

Should a Patient Be Extubated and Placed on Noninvasive Ventilation After Failing a Spontaneous Breathing Trial?

Scott K Epstein MD and Charles G Durbin Jr MD FAARC

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Between 15% and 35% of mechanically ventilated patients fail an initial spontaneous breathing trial. For these patients, 40% of total time on mechanical ventilation is consumed by the weaning process (60% for patients with chronic obstructive pulmonary disease). Longer duration of mechanical ventilation is associated with higher risk of complications and probably with higher mortality. Noninvasive ventilation (NIV) has been used successfully in some forms of acute respiratory failure. Randomized controlled trials have indicated that, in selected patients with chronic obstructive pulmonary disease and acute-on-chronic respiratory failure, NIV can facilitate weaning, reduce the duration of invasive mechanical ventilation, decrease complications, and reduce mortality, compared to weaning on continued invasive ventilation. However, extubation failure resulting in re-intubation is associated with higher mortality, and this mortality risk increases with delay of re-intubation and may not be prevented by application of NIV. Patients extubated to NIV must have careful monitoring by skilled clinicians able to provide timely re-intubation if the patient shows signs of intolerance or worsening respiratory failure. *Key words: extubation; mechanical ventilation; extubation failure; re-intubation; noninvasive ventilation; weaning.* [Respir Care 2010;55(2): 198–206. © 2010 Daedalus Enterprises]

Scott K Epstein MD is affiliated with the Office of Educational Affairs, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts. Charles G Durbin Jr MD FAARC is affiliated with the Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia.

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Correspondence: Scott K Epstein MD, Office of Educational Affairs, Tufts University School of Medicine, 136 Harrison Avenue, Sackler 317, Boston MA 02111. E-mail: scott.epstein@tufts.edu.

Introduction

A large body of evidence supports the use of noninvasive ventilation (NIV) to treat various forms of acute respiratory failure (ARF). Randomized controlled trials (RCTs) have indicated that NIV improves outcome in patients with exacerbation of chronic obstructive pulmonary disease (COPD), acute cardiogenic pulmonary edema, and immunocompromised patients with hypoxemic respiratory failure and diffuse infiltrates. Another application of NIV is to shorten the duration of mechanical ventilation. Specifically, NIV can be used to facilitate weaning (earlier extubation),¹⁻³ to prevent re-intubation in post-surgical respiratory distress, and in patients with respiratory failure after planned extubation.⁴⁻⁷ In the latter instance NIV has been used immediately after extubation in patients at elevated risk for extubation failure.^{5,7} On the other hand, NIV has been applied in patients who developed overt respiratory failure after extubation, with the goal of avoiding re-intubation.^{4,6} Of all these uses, extubation and application of NIV in the patient who has failed a spontaneous breathing trial (SBT) has proved to be the most controversial. Yet, in one 22-bed medical intensive care unit (ICU), 30% of NIV applications for ARF were for facilitating weaning or after extubation.⁸

Observational and uncontrolled studies have indicated the potential role of NIV to facilitate weaning from mechanical ventilation.⁹⁻¹¹ RCTs have better defined the patient population and criteria for effective NIV weaning in patients who fail SBT.

Pro: A Patient Who Fails a Spontaneous Breathing Trial Should Be Extubated to Noninvasive Ventilation for Weaning

Rationale for Facilitating Weaning

Although some cases of ARF can be successfully managed with NIV, the vast majority of cases are treated with intubation and mechanical ventilation. Intubation and mechanical ventilation are associated with numerous complications, including upper-airway injury, gastrointestinal bleeding, thromboembolism, and ventilator-associated pneumonia.¹² Complications are more common when mechanical ventilation is prolonged—a not uncommon occurrence. For example, in one large study of patients intubated with ARF, approximately 25% required ≥ 7 days of mechanical ventilation, and 10% remained intubated more than 21 days.¹³ Prolonged intubation and mechanical ventilation are clinically important because mortality increases with increasing duration.¹³

Determining readiness for weaning consists of assessing the adequacy of oxygenation (eg, ratio of P_{aO_2} to fraction of inspired oxygen [F_{IO_2}] > 150 mm Hg on positive end-

expiratory pressure [PEEP] of 5 cm H_2O), hemodynamics (eg, adequate blood pressure with minimal need for vasopressors), and, in some studies, satisfactory weaning predictors (eg, ratio of frequency to tidal volume < 100 breaths/L/min). Sixty-five to 85% of patients who satisfy the readiness criteria will pass an SBT, conducted on no or minimal ventilatory support, and go on to extubation.¹⁴⁻¹⁸ The remaining 15–35% of patients require a more prolonged weaning process. Importantly, a substantial proportion of ventilator time is taken up by weaning efforts. In one study, 40% of ventilator time was devoted to weaning, and 60% in patients with COPD.¹⁹

Unnecessarily delaying extubation results in adverse outcomes. In a prospective observational cohort study with 136 brain-injured patients, the investigators determined readiness for extubation each day.²⁰ Twenty-seven percent of the patients had delayed extubation (extubation ≥ 48 h after satisfying readiness criteria), which was associated with longer ICU and hospital stay, greater risk of pneumonia, and greater hospital mortality.

Rationale for Noninvasive Ventilation to Facilitate Weaning

NIV has been used to successfully treat several forms of ARF. In patients with COPD and acute-on-chronic respiratory failure, NIV results in a 28% risk reduction in the need for intubation, a 10% risk reduction in mortality, and 4.6-day shorter stay.²¹ RCTs have indicated that NIV can improve outcome in some patients with acute hypoxemic respiratory failure, including immunocompromised patients and heterogeneous populations with diffuse pulmonary infiltrates.²²⁻²⁴ In those settings NIV decreased the need for intubation, decreased complications, and improved survival. NIV also reduced the need for intubation in acute cardiogenic pulmonary edema.²⁵

In the above instances the success of NIV probably hinged on its ability to reverse the underlying pathophysiology of those forms of ARF. The pathophysiology of weaning failure, studied by comparing patients who fail an SBT to those who succeed, is best described as an imbalance between respiratory load and capacity. This occurs when there is increased work of breathing (WOB) (resistive and elastic), increased intrinsic PEEP, or abnormal gas exchange. The latter occurs when there is respiratory muscles weakness. The load/capacity imbalance may manifest as rapid shallow breathing. Abnormal cardiovascular response can also result in weaning failure. The physiologic effects of NIV can correct many of these abnormalities. NIV decreases rapid shallow breathing, improves gas exchange, improves alveolar ventilation, and decreases WOB.^{26,27} In the setting of COPD and dynamic hyperinflation, NIV with PEEP can offset intrinsic PEEP by making it easier to trigger the ventilator. Specifically, applied

Table 1. Advantages of Removing the Endotracheal Tube

Eliminates the work of breathing imposed by the tube
Decreases the risk of nosocomial infection and pneumonia
Improves communication
Improves patient comfort
Decreases need for sedation
Allows effective cough
Improves mucociliary secretion clearance
Improves sinus drainage

PEEP decreases the WOB and reduces the elevated inspiratory threshold load.^{26,27}

Weaning can be limited by the cardiovascular system by several mechanisms, including an inability to increase cardiac output to respond to the metabolic stress of weaning, precipitating ischemia, and the increase in left-ventricular preload and afterload that occurs when shifting from positive to negative (spontaneous breathing) intrathoracic pressure. In a study of COPD patients, placing the patients on a T-piece resulted in an almost immediate rise in the transmural pulmonary artery occlusion pressure.²⁸ The positive intrathoracic pressure associated with NIV can prevent the development of these unfavorable loading conditions.

Additional advantages occur when NIV allows for removal of the endotracheal tube (ETT) (Table 1). Conversely, in the absence of the ETT there is no guaranteed minute ventilation. NIV does not enhance airway clearance because it does not provide the access of an ETT to suction airway secretions when these are abundant or when cough strength is poor. Also, sedating an agitated mechanically ventilated patient can be challenging without the airway protection of an ETT.

Noninvasive Ventilation to Facilitate Weaning From Mechanical Ventilation: Observational Studies

Observational studies conducted in the 1990s suggested that NIV could facilitate weaning. The initial reports focused on patients who had prolonged mechanical ventilation. NIV was often applied in patients ventilated via tracheostomy.^{10,11,29}

Goodenberger et al reported successful discontinuation of tracheostomy ventilation by using nasal NIV in 2 patients with neuromuscular respiratory failure.²⁹ Udwardia and co-workers investigated the use of NIV in 22 patients ventilated for a median of 31 days, with either an ETT or tracheostomy, and who had been difficult to wean.¹¹ The patients had been intubated for acute cardiopulmonary disease ($n = 13$) or postoperative respiratory failure ($n = 9$). Underlying conditions included chest wall abnormalities or primary pulmonary disease ($n = 9$), cardiac disease in the setting of additional pulmonary disease ($n = 7$), and

neuromuscular disease ($n = 6$). Using NIV applied via nasal mask, 18 patients (82%) were successfully weaned from mechanical ventilation after a median of 11 days (range 8–13 d).¹¹ In another study, NIV was used to wean 14 patients with respiratory disease and who had failed to wean.¹⁰ Twelve patients had been ventilated for ARF (8 had COPD, and 4 had neuromuscular or chest wall disease), and 2 were ventilated for postoperative respiratory failure. NIV via nasal mask resulted in successful weaning in 13 of 14 patients (93%).

Kilger and colleagues used NIV in 15 patients intubated for ARF and who were extubated after satisfying criteria not typically indicative of readiness for extubation. In other words, NIV was used to facilitate earlier weaning and extubation.³⁰ The early extubation criteria included: $P_{aO_2} \geq 40$ mm Hg on F_{IO_2} of 0.21, $P_{aCO_2} \leq 55$ mm Hg, $pH > 7.32$, respiratory rate ≤ 40 breaths/min, tidal volume ≥ 3 mL/kg, frequency/tidal-volume ratio ≤ 190 breaths/L/min, and negative inspiratory force ≥ 20 cm H_2O . Two NIV modes were used (CPAP of 5 cm H_2O , and pressure-support ventilation of 15 cm H_2O), for a median of 2 days. Both NIV modes improved physiologic variables, including P_{aO_2} and tidal volume, and decreased respiratory rate. In pressure-support mode, NIV also decreased P_{aCO_2} and increased minute ventilation and pH. Two of 15 patients in the study required re-intubation: a rate lower than expected.

Noninvasive Ventilation to Facilitate Weaning From Mechanical Ventilation: Randomized Controlled Trials

There are now 8 reported RCTs of NIV to facilitate weaning in patients who failed at least one SBT, including 3 presented only in abstract form, and another published in the Chinese language literature.^{1-3,31-35} (Table 2) Four additional RCTs published in the Chinese language included patients intubated with COPD and pneumonia, who were randomized to NIV versus continued invasive mechanical ventilation after pulmonary infection was thought to be under control.³⁶ These studies differed fundamentally from the studies described in Table 2, in that the patients did not fail an SBT before being randomized.

The first RCT was conducted by Nava et al, with 68 COPD patients with severe acute-on-chronic respiratory failure.³ At presentation these patients had an average P_{aCO_2} of 90 mm Hg, and approximately 40% were intubated after failing NIV. After intubation, patients were initially ventilated with continuous mandatory ventilation and received heavy sedation and neuromuscular blockade (Fig. 1). Approximately 12 hours later the patients were changed to pressure-support ventilation. Approximately 48 hours after intubation, a 2-hour T-piece SBT was performed. Eighteen patients tolerated the T-piece SBT and were extubated.

Table 2. Randomized Controlled Trials of Noninvasive Ventilation to Allow Earlier Extubation

First Author	Year	Patients (n)	Percent With COPD	Benefits of NIV
Nava ³	1998	50	100	↓ Mechanical ventilation days ↓ ICU stay ↓ 60-d weaning failure ↓ Pneumonia ↑ 60-d survival
Girault ²	1999	53	76	↓ Duration of intubation
Ferrer ¹	2003	43	58	↓ Duration of intubation ↓ ICU stay ↓ Hospital stay ↓ Tracheostomy ↓ Nosocomial pneumonia ↑ ICU survival ↑ 90-d survival
Hill ³²	2000	21	33	↓ Duration of intubation
Chen ³¹	2001	24	100	↓ Duration of intubation ↓ Hospital stay ↓ Nosocomial pneumonia
Rabie ³⁴	2004	37	100	↓ Duration of intubation ↓ Weaning failure ↓ ICU stay ↓ Hospital stay ↓ Nosocomial pneumonia
Trevisan ³³	2008	65	35*	↓ Complications
Girault ³⁵	2009	208	100	None

* Included patients with chronic obstructive pulmonary disease (COPD) and asthma.
ICU = intensive care unit

The 50 patients who failed the T-piece SBT were randomized. Twenty-five patients remained intubated and underwent weaning via gradual reduction in pressure support, with monitoring of arterial blood gas values, and with a respiratory rate goal of < 25 breaths/min. Intubated patients received twice-daily SBTs on CPAP or T-piece. The other 25 patients were extubated to NIV delivered with an oronasal interface and an ICU ventilator in pressure-support mode, with a weaning protocol similar to that used in the invasive-ventilation group. The NIV patients had better outcomes, including shorter mechanical ventilation (10 d vs 17 d) and ICU stay (15 d vs 24 d). The NIV patients were more likely to succeed in weaning (88% vs 68%) and to be alive at 60 days (92% vs 72%). None of the NIV patients developed pneumonia, compared to 25% of those who remained intubated. NIV complications were common but not severe, consisting predominantly of nasal-bridge abrasions. This study is instructive in demonstrating that initial NIV failure does not preclude NIV success later.

The second RCT, by Girault et al, used a design similar to that of Nava et al (Fig. 2). Girault et al randomized

33 patients with acute-on-chronic respiratory failure and who failed a 2-hour T-piece SBT, to either extubation to NIV or continued invasive weaning (pressure-support mode).² Unlike in the Nava et al study, NIV could be delivered either via nasal or oronasal mask, and either pressure-support ventilation or continuous mandatory ventilation. The principal benefit of NIV weaning was a 3-day reduction in duration of intubation (4.6 d vs 7.7 d). There were no differences in weaning success (77% vs 75%), ICU stay (12 d vs 14 d), hospital stay (27 d vs 28 d), need for re-intubation (23% vs 25%), or 3-month survival (100% vs 88%). In contrast to the findings from Nava et al, overall mechanical ventilation duration (defined as time intubated plus time on NIV) was higher in the NIV group (16.1 d vs 7.7 d). Seven patients were discharged on nocturnal NIV.

Ferrer et al applied a different design in randomizing 43 patients (77% with chronic lung disease) who had failed at least 3 SBTs.¹ NIV was applied for at least 24 hours, using a bi-level mode (inspiratory pressure 10–20 cm H₂O, expiratory pressure 4–5 cm H₂O) delivered via nasal or oronasal interface. The study was powered to detect a reduction in the duration of invasive ventilation, and was stopped after the first interim analysis. Compared to invasive weaning, NIV weaning was associated with significant and substantial reductions in duration of invasive ventilation, duration of ICU and hospital stay, incidence of septic shock and pneumonia, and need for tracheostomy (Table 3). NIV was associated with an approximately 50% reduction in need for re-intubation, although that difference was not statistically significant. NIV weaning was associated with better ICU and 90-day survival.

In a study published only in abstract form, Hill et al screened 303 patients with ARF and identified 45 patients who failed a 30-min T-piece SBT.³² Sixteen were ineligible for randomization because of excessive secretions or abnormal mental status. Of the remaining 29 eligible patients (which was < 10% of the patients screened), 21 were enrolled. Twelve were randomized to weaning via NIV, and 9 to ETT weaning. Four of the 12 NIV patients required re-intubation, whereas 8 of the 9 control patients weaned successfully. There was no difference in hospital survival: 11 of the 12 NIV patients survived, and 8 of the 9 ETT patients survived. NIV was associated with shorter intubation (6.6 d vs 15.2 d).

Chen and colleagues quasi-randomized (allocation based on order) 24 COPD patients who had been intubated for at least 3 days for COPD exacerbation.³¹ As reported by Nava and Ferrer, NIV weaning was associated with less ventilator-associated pneumonia (0/12 vs 7/12, $P = .03$). Chen et al also found that NIV reduced the duration of invasive ventilation (7 d vs 15 d, $P > .05$) and hospital stay (16 d vs 25 d, $P < .05$) after randomization. There

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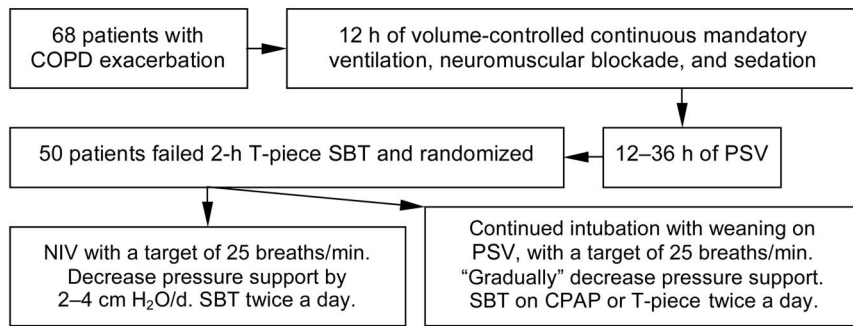


Fig. 1. Design of a randomized controlled trial of noninvasive ventilation (NIV) to wean patients with acute-on-chronic respiratory failure secondary to chronic obstructive pulmonary disease (COPD).³ Fifty patients who failed a T-piece spontaneous breathing trial (SBT) were randomized to continued intubation and weaning with pressure-support ventilation (PSV), or weaning with NIV. CPAP = continuous positive airway pressure.

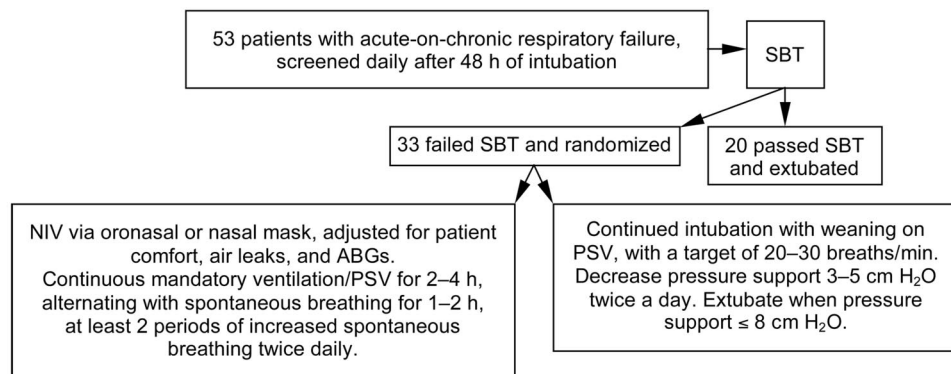


Fig. 2. Design of a randomized controlled trial of noninvasive ventilation (NIV) to wean patients with acute-on-chronic respiratory failure.² Thirty-three patients who failed a T-piece spontaneous breathing trial (SBT) were randomized to continued intubation and weaning with pressure-support ventilation (PSV), or weaning with NIV. ABGs = arterial blood gas values.

Table 3. Results of a Randomized Controlled Trial of Weaning Via Endotracheal Tube Versus Via Noninvasive Ventilation¹

	Weaning Via NIV (n = 21)	Weaning Via Endotracheal Tube (n = 22)	P
Duration of intubation (mean ± SD d)	9.5 ± 8.3	20.1 ± 13.1	.003
ICU stay (mean ± SD d)	14.1 ± 9.2	25.0 ± 12.5	.002
Hospital stay (mean ± SD d)	27.8 ± 14.6	40.8 ± 21.4	.03
Tracheostomy (n, %)	1 (5)	13 (59)	<.001
ICU survival (n, %)	19 (90)	13 (59)	.045
90-d survival (%)	71	41	.044
Nosocomial pneumonia (n, %)	5 (24)	13 (59)	.042
Septic shock (n, %)	2 (10)	9 (41)	.045
Re-intubation (n, %)	3 (14)	6 (27)	.46

NIV = noninvasive ventilation
ICU = intensive care unit

was no statistical difference in mortality (0/12 vs 3/12, $P = .2$).

After the publication of those 5 RCT, Burns and co-workers performed a meta-analysis of NIV versus ETT weaning.³⁷ They noted that the 5 studies encompassed

only 171 patients (81% with COPD) and had design weaknesses; only one study used blinded assessment of outcome and fully controlled for co-interventions; 2 studies did not use a weaning protocol; and 2 did not have re-intubation criteria. Noting those limitations, Burns et al

found that NIV was associated with lower mortality (risk ratio 0.41), less ventilator-associated pneumonia (risk ratio 0.28), shorter mechanical ventilation (-7.3 d), ICU stay (-6.9 d), and hospital stay (-7.3 d). NIV had no effect on the probability of weaning success.

A sixth RCT, published only in abstract form, randomized 37 patients with COPD intubated for acute-on-chronic respiratory failure and who failed a 2-hour SBT.³⁴ The NIV patients were more likely to be successfully weaned and extubated (15/19 vs 12/18), and had shorter intubation (4.8 d vs 8 d), shorter ICU and hospital stay, and less pneumonia.

A seventh RCT, by Trevisan and Vieira, screened 156 patients who were ventilated for ≥ 48 hours and enrolled the 65 patients who failed a 30-min SBT.³³ The patient population differed from those in the studies by Nava, Girault, Ferrer, and Chen, in which 58–100% of the patients had COPD. In contrast, Trevisan and Vieira's patients had COPD or asthma (35%), heart disease (16%), pneumonia, tuberculosis, other respiratory disease (18%), or were post-surgery/thoracic trauma (28%). Thirty-seven patients were randomized to continued intubation with a weaning strategy that employed daily SBTs. The 28 patients randomized to NIV received bi-level positive airway pressure (inspiratory pressure 10–30 cm H₂O) via face mask, with daily weaning carried out by reducing the level of pressure support. In comparing NIV weaning to continued intubation, there were no statistically significant differences in ICU stay (18.9 d vs 20.8 d), hospital stay (34.5 d vs 42.4 d), hospital survival (68% vs 73%), or duration of mechanical ventilation (14.9 d vs 17.3 d). NIV was associated with fewer complications, defined as pneumonia, sepsis, congestive heart failure, and need for tracheostomy (29% vs 76%). Six (21%) of the 28 NIV patients required re-intubation.

Recently, Burns and colleagues updated their meta-analysis, including the 7 studies listed above, one unpublished dissertation, and 4 Chinese studies, totaling 227 COPD patients with pneumonia, that randomized patients after they met criteria indicating control of pulmonary infection, rather than after failure to tolerate an SBT.³⁶ In addition, 3 of these 4 studies differed fundamentally from other studies in that the weaning mode differed in the 2 groups: NIV weaning was conducted with pressure support while invasive weaning was performed with synchronized intermittent mandatory ventilation plus pressure support.³⁶ With these caveats in mind, this meta-analysis³⁶ of 12 studies and 530 patients, principally with COPD, showed that NIV weaning significantly reduced mortality (risk ratio 0.55, 95% CI 0.38–0.79), nosocomial pneumonia (risk ratio 0.29, 95% CI 0.19–0.45), ICU stay (weighted mean difference -6.3 d), hospital stay (-7.2 d), total duration of ventilation (-5.6 d), and duration of invasive ventilation (-7.8 d). NIV had no effect on the percentage of

weaning failures or the need for re-intubation, but was associated with fewer tracheostomies. Burns et al found a nonsignificant benefit from NIV in patients with COPD, based on the 8 studies with exclusively COPD patients, compared to those with mixed populations (the 4 studies with $< 100\%$ COPD patients).

The studies discussed so far indicate that NIV weaning, principally in COPD patients with acute-on-chronic respiratory failure, is associated with better outcomes than is continued intubation. This raises the question of why NIV may be more effective. NIV could be a superior mode of weaning because it is associated with fewer complications. For example, compared to ventilation via ETT, NIV is associated with lower risk of pneumonia and other infections.^{38,39} NIV probably reduces the need for sedation, especially continuous intravenous sedation, a factor associated with longer mechanical ventilation.⁴⁰⁻⁴² Alternatively, NIV may enhance the clinician's ability to identify the patient who, though apparently intolerant of weaning, is in fact ready to be weaned. This might occur if weaning intolerance results from psychological reasons (eg, anxiety) or from the WOB imposed by the ETT. Indeed, in one study, measurement of the imposed WOB allowed identification of patients who could be successfully extubated despite substantial tachypnea and apparent intolerance of a CPAP SBT.⁴³ In these instances there is no direct benefit from NIV; rather, it is the removal of the ETT that discloses that the patient is ready for weaning.

To shed light on this issue, Girault et al recently completed an RCT with 208 patients in 17 centers in France.³⁵ Patients were included if they had been intubated for at least 48 hours with acute-on-chronic respiratory failure, and had failed an SBT of 5–120 min. Patients were randomized into 3 groups: continued intubation with conventional weaning on pressure support ($n = 69$); extubation to NIV ($n = 69$); or extubation to oxygen but without NIV ($n = 70$). There were no differences in weaning failure (predominately re-intubation within 7 d of extubation), complications, ICU or hospital stay, or hospital survival (Table 4). Interestingly, NIV was used effectively as salvage therapy in 14 (45%) of 31 patients weaned invasively and 23 (58%) of the 40 patients extubated to oxygen alone.

When analyzed individually, the majority of the studies cited in the present article found NIV superior to invasive weaning: none found NIV inferior. The latter observation is important, given that mechanical ventilation via NIV is more comfortable than via ETT. Taken together, the RCTs and the meta-analyses by Burns indicate that NIV is an effective tool for facilitating weaning, *but only in a very selected group of patients*, those with acute-on-chronic respiratory failure (eg, COPD exacerbation). NIV's effectiveness in this population is not surprising, given its success as primary therapy in COPD. In addition, NIV appears to be effective in COPD patients at high risk for

Table 4. Comparison of Patients Randomized to Weaning Via Continued Intubation, Extubation to Oxygen Alone, or Extubation to Noninvasive Ventilation³⁵

	Continued Intubation	Oxygen	NIV
Patients (<i>n</i>)	69	70	69
Weaning failure (%)	32	37	33
Complications (%)	51	61	48
ICU stay (mean ± SD d)	7.5	7.5	7.5
Hospital stay (mean ± SD d)	18.5	19.5	17.5
Hospital survival (%)	87	87	77

* Weaning failure was defined as re-intubation or death within 7 d of extubation.
NIV = noninvasive ventilation
ICU = intensive care unit

extubation failure⁴⁴ and those who develop respiratory distress after extubation.⁴⁵

Con: A Patient Who Fails a Spontaneous Breathing Trial Should Not Be Extubated to Noninvasive Ventilation for Weaning

Risks Associated With Failed Extubation

Patients who fail extubation and undergo re-intubation have longer mechanical ventilation, more associated morbidity, and higher mortality than those not requiring re-intubation.^{15,16,46-48} This may be because they had a higher severity of illness at the time of extubation, they experienced worsening respiratory failure while extubated, or they experienced additional injury associated with the re-intubation process. The longer re-intubation is delayed, the higher the mortality.^{16,49-51} In evaluating the impact of re-intubation, a prospective study by Epstein et al found that almost 30% of patients experienced an important complication associated with the re-intubation process. The observed complications included development of pneumonia (18%), arrhythmia (4%), atelectasis or lobar collapse (4%), acute myocardial infarction (3%), and stroke (3%).⁵⁰ Thirty-one (42%) of the 74 re-intubated patients died, versus 12% of the cohort not re-intubated. The proximate cause for re-intubation influenced mortality; respiratory failure was associated with a mortality of 57%, while upper-airway obstruction as a cause was associated with only an 18% mortality (Table 5). The relationship of how soon the patient was re-intubated and mortality was clearly demonstrated (Table 6): patients re-intubated later were more likely to die.

In the study mentioned above by Esteban et al,⁴ 221 patients who developed respiratory failure within 48 hours of extubation were randomized to receive either NIV or standard therapy (supplemental oxygen, respiratory phys-

Table 5. Causes of Extubation Failure⁵⁰

Reason for Re-intubation	Patients <i>n</i> (%)	Deaths <i>n</i> (%)
Respiratory failure	21 (28)	12 (57)
Heart failure	17 (23)	8 (47)
Excessive secretions/aspiration	12 (16)	2 (17)
Upper-airway obstruction	11 (15)	2 (18)
Mental status	7 (9)	3 (43)
Other causes	6 (8)	4 (67)

Table 6. Duration of Extubation Prior to Re-intubation and Mortality⁵⁰

Time to Re-intubation (h)	All Patients <i>n</i> (%) [*]	Non-survivors <i>n</i> (%) [†]
< 13	25 (33)	6 (24)
13-24	18 (25)	7 (39)
25-48	18 (25)	9 (50)
49-72	13 (17)	9 (69)

* Percentage of all patients (*n* = 74) who required re-intubation.

† Percentage of patients who died, compared to all patients reintubated during that time frame.

iotherapy, bronchodilators, and any other therapies dictated by the attending physician). At an interim analysis, NIV was no more successful at preventing re-intubation than was standard therapy: 48% failed in each group. Surprisingly, the NIV group had significantly higher mortality (ICU death rate 25%, versus 14% in the standard-therapy group, relative risk 1.78; 95% CI 1.03-3.20, *P* = .048). This large multinational multi-institutional trial was stopped prematurely at that point because of safety concerns. The time from respiratory failure to re-intubation was significantly shorter in the standard-therapy group (2.5 h vs 12 h), and that difference was believed to contribute to the worse outcomes in the NIV group. The reasons for the higher mortality with later re-intubation are not clear, but this observation is consistent in many reports. When using NIV to prevent intubation, clinicians may be reluctant to accept NIV failure, and the intubation delay may be the cause of increased mortality. This study gives pause to those planning to extubate patients to NIV who repeatedly fail an SBT.

Who May Benefit and Where Should Noninvasive Weaning Be Attempted?

In evaluating the prospective NIV weaning trials described above, Burns and colleagues, in their 2 meta-analyses, concluded that NIV is a promising technique for weaning COPD patients but that there is insufficient evidence of benefit to definitively recommend it.^{36,37} Their

meta-analyses, which included 171 and 530 patients, respectively, in studies of moderate to good quality, consistently showed lower mortality, less nosocomial pneumonia, shorter ICU and hospital stay, and less time intubated on mechanical ventilation when patients who failed weaning were extubated to NIV. They expressed caution at the conclusion of their most recent report and stated:

The evidence of benefit is promising, but additional trials are required to fully evaluate the net clinical benefits on clinical outcomes associated with noninvasive weaning, especially the risks associated with extubation and the impact of re-intubation after a failed attempt at extubation on clinical outcomes.³⁶

The application of NIV as a weaning tool should be considered only in selected patients with acute-on-chronic respiratory failure due to COPD and only applied in a highly monitored environment.

Summary

RCTs indicate that NIV can be used to facilitate the weaning process, *but only in selected patients* with COPD and acute-on-chronic respiratory failure. However, extubation failure resulting in re-intubation is associated with increased mortality. This mortality risk increases with delay of re-intubation and may not be prevented by application of NIV. To be used safely and effectively in patients with COPD, NIV should be applied only when SBT criteria are satisfied: the patient is ready to breathe (even for a short period) on their own. Extubation criteria must also be satisfied; secretions should not be limiting (suctioning required less than every 2 hours); a strong cough should be demonstrated; and mental status should be adequate, especially if there are problems with cough and secretions. The patient must be a “good candidate” for NIV, with the capacity to tolerate the interface and breathe spontaneously for at least 5–10 min to allow for necessary mask and ventilator setting adjustments. Extubation to NIV should not be used if the patient would be technically difficult to re-intubate. To prevent delay in detection of worsening failure after institution of NIV, careful monitoring by skilled clinicians must be provided, generally in an ICU setting. To prevent delay of required re-intubation (and the associated higher mortality risk), personnel skilled in airway management must be rapidly available. When NIV is applied in this selective manner, patients thus extubated will have lower mortality, less morbidity, and shorter ICU and hospital stay, compared to continued invasive weaning. Based on currently available data, NIV should not be used to extubate non-COPD patients who fail SBT.

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Discussion

Gay: I've heard discussions about the true mechanism of the benefit of NIV versus say, just supplemental oxygen, so the VENISE trial¹ is very interesting to me. I suspect, in looking at those data, that the equivalence of those findings for NIV versus oxygen alone has a lot to do with the fact that those 2 groups fail for different reasons. By virtue of not putting those patients extubated early to oxygen only on NIV, you would predict that those patients primarily had ventilatory failure, whereas the NIV patients may have failed due more to NIV intolerance. I think the VENISE trial actually had a wrong arm with the oxygen, because I'm convinced that you need something more, that gives a little bit of ventilation as well as oxygenation in your alternative group.

Have either of you used humidified high-flow therapy as an alternative to early extubation, because that's what I'm becoming intrigued with, to avoid encountering those patients who are intolerant of NIV and going straight to re-intubation. You would then have a crossover arm for NIV patients who are intolerant and could use humidified high-flow therapy.

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Epstein: You don't mean high F_{IO_2} , right? I just want to make sure you're talking about just humidified high-flow, not high F_{IO_2} .

MacIntyre: High flow, not high F_{IO_2} .

Gay: Right. Most humidified high-flow patients don't fail because of oxygenation problems.

Siobal: You're speaking about high-flow nasal cannula?

Gay: Correct.

Siobal: I've seen patients who had higher P_{CO_2} while they were on the ventilator, and when I put them on high-flow nasal cannula, the P_{CO_2} went down. But that's with an airway with some mechanical dead space. I had an asthmatic patient who had P_{CO_2} in the 100s. He was on a low-flow nasal cannula, and I asked the ICU team and the attending if I could put him on a high-flow nasal cannula, and to do a blood gas before I did it, on the same F_{IO_2} with just high-flow oxygen via face mask and then another blood gas during high-flow nasal cannula. The P_{CO_2} started at 87 mm Hg on the mask and went down to 75 mm Hg, so about a 14% decrease. I think the added benefit is that it's flushing out the anatomical dead space in the nasopharynx, so you're reducing some CO_2 rebreathing.

Epstein: I'd be cautious with asthmatic patients; they improve very rapidly. About 20 years ago, Mountain and Sahn looked at patients with profound hypercapnia during asthma exacerbation, and found that they improved very rapidly and most of them don't need to be intubated. So those patients might have gotten better.

1. Mountain RD, Sahn SA. Clinical features and outcome in patients with acute asthma presenting with hypercapnia. *Am Rev Respir Dis* 1988;138(3):535-539.

Siobal: Well, it was only 15 minutes.

Durbin: I've used it a couple of times. I am not aware of any good studies that suggest it's useful, but I think since it provides flows of 40–50 L/min, it's probably providing airway pressure as well as reducing dead space.

Gay: Some of the studies¹ indicate anecdotally that you get about 3–5 cm H_2O CPAP equivalent with this, so it has some ventilation capability.

1. Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? *Pediatrics* 2008; 121(1):82-88.

MacIntyre: And if you've got a triggering problem with intrinsic PEEP, that 3–5 cm H_2O may improve that.

Gentile: I was going to add the 5 cm H_2O , but he's already seen it.

Branson: I think that with the high-flow nasal cannula, when the patient takes a breath and there's 40 L/min entering the nares, the gas may assist the patient's breathing. I don't know if we can really call it pressure support, but the flow probably does facilitate the tidal volume, and a couple of studies reported only in abstract used inductive plethysmography to look at the V_T , which was increased with the high-flow nasal cannula. NIV has been so great for COPD, but then, unfortunately, people misinterpret it and try to use NIV in obese postoperative patients, and then we have problems. What is it about re-intubation that makes it a high predictor of mortality?

Epstein: The question is whether it's a marker, or if it causes a bad outcome. A couple of multiple logistic regression analyses found that if you control for the things that we can control for, it's an independent predictor.^{1,2} I think these patients do deteriorate. I've certainly seen patients rule in for myocardial infarctions while we were administering bronchodilators, chest physical therapy, and nitroglycerin, to prevent re-intubation. Most studies show that the more rapidly you re-intubate, the better the patient does, and the same thing is true with regard

to unplanned extubation. I think those patients don't have higher mortality because they get re-intubated very quickly. I can't prove it, but I think there's a lot of suggestive evidence.

1. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112(1):186-192.
2. Esteban A, Alía I, Gordo F, Fernández R, Solsona JF, Vallverdú I, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. *Am J Respir Crit Care Med*. 1997;156(2 Pt 1):459-465. Erratum in: *Am J Respir Crit Care Med* 1997;156(6):2028.

Branson: This is a problem in my ICU. We have quite a few patients with post-extubation hypoxemia who get a trial of NIV (often inappropriately, in my opinion). I think the most important thing we can convince people of is that, whenever you try NIV, the physician, nurse, and respiratory therapist have to "draw a line in the sand" and say, "If these things don't happen by this time, we will re-intubate." Otherwise, you get people saying, "Let's give him a little more time," and the poor patient is suffering and not getting any better, and I think that leads to worse mortality. It's a process that needs to be fixed.

Epstein: I agree. We should apply the same rules to NIV here that we apply whenever we use NIV, which is to give the patient at most 4 hours, and if they're not showing clear unequivocal improvement, we intubate, if they're to be intubated.

Durbin: I can indirectly address the question of re-intubation and higher mortality. We looked at all the patients who were re-admitted to the ICU, and we asked whether the re-admission was for a new problem or an exacerbation of the old problem. Amazingly, the impact on mortality if it was the old problem was horrendous. For instance, if respiratory failure was the reason they came in the first time, and they came back with respiratory failure, their mortality was doubled. But if they came back in with a new problem, such as sepsis, they looked more like a first-time visitor for sepsis. I'm wondering if a patient who takes 3 days for us to figure out they're in respiratory failure hasn't developed a new problem, or if their first problem hasn't really been corrected. It may be a marker of disease progression and we're selecting out the ones who are not really getting better. I still have a little trouble understanding the dramatic impact of the timing of re-intubation on mortality.

Epstein: This is a weakness of all these studies: we arbitrarily select 24, 48, or 72 hours, and we make the assumption that if they fail in that period, it's because they haven't gotten better from the original problem; and that if they fail after that period, it's something new. That's completely arbitrary, and I'm sure it works both ways. There are people who fail for a new problem 3 hours after they're extubated, and there are people who come back 6 days later who just never fully got better from a COPD exacer-

bation. These cutoffs are absolutely arbitrary.

Siobal: With regard to NIV failure, are there any data on whether it could be device-related? On some of these single-limb-circuit devices there can be considerable CO₂ rebreathing, especially if the patient is tachypneic and breathing large tidal volumes. A bigger V_T blows CO₂ way down the circuit, and if there is not enough time to flush it out before the next breath, it just it goes back down into their lungs again.¹

1. Siobal M, Ong H, Toy W, Tang J. CO₂ rebreathing during simulated noninvasive ventilation: comparison of device, tidal volume size, respiratory rate, and exhalation valve type (abstract). *Respir Care* 2008;53(11):1561.

Epstein: In this particular set of studies I don't think people have looked at the reason for failure. I'm assuming leaks are a major issue, just because they're a problem everywhere, and leaks contribute to dyssynchrony. But I don't think anybody has looked at that specifically.

Gay: And we haven't got a clue about how and how much to control the tidal volumes that these patients take, particularly the more hypoxic ones who are air-hungry. You can see at least from the estimated volumes on the ventilator, that they're sometimes inhaling up to a liter while in respiratory distress. I understand that we have no data for NIV, but I get very nervous watching somebody in hypoxic respiratory failure do that.