is available.

Clinical Trials Evaluating Pressure Support and PEEP

Until the late 1990s, the most convincing successes with NIV were obtained in patients with acute respiratory acidosis in whom hypoxemia was not the main reason for respiratory failure. One randomized controlled trial by Wysocki et al. found no benefit of NIV in patients with no previous history of chronic lung disease, except in the subgroup of patients who developed acute hypercapnia [36]. However, the beneficial results of NIV have now been extended to different forms of hypoxemic respiratory failure with carefully selected patients [37-39]. Recently, studies have shown that, in selected patients, NIV may reduce the need for intubation and improve outcomes [37-42]. One randomized controlled study by Antonelli et al., showed marked benefits of NIV using pressure support and PEEP in hypoxemic patients free from COPD, hemodynamic instability or neurological impairment, who were randomized when they reached pre-defined criteria for intubation [37]. Improvements in oxygenation were similar with the non-invasive or the invasive approach. Despite a 30% failure rate, patients treated with NIV had shorter duration of ventilation and ICU stay and experienced fewer complications. Thus, NIV can be effective in selected patients with hypoxemic respiratory failure but with no hemodynamic or mental impairment. Other randomized con-

Table 3. Main studies of the efficacy of non-invasive ventilation (NIV) in patients with hypoxemic respiratory failure

Author, year [ref] Number of pts	Population/ Location/Mode of ventilation	Type of study	Conclusions for NIV
Wysocki, 1995 [36] n = 41	COPD/ICU	Case-control study	No benefit of NIV Except in the sub-group with acute hypercapnia (n = 17)
Wood, 1998 [22] n = 27	RCT/ Emergency department	RCT	No benefit of NIV Trends for poorer outcome (p=0.1) *Note*: imbalance in randomisation, small samples
Antonelli, 1998 [37] n = 64	ALI/ICU/PSV + PEEP	RCT	Improvement of ABG Reduction of ETI (10/32 vs 100%), of complications, ICU stay Trends for better survival
Antonelli, 2000 [38] n = 40	Organ transplant/ ICU/ PSV + PEEP	RCT	Improvement of ABG Reduction of ETI (20% vs 70%), of complications Reduction in ICU mortality (20% vs 50%)
Delclaux, 2001 [35] n = 123	ALI/ICU/CPAP	RCT	No benefit of CPAP More adverse events (p = 0.01)
Martin, 2001 [39] n = 61	Mixed/ICU/ PSV + PEEP	RCT	Improvement of ABG Reduction of ETI (21 % to 6% ETI/100 days), of LOS
Hilbert, 2001] [41] n = 52	Cancer, hematologic malignancies/ ICU/PSV + PEEP	RCT	Improvement of ABG Reduction of ETI (77% to 41%), of complications Reduction in ICU and hospital mortality (81% to 50%)
Azoulay, 2001 [46] n = 237	Cancer, hematologic malignancies/ ICU/PSV + PEEP	Cohort, case-control study	Reduction of ETI, improved survival
Auriant, 2001 [49] n = 48	Lung surgery/ ICU/PSV + PEEP	RCT	Improvement of ABG Reduction of ETI (50% to 21 %), of complications Reduction in mortality (37.5% to 12.5%)
Rocco, 2001 [50] n = 21	Bilateral lung transplant/ ICU/PSV + PEEP		Low rate of complications and death (18/21 with no need for ETI)

Table 3. *Continued*

Author, year [ref] Number of pts	Population/ Location/Mode of ventilation	Type of study	Conclusions for NIV
Keenan, 2002 [56] n = 81	Post extubation respiratory distress	RCT	No benefit of NIV
Confalonieri, 2002 [47] n = 24	Pneumocystis carinii pneumonia	Case-control study	Improvement of ABG Reduction of ETI, of complications Reduction in mortality
Ferrer, 2002 [70] N= 105	Hypoxemic acute respiratory failure	RCT	Improvement of ABG Reduction of ETI (13 vs 29%), of septic shock Reduction in ICU mortality (18 vs 39%) and at 90 days.
Community acquired pneumonia			
Confalonieri, 1999 [40] n = 56	Community acquired pneumonia some COPD	RCT	No benefit in non COPD
Jolliet, 2001 [52] n = 24	Community acquired pneumonia	Cohort study	High intubation rate
Antonelli, 2001 [43]	Community acquired peumonia	Prospective observational study	ARDS and pneumonia: risk factors for failure
Domenighetti, 2002 [53] n = 18	Community acquired pneumonia	Cohort	Less efficacy of NIV in CAP than in pulmonary edema

trolled trials have confirmed these beneficial results ([18, 39]). As discussed later, however, patients with severe community-acquired pneumonia and hypoxemia may not represent a good indication for NIV [43].

Clinical Trials Evaluating Different Subgroups of Hypoxemic Respiratory Failure

Immunosuppression: Because one of the main benefits of NIV may be a reduction in infectious complications [44, 45], patients at high risk for nosocomial infection when mechanically ventilated may be particularly likely to benefit from NIV.

Several recent trials have shown major benefits of NIV as a preventive measure during episodes of acute hypoxemic respiratory failure in solid organ-transplant patients or in patients with severe immunosuppression, particularly related to hematological malignancies and neutropenia [38, 41, 46]. The rates of intubation and of infectious complications, length of stay, and mortality were significantly reduced by the use of NIV. Because of the high risk associated with endotracheal intubation in patients with severe immunosuppression, NIV seems to be of particular interest in this group [38, 41, 46].

Along a similar line, patients suffering from pneumocystis cariniii pneumonia during the course of human immunodeficiency virus (HIV) infection seem to benefit from NIV, as shown in a case-control study by Confalonieri et al. [47].

In immunosuppressed patients, careful selection of patients and early onset of NIV are necessary to avoid endotracheal intubation and to be beneficial to the patients.

Lung surgery: Several studies looked at the use of NIV after lung surgery [48-50]. Auriant et al. conducted a randomized controlled trial in patients who experienced respiratory distress after lung resection [49]. The reason why intubation should be avoided is the very poor outcome of patients who usually require reintubation shortly after lung surgery. A reduction in endotracheal intubation and a clear benefit in terms of hospital survival was observed with NIV. A non-controlled study suggested interesting results of using NIV in patients with respiratory distress after bilateral lung transplant [50]. NIV seems to be useful tool to prevent reintubation after lung surgery.

Community-acquired pneumonia: Confalonieri et al, in a randomized controlled trial showed major benefit of NIV in patients with community-acquired pneumonia, by reducing the number of endotracheal intubations, complications, and length of stay [40]. This benefit, however, was almost entirely explained by the subgroup of patients with COPD. The same group showed in a case-control study a benefit of NIV in patients with pneumocystis carinii pneumonia, reducing intubation, length of stay, and mortality [47]. Other studies with severely hypoxemic patients with pneumonia have shown a high rate of failure in this subgroup [43, 51-53]. More data are necessary in this group of patients and it is difficult today to recommend NIV for severe community-acquired pneumonia.

Post-extubation respiratory failure: The physiological rationale for this approach was recently demonstrated by Vitacca et al. [54]. One case-control study by Hilbert et al., suggested favorable effects of NIV to prevent reintubation in patients with COPD [55]. The prospective randomized trial by Keenan et al. was performed in all patients experiencing post-extubation respiratory distress. The study by Keenan did not find any benefit of NIV [56]. Another prospective randomized trial did not find any preventive effect of NIV [57]. In contrast, another randomized trial in COPD showed beneficial effects [58]. The question of the efficacy of NIV in preventing reintubation in all patients, therefore, remains open. The benefits of this technique may be observed only in patients with COPD.

Non-invasive Ventilation to Shorten Invasive Ventilation (Table 1)

A number of patients with COPD still require endotracheal intubation because they fail NIV, have a contraindication to NIV (such as a need for surgery), or have criteria for immediate intubation. However, when there is a need for prolonged ventilatory assistance, these patients can be switched to NIV after a few days of endotracheal intubation [59, 60]. This approach was shown to reduce the intubation time in two randomized controlled trials [59, 60]. In a study by Nava et al., complications were reduced and survival rates at day 60 were higher with this approach [59]. This benefit was not found in another study, in which the total length of ventilation was increased in the NIV arm [60]. Further studies on this potentially attractive indication for NIV are, therefore, needed.

Non-invasive Ventilation for Other Conditions

Patients not to be Intubated

Several reports have described the effects of NIV in patients with acute respiratory failure who were poor candidates for endotracheal intubation because of advanced age, debilitation, or a 'do not resuscitate` order [61, 62]. The overall success rate in these reports approximated 60 to 70 %. Gas exchange improved rapidly in successfully treated patients. Even when respiratory failure did not resolve, NIV provided symptomatic relief from dyspnea.

Patients with Acute Severe Asthma

A few studies indicate that NIV can be used in asthmatic patients [51, 63]. Two cohort studies described the beneficial short-term effects of using NIV in asthmatic patients deteriorating despite medical therapy [51, 63].

Fiberoptic Bronchoscopy

Several studies have suggested or demonstrated that fiberoptic bronchoscopy could be performed under delivery of NIV (CPAP for hypoxemic patients or pressure support + PEEP) [67–69] and that this approach improved the tolerance of bronchoscopy and could also prevent subsequent complications and need for endotracheal intubation [68].

Non-invasive Ventilation with Other Modes

Several recent studies have compared PSV to proportional assist ventilation [64–66]. The efficacy of the two techniques seemed similar, although very few patients required intubation. Studies in more severe patients are needed.

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