Noninvasive Ventilation to Shorten the Duration of Mechanical Ventilation

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Noninvasive ventilation (NIV) successfully treats primary respiratory failure in chronic obstructive pulmonary disease (COPD), acute pulmonary edema, and, in some patients, hypoxemic respiratory failure. Increasingly clinicians have applied NIV in an effort to shorten the duration of mechanical ventilation by facilitating weaning and preventing or treating post-extubation respiratory failure. Randomized controlled trials (RCTs) indicate that NIV may be an effective weaning tool in a subset of patients with acute-on-chronic respiratory failure from COPD, and that applying immediate NIV to extubated patients at high risk for extubation failure improves outcome by decreasing the need for reintubation. In contrast, there is mixed evidence about the effectiveness of NIV to treat established post-extubation respiratory failure. NIV appeared to be ineffective in heterogeneous patient populations in some randomized trials that enrolled relatively few patients with COPD, and a case-control study found that NIV decreased the need for reintubation in this group. Therefore, as with primary therapy, NIV should be considered for patients with COPD and post-extubation respiratory distress. *Key words: noninvasive ventilation, NIV, extubation, mechanical ventilation, extubation failure, reintubation, weaning.* [Respir Care 2009;54(2):198–208. © 2009 Daedalus Enterprises]

Introduction

The use of noninvasive ventilation (NIV) has expanded dramatically over the last 2 decades.[1] Important NIV ap- plications have included: to shorten the duration of me- chanical ventilation by facilitating weaning (earlier extu- bation);[2-4] in the postoperative period, to prevent

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reintubation;[5-7] and after planned extubation.[8-11] In the latter case, NIV has been applied immediately after extubation in patients deemed to be at elevated risk for extubation failure (ie, to prevent extubation failure).[9,11] Alternatively, NIV has been applied to prevent reintubation in patients who develop overt respiratory failure after extubation.[8,10] The use of NIV for these applications has increased substantially. In a 2-year observational study in a 22-bed medical intensive care unit (ICU), 30% of the applications of NIV for acute respiratory failure were for facilitating weaning or after extubation.[12] More recently, Schettino et al studied 458 patients who received NIV at Massachusetts General Hospital over a one-year period. Approximately 21% of all applications were for post-extubation respiratory failure, and 60% of those were successful.[13]

Several earlier observational studies examined NIV for shortening the duration of mechanical ventilation.[14-16] These uncontrolled and nonrandomized studies suggested that NIV is highly effective in facilitating weaning and treating or preventing extubation failure. More recent controlled (case or randomized) trials have better defined the patient population and criteria for effective use of NIV to shorten the duration of ventilation.

Rationale for Facilitating Weaning and Extubation

Invasive ventilation via endotracheal tube (ETT) can be life-saving in patients with acute respiratory failure, but invasive ventilation is associated with numerous complications, including airway injury, higher risk for gastrointestinal bleeding, thromboembolism, barotrauma, and ventilator-associated pneumonia.[17] Many of these complications are more likely if invasive ventilation is prolonged—a not-uncommon occurrence. Approximately 25% of patients intubated for acute respiratory failure require at least 7 days of mechanical ventilation, and up to 10% are intubated for more than 3-weeks.[18] In many patients much of that period is consumed by weaning from ventilatory support. One study found that 40% of ventilator time was devoted to weaning (60% in patients with chronic obstructive pulmonary disease [COPD]).[19] Morality increases with increased duration of ventilation.[18]

Once a patient demonstrates that ventilatory support is no longer required, the efforts turn to removing the ETT. Timely extubation is important because unnecessarily delaying extubation worsens outcome. As an example, Coplin et al studied 136 mechanically ventilated brain-injured patients by screening them daily to determine readiness for extubation.[20] Delayed extubation was defined by failure to remove the ETT within 48 hours of satisfying readiness criteria. With that definition 27% had extubation delay, and, compared to patients whose extubation was timely, they had more pneumonia, longer stay

Table 1.   Risk Factors Associated With Extubation Failure

Medical, pediatric, or multidisciplinary ICU patient
Older age
Pneumonia caused by mechanical ventilation
Higher severity of illness at extubation
Continuous intravenous sedation
Abnormal mental status, delirium
Semirecumbent patient position
Transport out of ICU for procedures
Physician and nurse staffing in the ICU

ICU = intensive care unit

in the ICU and hospital, and higher mortality. Therefore, there is a strong rationale for trying to shorten the duration of invasive mechanical ventilation.

Extubation failure occurs when respiratory failure, typically manifested as the need to re-start ventilatory support (reintubation or NIV), develops within 48–72 h of ETT removal.[21] In a mixed ICU population, signs of respiratory distress occurred in 25% of 980 extubated patients within 48 h of ETT removal.[8] Fifty percent of those patients required reintubation. Extubation failure rate depends on several factors (Table 1), the most important of which is the type of patient. As an example, extubation failure occurs in 5–8% of critically ill surgical patients (trauma, cardiothoracic surgery, and general surgery), whereas 12–20% of pediatric, medical, multidisciplinary, and neurologic ICU patients require reintubation (Fig. 1).[21,22]

Extubation failure has been associated with several adverse outcomes, including a marked prolongation of the duration of invasive ventilation. In medical ICU patients, reintubation resulted in 12 additional days of mechanical ventilation, 21 additional days in the ICU, and 30 additional days in the hospital.[23] Extubation failure is a major risk factor for tracheostomy: 18–60% of such patients eventually undergo tracheostomy.[23-30] Two studies that used multiple logistic regression techniques found that extubation failure was independently associated with the need for tracheostomy.[28,30]

Univariate analyses indicate that the mortality associated with extubation failure is 2–10 times that in successfully extubated patients.[23,27,29,31-37] The highest mortality rates (up to 50% of patients with extubation failure) are in general surgical, medical, multidisciplinary, and pediatric ICUs. Mortality has been lower (approximately 10%) among patients with extubation failure in trauma and cardiothoracic surgical patients. Calculated via multivariate analysis, with adjustment for severity of illness and comorbid conditions, most, but not all, studies have indicated an independent association between extubation failure and mortality.[23,29,31]
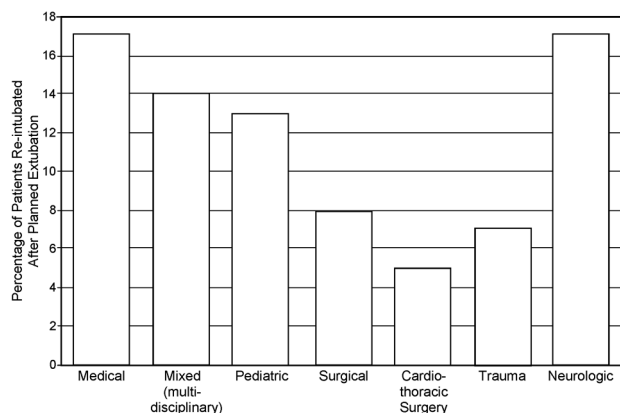
Fig. 1. Percentage of patients who failed extubation (ie, required reintubation) after planned extubation in various intensive care units (ICUs). (Data from References 21 and 22.)

Table 2.   Advantages of Removing the Endotracheal Tube

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

Some studies suggest that the cause of extubation failure is also a determinant of outcome. Mortality is lowest when reintubation results from upper-airway obstruction, aspiration, or excess pulmonary secretions.[23,36] The relationship between extubation failure and higher mortality may have several explanations. Extubation failure may be a marker of greater severity of illness. The higher mortality may be due to direct complications of reintubation, including ventilator-associated pneumonia. There may be clinical deterioration between extubation and reintubation. The adverse effects of prolonged total duration of ventilation may contribute to mortality. Delayed reintubation may allow patients with extubation failure to deteriorate before adequate ventilatory support is reinstituted. Indeed, indirect evidence supports this concept, as delayed time to reintubation is associated with higher mortality in patients with extubation failure.

Two investigations found that patients reintubated after self-extubation, often within an hour of extubation (ie, reintubation without delay) do not have higher hospital mortality.[25,38] In an investigation of reintubated medical patients, a greater time to reintubation was an independent predictor of mortality, even after controlling for the etiology of extubation failure.[26] A prospective follow-up study found that a reduced median time to reintubation (from 21 h in historical controls to 6 h) lowered hospital mortality from 43% to 20%.[39] Several other studies suggest that more delayed reintubation is associated with poor outcome.[27,34,40,41] Torres and co-workers identified a potential mechanism. They found a lower incidence of pneumonia in patients immediately reintubated than in patients with delayed reintubation.[41] The relationship between time to reintubation and outcome implies that early provision of ventilatory support (perhaps NIV) could prevent deterioration and improve outcome.

Physiologic Rationale for Noninvasive Ventilation to Facilitate Weaning

The pathophysiologic basis of weaning failure has been extensively studied by comparing patients who tolerate a spontaneous breathing trial (SBT) to those who do not. Findings in weaning-failure patients include rapid shallow breathing, increased resistive and elastic work of breathing (WOB), increased intrinsic positive end-expiratory pressure, abnormal gas exchange, respiratory muscle weakness, and abnormal cardiovascular response.[27,34,40-46] The physiologic effects of NIV can correct many of these abnormalities.[47] For example, NIV is associated with decreased rapid shallow breathing, improved gas exchange, improved alveolar ventilation, and decreased WOB.[48,49] Positive end-expiratory pressure delivered with NIV can counterbalance intrinsic positive end-expiratory pressure, which decreases WOB and reduces the elevated inspiratory threshold load that is often present in patients with COPD and dynamic hyperinflation.[48,49] Weaning can be limited by the cardiovascular system, through several mechanisms. As an example, Lemaire et al found that placing a patient on a T-piece resulted in an almost immediate rise in the transmural pulmonary artery occlusion pressure.[50] The positive intrathoracic pressure associated with NIV can prevent this by reducing cardiac pre-load and after-load.

Physiologic Rationale for Noninvasive Ventilation to Prevent Extubation Failure

Several advantages occur when NIV allows removal of the ETT (Table 2). Conversely, in the absence of the ETT there is no guaranteed minute ventilation. NIV does not enhance airway clearance and 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 patient on mechanical ventilation can be challenging without the airway protection of an ETT.

Noninvasive Ventilation to Facilitate Weaning From Mechanical Ventilation

Several uncontrolled studies suggested that NIV could help wean patients from mechanical ventilation. The earliest reports principally examined patients with prolonged mechanical ventilation, many of whom were ventilated via tracheostomy.[15,16,51]

Udwadia et al studied 22 patients (who had either ETT or tracheostomy) on mechanical ventilation for a median of 31 days and who had difficulty weaning.[16] Thirteen patients had been intubated for acute cardiopulmonary disease and 9 were postoperative. Nine patients had chest-wall abnormalities or primary pulmonary disease, 7 had both cardiac and pulmonary disease, and 6 had neuromuscular disease. With nasal NIV, 18 patients were successfully weaned from mechanical ventilation after a median of 11 days (range 8–13 d).[16]

Restrick and colleagues used NIV to wean 14 patients with respiratory disease who had failure to wean with standard techniques.[15] Twelve of the patients were ventilated for acute respiratory failure (8 had COPD, and 4 had neuromuscular or chest-wall disease) and 2 for postoperative respiratory failure. Weaning with NIV via nasal mask was successful in 13 patients.

Gregoretti et al studied 22 intubated trauma patients.[52] After a T-piece SBT to assess the patient's capacity for spontaneous breathing, the patient was extubated to noninvasive pressure support ventilation (PSV). There was no difference in blood gas values or respiratory variables between equivalent settings with invasive or noninvasive PSV. Of concern, 9 patients required reintubation and 6 eventually died on mechanical ventilation.

Kilger and co-workers used NIV in 15 patients who had been intubated for acute respiratory failure and then extubated after they satisfied criteria that typically would not signify extubation readiness (ie, they used NIV to facilitate earlier weaning and extubation).[53] The early-extubation criteria were: $P_{aO_2} \geq 40$ mm Hg (on a fraction of inspired oxygen [F_{IO_2}] of 0.21), $P_{aCO_2} \leq 55$ mm Hg, pH > 7.32, respiratory rate ≤ 40 breaths/min, tidal volume (V_T) ≥ 3 mL/kg, ratio of respiratory rate to $V_T \leq 190$ breaths/L/min, and negative inspiratory force ≥ 20 cm H_2O. After extubation, 2 ventilation modes were used: CPAP at 5 cm H_2O, and PSV at 15 cm H_2O, for a median of 2 days. Both modes improved oxygenation and V_T and decreased respiratory rate. PSV also decreased P_{aCO_2} and increased minute ventilation and pH. Two of the 15 patients required reintubation.

There are 5 reported RCTs of NIV to facilitate weaning, including one presented only in abstract form and another published in Chinese.[2-4,54,55]

Nava and co-workers studied 68 patients with COPD and severe acute-on-chronic respiratory failure.[4] At admission the average P_{aCO_2} was 90 mm Hg, and approximately 40% failed NIV before being intubated. Once intubated, the patients were heavily sedated, given neuromuscular blockade, and ventilated in the assist-control mode (Fig. 2). Patients were subsequently transitioned to PSV and underwent a 2-hour T-tube SBT approximately 48 hours after intubation. Eighteen patients tolerated the SBT and were extubated. Fifty patients failed the SBT and were randomized. Twenty-five patients remained intubated and underwent weaning via gradual reduction of PSV, targeted to arterial blood gas values and to keep the respiratory rate < 25 breaths/min. These patients also received twice-daily SBTs on CPAP or T-tube. The remaining 25 patients were extubated to noninvasive PSV via oronasal mask, an ICU ventilator, and a weaning protocol similar to that of the invasively ventilated group. Patients randomized to NIV had shorter ventilation (10 d vs 17 d) and shorter ICU stay (15 d vs 24 d) and were more likely to be successfully
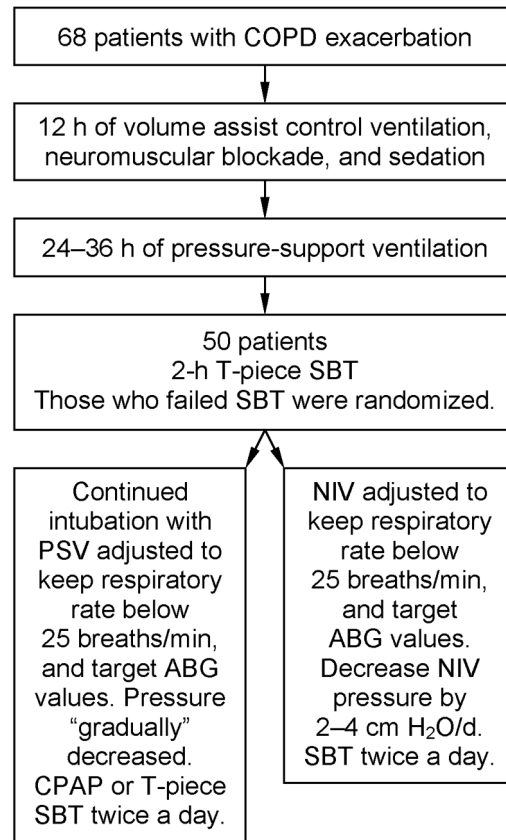

Fig. 2. Design of a randomized controlled trial of ventilator weaning with noninvasive ventilation (NIV) versus continued invasive ventilation after acute respiratory failure from an exacerbation of chronic obstructive pulmonary disease (COPD). The 50 patients who failed a T-piece spontaneous breathing trial (SBT) were randomized to either continued intubation and weaning with pressure-support ventilation (PSV) or weaning with NIV. ABG = arterial blood gas analysis. CPAP = continuous positive airway pressure. (Based on data in Reference 4.)

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weaned (88% vs 68%) and to be alive (92% vs 72%) at 60 days. One explanation for the better outcomes with NIV may be that none of those patients developed pneumonia, compared to 25% of those who remained intubated. Complications were common with NIV but principally consisted of abrasions of the bridge of the nose. The study[4] is notable in showing that failure of NIV as primary therapy does not preclude successful application at a later time. Also, use of neuromuscular blocking agents and sedation for the first 12 hours of invasive ventilation may allow recovery from respiratory muscle fatigue. That said, caution is recommended, because concurrent use of corticosteroids and neuromuscular blocking agent predisposes to prolonged respiratory muscle weakness, and controlled mechanical ventilation can lead to respiratory muscle injury (ventilator-induced diaphragmatic dysfunction).

Girault et al used a somewhat similar design and randomized 33 patients with acute-on-chronic respiratory failure who failed a 2-h T-tube SBT, to either continued invasive weaning (PSV) or extubation to NIV.[3] NIV could be delivered via nasal or oronasal mask, and either PSV or assist-control mode. The NIV patients had a mean 3-day shorter duration of intubation (4.6 d vs 7.7 d) but there was no differences in weaning success (77% vs 75%), ICU stay (12 d vs 14 d), hospital stay (27 d vs 28 d), need for reintubation (23% vs 25%), or survival at 3 months (100% vs 88%). Interestingly, the overall duration of mechanical ventilation (combined time intubated plus time on NIV) was higher in the NIV group (16.1 d vs 7.7 d), and 7 patients were discharged on nocturnal NIV.

Ferrer et al studied 43 patients (77% with chronic lung disease) who had failed at least 3 SBTs.[2] Patients were randomized to either continued weaning with the ETT or extubation to NIV (bi-level positive airway pressure with inspiratory pressure of 10–20 cm H_2O and expiratory pressure of 4–5 cm H_2O, via nasal or oronasal mask) for at least 24 hours. The study, which was powered to look for a reduction in the duration of invasive mechanical ventilation, was stopped after the first interim analysis. NIV was associated with significant reductions in the duration of invasive mechanical ventilation, duration of ICU and hospital stay, incidence of septic shock and pneumonia, and need for tracheostomy. There was a trend for less need for reintubation with NIV. NIV was associated with better ICU survival and 90-day survival. The study is notable for the dramatic benefit from NIV, despite the enrollment of a relatively small cohort of patients.

In a preliminary study, Hill et al screened 303 patients with acute respiratory failure and sought to enroll the 45 patients who failed a 30-min T-piece SBT.[55] Sixteen were ineligible because of excessive secretions or abnormal mental status, which left 29 eligible patients (< 10% of those screened). Twenty-one patients were enrolled and randomized: 12 to weaning with NIV, and 9 to continued intuba-

tion with conventional weaning. One third of the NIV patients required reintubation, whereas 8 of the controls weaned successfully. The study re-emphasizes that only a small fraction of intubated patients are appropriate candidates for weaning via NIV.

Chen and co-workers randomized 24 patients intubated (for 3 d) for COPD exacerbation to weaning via NIV versus continued weaning on invasive ventilation (control group).[54] Weaning with NIV was associated with a lower incidence of ventilator-associated pneumonia (0/12 vs 7/12, $P = .03$), shorter invasive ventilation (7 d vs 15 d, $P > .05$), and shorter hospitalization (16 d vs 25 d, $P < .05$) after randomization. There was no statistical difference in mortality (0/12 vs 3/12, $P = .2$).

Burns and colleagues performed an elegant meta-analysis on the above-described 5 RCTs of NIV to facilitate weaning.[56] The 5 studies encompassed only 171 patients (81% with COPD) and had several study-design weaknesses. Specifically, only one of the 5 studies used blinded assessment of outcome and fully controlled for co-interventions. Two studies did not use a weaning protocol, and 2 did not have reintubation criteria. With those limitations in mind, Burns et al found that, compared to invasive weaning, NIV was associated with lower mortality (relative risk 0.41), less ventilator-associated pneumonia (relative risk 0.28), shorter mechanical ventilation (by 7.33 d), shorter ICU stay (by 6.88 d), and shorter hospital stay (by 7.33 d). There was no effect on the probability of weaning success.

To summarize the 5 studies and the analysis by Burns et al, I conclude that NIV can be an effective tool for facilitating weaning, but only in very selected patients with acute-on-chronic respiratory failure (eg, COPD exacerbation). The effectiveness of NIV as primary therapy for COPD exacerbation has been well demonstrated. When considering whether to use NIV to facilitate weaning, I recommend the following criteria. The criteria for an SBT must be satisfied: the patient must be ready to breathe (even for a short period) on his own. Extubation criteria must be satisfied: secretions should not be excessive (suctioning required less often than every 2 h), a strong cough should be present, and mental status should be acceptable. The patient should be a good candidate for NIV, able to tolerate the interface and to breathe spontaneously for at least 5–10 min to allow for necessary mask and ventilator adjustments. NIV for weaning is strongly discouraged if the patient would be technically difficult to reintubate.

One interesting question is, why is NIV more effective? NIV could be a better mode of weaning. Compared to weaning with the ETT in place, NIV decreases the risk of infection (ventilator-associated pneumonia) and the need for sedation, which are factors that increase the duration of mechanical ventilation.[57,58] Alternatively, NIV may allow the clinician to recognize that a patient who appears to be

intolerant of weaning is in fact ready to be liberated from the ventilator. This might occur if weaning intolerance results from the imposed WOB from the ETT or because of psychological reasons (eg, anxiety). 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 liberation. To address this issue, Girault and colleagues are conducting a RCT with 205 patients in 17 centers in France.[59] Patients are eligible if intubated for at least 48 hours with acute-on-chronic respiratory failure and have failed an SBT. Patients are randomized to continued intubation with conventional weaning, extubation to NIV, or extubation to oxygen therapy but without NIV. The study results should be available soon.

Several questions remain about NIV for weaning. What is the best mode? What is the best interface? How time-consuming is weaning with NIV compared to invasive weaning?

Noninvasive Ventilation to Treat Post-Extubation Respiratory Failure

Several uncontrolled studies have indicated that NIV may be an effective therapy for extubation failure and obviate reintubation in 65–70% of patients. As an example, Meduri et al analyzed the effect of NIV in 158 patients, 39 (17 with COPD) of whom received NIV for post-extubation respiratory distress.[14] Eighty-six percent showed an improvement in blood gases, and 65% avoided reintubation. Another observational study of 19 patients found the technique successful in 11 patients; failures were associated with mask leaks, secretions, and hypoxemia.

Hilbert et al conducted a case-control study of NIV (PSV via full face mask) in patients with COPD who developed respiratory distress (respiratory rate > 25 breaths/min or P_{aCO_2} increased $> 25\%$ with pH < 7.35) within 72 hours of extubation.[60] NIV was delivered for at least 30 min every 4 hours (mean 5.2 d), with a mean of 16 cm H_2O inspiratory pressure, to achieve a respiratory rate ≤ 25 breaths/min and a $V_T \geq 7$ mL/kg. Compared to 30 matched controls, NIV was associated with less reintubation (20% v 67%) and shorter ICU stay (8 d vs 14 d).

There have been 2 RCTs of NIV for patients with established post-extubation respiratory failure. The first, by Keenan and co-workers, randomized 81 patients who had been ventilated for 48 hours with cardiac or pulmonary disease and who developed respiratory distress (respiratory rate > 30 breaths/min or $> 50\%$ increase or signs of increased WOB) within 48 hours of extubation.[10] Patients received either standard post-extubation care (controls) or bi-level-mode NIV continuously for at least the first 12 hours.[10] There were no differences in need for reintubation (72% vs 69%), development of pneumonia (47% vs 41%),
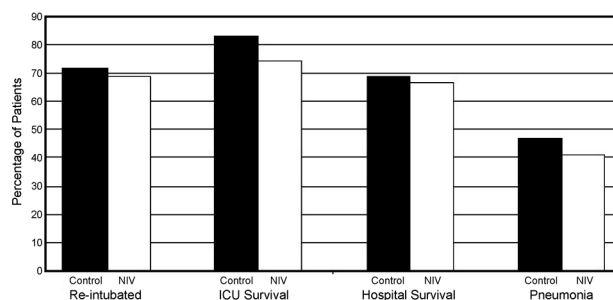

Fig. 3. Results of a randomized controlled trial of noninvasive ventilation (NIV) in post-extubation respiratory failure. ICU = intensive care unit. (Based on data in Reference 10.)

ICU survival (83% vs 74%), or hospital survival (69% vs 67%) (Fig. 3). Notably, after the first year, patients with COPD were excluded, presumably because physicians were reluctant to have these patients "risk" randomization to the control group. The consequence was that only 11% of the study patients had COPD. The study is also notable because of the very high reintubation rate, which suggests that NIV may have been employed too late in these patients.

The second RCT examined earlier intervention with NIV. Esteban et al enrolled nearly 1,000 patients in 37 ICUs in 8 countries.[8] The patients had been ventilated for at least 48 hours and had passed an SBT. Patients were randomized if they exhibited 2 or more of the following criteria within 48 hours of extubation: respiratory rate > 25 breaths/min for 2 consecutive hours; clinical signs of respiratory muscle fatigue or increased WOB; hypercapnia (P_{aCO_2} > 45 mm Hg or $> 20\%$ increase from pre-extubation); respiratory acidosis (pH < 7.33 with $P_{aCO_2} > 45$ mm Hg); and hypoxemia (arterial oxygen saturation $< 90\%$ or P_{aO_2} < 80 mm Hg on $F_{IO_2} \geq 0.50$). Patients with COPD were randomized separately to ensure equal allocation to the control and NIV groups. Two hundred forty-four patients developed post-extubation respiratory distress, 23 of whom could not be randomized because of immediate need for reintubation, so 221 were randomized (114 to NIV, 107 to control). Between the NIV and control groups there were no significant differences in: age; sex; Simplified Acute Physiology Score II; duration of mechanical ventilation prior to extubation; pre-extubation respiratory variables (spontaneous V_T, ratio of respiratory rate to V_T, maximum inspiratory pressure); SBT method; or satisfying the criteria for post-extubation respiratory distress (mean 9-h). When analyzing outcomes, there was no difference in need for reintubation or ICU stay (Fig. 4). In contrast, NIV was associated with higher ICU mortality (25% vs 14%). This may have resulted from the higher mortality in the reintubated NIV patients than in the reintubated control patients. One possible explanation is the longer time between onset of post-extubation respiratory distress and reintuba-
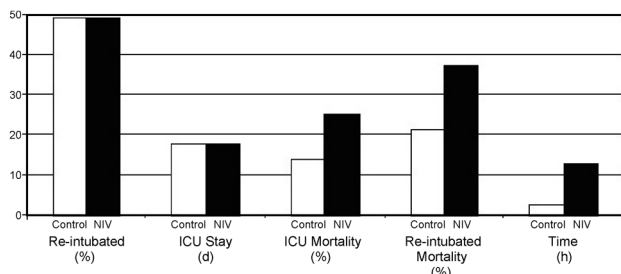
Fig. 4. Results of a randomized controlled trial of noninvasive ventilation (NIV) in patients with post-extubation respiratory failure. ICU = intensive care unit. Time = time between extubation and reintubation. (Based on data in Reference 8.)

tion in those randomized to NIV (12.7 h vs 2.4 h). The study[8] has been criticized because only 10% of the randomized patients had COPD. Also, inexplicably, when NIV had to be used in control patients, the success rate appeared to be higher (75%) than in patients randomized to NIV (50%).

In summary, these RCTs indicate that NIV is not effective in treating established post-extubation respiratory failure. This may not be true for patients with COPD, because the RCTs contained few patients with COPD.

Noninvasive Ventilation to Prevent Post-Extubation Respiratory Failure

Jiang et al randomized 93 patients to standard care or routine application of NIV after extubation (40% had unplanned extubation). NIV was applied with a bi-level ventilator and oronasal mask.[61] There was no difference in the need for reintubation. One must question the rationale for using NIV in all extubated patients, as 80–95% of such patients do not require reintubation.

A better approach would be to identify patients at highest risk for extubation failure. El Solh et al applied NIV immediately after extubation in morbidly obese patients (body mass index > 35 kg/m^2) who had been ventilated for > 48 hours.[62] NIV was delivered for a mean of 16 h/d in a bi-level mode (inspiratory pressure 12 cm H_2O, expiratory pressure 4 cm H_2O) via nasal mask, and titrated to keep the respiratory rate < 25 breaths/min. Compared to controls matched for age, body mass index, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and weaning protocol, NIV was associated with less post-extubation respiratory failure (10% vs 26%) and less need for reintubation (10% vs 21%), though there was no difference in mortality. Of note, obstructive sleep apnea was documented in 22% of the NIV patients and 27% of the controls.

There have been 2 RCTs of NIV to prevent extubation failure in high-risk patients. Nava and colleagues randomized 97 patients (33% with COPD, 10% with heart failure) who passed an SBT but were deemed to be at high risk for extubation failure, based on the presence of one or more of: more than one consecutive failed SBT, chronic heart failure, $P_{aCO_2} > 45$ mm Hg (measured 1 h after extubation), more than one comorbidity, and weak cough.[11] NIV was delivered for at least 6 h/d with either a bi-level ventilator or a standard ICU ventilator. Post-extubation NIV was associated with less need for reintubation (4.8% vs 12.2%) and lower ICU mortality. There were no differences in hospital mortality or stay.

Ferrer et al randomized 162 patients judged to be at high risk of extubation failure, based on the presence of one or more of: age > 65 years, cardiac failure, and APACHE II score > 12 at the time of extubation.[9] Fifty percent of those patients had chronic respiratory disease, and 50% had been intubated for an exacerbation. NIV was delivered with a bi-level ventilator (inspiratory pressure range 12–20 cm H_2O, expiratory pressure range 4–6 cm H_2O). NIV was associated with less post-extubation respiratory distress (13.2% vs 27.3%), a trend toward less need for reintubation (2% vs 12%), and lower ICU mortality. There were no differences in ICU stay, hospital stay, hospital mortality, or 90-day mortality. Subgroup analysis found better 90-day survival in patients with hypercapnia.

A meta-analysis of these 2 studies (which included a total of 259 patients) found that NIV decreased the need for reintubation (relative risk 0.46, 95% confidence interval 0.25–0.84) and ICU mortality (relative risk 0.26, 95% confidence interval 0.1–0.66) but not hospital mortality (relative risk 0.71, 95% confidence interval 0.42–1.2).[63]

In summary, in general, NIV should not be used routinely after extubation or in established post-extubation respiratory failure (Table 3). An exception is in patients with COPD and acute-on-chronic respiratory failure. Here the RCTs after extubation do not provide definitive evidence, because relatively few patients with COPD have been studied. The case-control study by Hilbert et al[60] and the many studies that have used NIV as primary therapy for COPD[64] indicate that this application may be effective after extubation in patients who develop respiratory distress. Routine use of NIV immediately after extubation is not recommended, except in patients at high risk for extubation failure. The case-control study by El Solh et al[62] suggests that this approach is effective in morbidly obese patients. Two RCTs indicated that preventive NIV in at-risk patients reduces the need for reintubation.

Whenever NIV is applied post-extubation, the patient must be watched carefully. If there is no clear evidence of improvement (reduced dyspnea, decreased use of accessory respiratory muscles, decreased respiratory rate, and lower P_{aCO_2}) within 2–4 hours of NIV application, reintubation should be considered.

Table 3. Summary of Recommendations for Using NIV to Shorten the Duration of Mechanical Ventilation.

Application	First Author	Conclusion/Recommendation
Facilitate weaning	Nava[4] Girault[3] Ferrer[2] Chen[54] Hill[55]	NIV reduces the need for reintubation in selected patients with acute-on-chronic respiratory failure (eg, COPD).
Prevent extubation failure	Jiang[61] El-Solh[62*] Nava[11] Ferrer[9]	NIV is not effective when used routinely after extubation in unselected patients. NIV is effective when used immediately after extubation in patients at high risk for extubation failure.
Treat extubation failure	Hilbert[60*] Keenan[10] Esteban[8]	NIV is not effective in established post-extubation respiratory failure in patients without COPD. NIV is likely to be effective in established post-extubation respiratory failure in patients with COPD.

* Case-controlled studies. All others are randomized controlled trials.
NIV = noninvasive ventilation
COPD = chronic obstructive pulmonary disease

Cough-Enhancement Techniques to Prevent Extubation Failure

An ineffective cough (especially in the presence of excess respiratory secretions and/or poor mental status) predisposes to extubation failure. This raises the question of whether cough-enhancement techniques could improve extubation outcome. The majority of research on cough-enhancement techniques has focused on patients with neuromuscular diseases. Inspiratory, expiratory, and upper-airway muscle weakness conspires to decrease cough effectiveness, which predisposes to aspiration, pneumonia, and respiratory failure. In a retrospective report on ventilated myasthenic patients, an aggressive approach to airway care (ie, that combined intermittent positive-pressure breathing, bronchodilators, suctioning, sighs, and chest physiotherapy) was associated with less atelectasis and pneumonia and shorter duration of mechanical ventilation than that in previous studies.[65] Several other interventions may be useful for improving cough and secretion clearance.

Manually assisted ("quad") cough has been effective in patients with spinal cord injury who have expiratory muscle weakness but preserved inspiratory muscle function. It may prove useful in neuromuscular diseases, in patients who have a similar distribution of respiratory muscle involvement. In the manually assisted cough maneuver, a caregiver provides an abdominal thrust timed to the patient's voluntary cough effort. The maneuver can be combined with a hyperinflation maneuver (see below) in patients who have inspiratory muscle weakness.

The hyperinflation maneuver, designed to increase inspiratory V_T, improves cough effectiveness. Some patients can achieve hyperinflation without assistance, via glossopharyngeal breathing (repetitive air gulping). More commonly, a resuscitation bag with a one-way valve and mouthpiece is used to deliver a series of stacked breaths. A mechanical inspiration can also be delivered with a mechanical insufflator or a volume-cycled ventilator. Intact bulbar function is essential for hyperinflation maneuvers, because the patient has to "retain" the delivered V_T.[66]

Mechanical insufflation-exsufflation can be delivered in spontaneously breathing patients or patients on mechanical ventilation, with the CoughAssist In-Exsufflator (Respironics, Murrysville, Pennsylvania). The insufflation (usually at 40 cm H_2O) is followed by a rapid transition to negative pressure (exsufflation, usually -40 cm H_2O), which enhances secretion clearance. In general the In-Exsufflator is associated with few complications and is well tolerated, but it worsens expiratory airway collapse and therefore may be less effective in patients with expiratory flow limitation (eg, COPD); in those patients studies have found either a decrease or no improvement in peak cough flow.[67,68]

When compared to historical controls managed with chest physiotherapy alone, the addition of in-exsufflation reduced treatment failure in patients with neuromuscular disease complicated by respiratory tract infection.[69] In patients with amyotrophic lateral sclerosis, in-exsufflation via tracheostomy tube cleared secretions better than tracheal suctioning.[70] In-exsufflation increases peak cough flow more than does manually assisted cough.[71]

Secretion-mobilization techniques have also been employed to improve respiratory function. High-frequency chest-wall oscillation and intrapulmonary percussive ventilation can mobilize airway secretions.[66]

A prospective observational study found that a strategy that combined NIV with manual and mechanical cough-assistance techniques prevented intubation and death in 79% of 25 episodes of acute respiratory failure. Bulbar dysfunction independently predicted failure of the noninvasive strategy.[72] Lung-expansion maneuvers with NIV allowed tracheostomy decannulation in patients with neuromuscular disease.[73]

In summary, several manual and mechanical approaches can enhance cough effectiveness and secretion clearance. In certain circumstances these techniques appear to obviate intubation or facilitate tracheostomy decannulation in patients with neuromuscular disease. Whether these techniques effectively prevent or treat post-extubation respiratory failure remains to be proven.

Summary

Efforts to shorten the duration of mechanical ventilation, while avoiding the need for reintubation, are justified by the adverse outcomes associated with prolonged mechanical ventilation and extubation failure. NIV may facilitate early extubation in very selected patients with acute-on-chronic respiratory failure who have failed weaning. Similarly, immediate application of NIV appears to prevent post-extubation respiratory distress in patients at high risk of extubation failure. However, caution is warranted, because NIV appears to be ineffective for established post-extubation respiratory failure. The one exception may be patients with COPD, in whom NIV appears to be effective in many circumstances. Cough-enhancement techniques may improve tolerance of extubation.

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Discussion

Mehta: I carefully evaluated the literature regarding early extubation to NIV in patients with COPD. We're not doing it at Mount Sinai Hospital, and when I informally surveyed clinicians, nobody seemed to be doing it, because these patients failed a trial of NIV and were therefore intubated. I feel very uncomfortable extubating them back to NIV after 24–48 hours.

Epstein: Keep in mind that in Stefano's [Nava] study,[1] about 40% of the patients enrolled had failed NIV at their first go, so that study suggests that preliminary NIV failure does not preclude later NIV success, because initially the patient is almost certain to have severe respiratory muscle fatigue, whereas after 48 hours of ventilation, he might be rested and better suited for NIV. That's just speculation though.

1. Nava S, Ambrosino N, Clini E, Prato M, Orlando G, Vitacca M, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease: a randomized controlled trial. Ann Intern Med 1998;128(9):721-728.

Kacmarek: Stefano, was there a difference between the 40% who had prior NIV and the 60% who didn't? I share Geeta's [Mehta] general impression that if a patient with COPD fails NIV, you intubate them, so to extubate 24–48 hours after failing an SBT seems extremely risky. In the Ferrer[1] and Girault[2] studies did the patients receive NIV prior to intubation?

1. Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med 2006;173(2):164-170.

2. Girault C, Daudenthun I, Chevron V, Tamion F, Leroy J, Bonmarchand G. Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure: a prospective, randomized controlled study. Am J Respir Crit Care 1999;160(1):86-92.

Nava: We did a post-hoc analysis of the group who underwent NIV before intubation and the group who did not, and there was no difference. Now we are not applying this technique very often because we intubate very few patients with COPD. This is a problem. Every single patient with COPD gets at least a trial of NIV. The literature tells us that if you fail NIV you are not at risk of death. Since NIV is the gold standard for COPD exacerbation, once the patient fails NIV and needs to be intubated for any reason (for example, respiratory arrest), the main goal after intubation is to quickly recover the conditions that will enable the patient to be extubated to NIV.

If you remove the secretions problem, get rid of hypercapnic encephalopathy, and restore the respiratory muscles, then the patient is ready again to undergo NIV, even though he does not pass an SBT. Nothing here is a major obstacle.

Pierson: I would like to remind everyone that the people discussing this issue right now in this room represent tremendous expertise, people with a great deal of personal and institutional success in NIV, but I remind you of the meager and not-very-good-quality epidemiologic data we have, which indicates that only a relatively small minority of patients with COPD exacerbation who wind up on ventilators have the opportunity for a trial of NIV. So I submit that, at least in the United States, there is probably a fairly large number of patients with COPD in our ICUs who are intubated but would have been good NIV candidates, but they did not have the opportunity to have NIV tried.

Kacmarek: How many of you who work in centers that regularly do NIV extubate to NIV after a day or two with a patient with COPD, if the patient failed an SBT? I won't say that we don't do it, but it's rare.

Hill: I have unpublished data that the frequency of that is pretty low, probably fewer than 10% of cases. Also, the patients with COPD exacerbation that we intubate usually have excessive secretions or some other comorbidity that made them a poor candidate for NIV, and they're usually not ready for extubation within 48 hours.

Gay: There's one NIV use our cardiologists have caught on to, and the data certainly support this; after an

acute ischemic episode or pulmonary edema NIV has become very popular to speed extubation and weaning.

Kacmarek: Even though they failed the SBT? I agree with Stefano's [Nava] most recent weaning study,[1] but *failing* the SBT and then extubating….

1. Frutos-Vivar F, Ferguson ND, Esteban A, Epstein SK, Arabi Y, Apeztequía C, et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. Chest 2006;130(6):1663-1671.

Hill: You have to be careful to exclude the people who really should be extubated anyway.

Epstein: I did this twice in the past 2 weeks. The patients were 2 people I was not convinced would fail the SBT, for physiologic reasons. One was a woman who had a narrow endotracheal tube, and the other patient was really delirious on the ventilator and so I could not find a good physiologic reason for SBT failure. I predicted they would do well without the tube, and was sort of protecting myself by putting them on NIV after extubation. The Girault study[1] is very helpful in understanding how this works.

1. Girault C, Chajara A, Cachraoui F, Chambaretaud V, Hellot MF, Benichou J, Bonmarchand G; Groupe d'Etude VENISE [VENISE: Non-invasive ventilation during mechanical ventilation weaning in chronic respiratory failure patients. A prospective randomised controlled and multicenter trial]. Rev Mal Respir 2003;20(6 Pt 1):940-945. *Article in French.*

Kallet: I'd like some clarification on this. There's failing, and then there's *failing*. There are patients who fail an SBT within 5 or 10 minutes; they just sink like a rock. And then there are patients who take 30 minutes, an hour, or 90 minutes before they fail. I think you have to define who's failing and when. If the patient only starts to tire after 2 hours, NIV might be appropriate, but if they fail an SBT within 15

or 20 minutes, I don't think NIV is likely to help.

Epstein: I don't think we have that level of detail with these studies. The only one we have is the Ferrer study.[1] At least we know that they failed on 3 consecutive days.

1. Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med 2006;173(2):164-170.

Pierson: I'd like to remind us all of the 2 biggest weaning studies done in the mid-1990s: the European trials by Brochard[1] and Esteban.[2] To be included in those studies, which compared pressure support, T-piece, and intermittent mandatory ventilation as weaning techniques, a patient had to be considered by their physicians to be not yet ready for weaning and anticipated to be a "problem-weaning" patient, and then they had to have a 2-hour T-piece SBT to qualify. At least 70% of the patients they considered could not be entered into the trials because the physicians were wrong and the patients could just be extubated and did fine. So I guess if NIV had been used immediately in those patients they also would have done fine.

1. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, et al. Comparison of 3 methods of gradual withdrawal from mechanical ventilation. Am J Respir Crit Care Med 1994;150(4):896-903.
2. Esteban A, Frutos-Vivar F, Tobin MJ, Alía I, Solsona JF, Valverdú I, et al. A comparison of 4 methods of weaning patients from mechanical ventilation. N Engl J Med 1995;332(6):345-350.

Hill: I think you could argue that NIV for patients with COPD in the extubation-failure group should be rated at least a "probably" if not a "yes." Ferrer's post-hoc analysis on post-extubation patients with hypercapnic respiratory failure found very impressive favorable results. But you seem to be cautious. I guess you want firmer

evidence. You have your evidence-based-medicine hat on.

Epstein: I believe in it, but the analysis was post-hoc and therefore not of the highest quality.

Hill: I have a theory about why the Esteban trial[1] found a greater difference in the failure to reduce reintubation rate. It's based partly on some of your observations on early versus late extubation failure. Didn't you find that the causes of early extubation failure were different than the causes of later extubation failure?

1. Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguía C, González M, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med 2004;350(24):2452-2460.

Epstein: Not quite. I found that both cause and time of extubation were independent factors. But, yes, the patients who tend to fail due to things such as upper-airway obstruction tend to be reintubated earlier.

Hill: And later on the extubation failure was more often due to pneumonia, sepsis, or secretions?

Epstein: Right. Same issue. Even if you control for time to reintubation, it's an independent predictor. In general you're right: those etiologies did tend to occur later.

Hill: Maybe that weakens my theory a bit, but here it is. What we tried to do in that trial was pick out at-risk people and intervene early so we could prevent extubation failure. But it didn't work. Now my theory is that we don't do a very good job of identifying early the patients who were going to develop the things that would make them poor NIV candidates. Thus, people who are later going to get pneumonia, sepsis, secretions problems—things that will contribute to NIV failure—get started on NIV.

An interesting aspect of the Esteban trial is that the 28 crossovers from the control group who were allowed to meet the failure criteria and then were put on NIV had a reintubation rate half that (25% vs 50%) of those who were started on NIV up front. So maybe we started too early, and if we would wait until patients meet the standard failure criteria and use our standard NIV selection criteria at that point (eg, ruling out people who are having problems with secretions or are getting septic), our success rate would be better. And this is the same high-risk population that Stefano studied.[1]

1. Nava S, Gregoretti C, Fanfulla F, Squadrone E, Grassi M, Grassi M, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med 2005;33(11):2465-2470.

Epstein: So you don't mean we started too early; you're saying we didn't pick the right patients.

Hill: I'm saying that it's hard to pick the right patients *early*, which explains what happened in the Esteban study, I think.

Epstein: Well maybe, but Ferrer picked patients before they were even extubated. Actually, one of their risk criteria was secretions.

Hill: Stefano's study. That is correct.

Nava: Very few patients, about 5%, met our criteria. And then I think there was difficulty with a score of about 10, so that means it's not as effective as it should be, but we can at least clear the secretions.

Hill: So, what do you think of my theory?

Nava: I think you're right.

Epstein: One of the secondary studies[1] that came out of the study by Esteban[2] looked at predictors of extubation failure. Predictors were positive fluid balance 24 hours before extubation, rapid shallow breathing index (with a very bizarre cutoff value of 57), and then pneumonia as the diagnosis for mechanical ventilation in the first place.

1. Frutos-Vivar F, Ferguson ND, Esteban A, Epstein SK, Arabi Y, Apezteguía C, et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. Chest 2006;130(6):1664-1671.
2. Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguía C, González M, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med 2004;350(24):2452-2460.

Nava: And fluid balance?

Epstein: Yes, fluid balance 24 hours before extubation.

Hess: There's another group of patients who from time to time get extubated directly to NIV. Josh Benditt may want to comment on this, because he sees these patients, as I do. These are patients with neuromuscular disease who are on 24-hour NIV at home, and then they are admitted to the hospital and get intubated for a couple days, and then we extubate them directly to NIV. John Bach published some of his experience with patients who get tracheostomized and are decannulated to NIV.[1,2] There haven't been any RCTs, but certainly there's some observational experience.

1. Bach JR, Saporito LR. Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure: a different approach to weaning. Chest 1996;110(6):1566-1571.
2. Bach JR, Saporito LR. Indications and criteria for decannulation and transition from invasive to noninvasive long-term ventilatory support. Respir Care 1994;39(5):515-528.

Hill: I was taken to task by a letter-writer for not mentioning, in one of our review articles, NIV for neuromuscular disease patients with acute respiratory failure. The reason we didn't mention them is that in the acute-care hospital we see these patients very infrequently; they constitute only a few percent of all the acute NIV applications. Part of the reason is that I think we're doing a much better job of keeping them out of the hospital in the first place.

When they get a respiratory infection at home, I generally put them on 24-hour-a-day NIV for a few days, usually with a cough-assist device, as needed, and I try to avoid hospitalizing them. So they don't get admitted to our acute-care hospital unless we can't manage them noninvasively at home, which means that they're often so sick they need to be intubated.

I find acute-care hospitals often do a poor job of managing these patients, because our personnel aren't familiar with their needs, and the environment is so foreign to them. I've had the experience of these people being totally mismanaged after surgery. I was called by one of the patient's aides after the patient had had abdominal surgery, and they were trying to do an SBT on her before extubating her. This was on a woman who had severe restriction and required nearly continuous NIV.

1. Garpestad E, Brennan J, Hill NS. Noninvasive ventilation for critical care. Chest 2007;132(2):711-720.

Benditt: Yes, before a surgery with any of these neuromuscular patients we have a conference with the anesthesiologist and get everything set up in the post-anesthesia care unit.

Hess: We do that too.

Benditt: Planning is so crucial with these people.

Nava: Do you think age should be considered a risk factor?

Epstein: It's clearly a risk, but is it an incremental risk or is there a cutoff?

Nava: Most of the studies with the outcome of mechanical ventilated patients show that age is not a detrimental factor.

Epstein: Right, but that's a different issue. In extubated patients I think a lot of this has to do with poor cough and abnormal mental status in older patients, but that's speculation.

Hill: I was amused in looking at the Antonelli study's[1] risk factors for failure of patients with hypoxemic respiratory failure, because age 40 is the cutoff. Makes me feel very old.

1. Antonelli M, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, Confalonieri M, et al. Predictors of failure of noninvasive positive-pressure ventilation in patients with acute hypoxemic respiratory failure: a multicenter study. Intensive Care Med 2001; 27(11):1718-1728.

Epstein: Looks like we'll all be intubated shortly.

Mehta: In the Ferrer trial[1] they applied NIV in all patients who were considered high-risk, which they defined as over age 65. A very high percentage of my patients are over 65, so using NIV in all of them is just not practical.

1. Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med 2006;173(2): 164-170.

Epstein: Whether it's practical depends on your resources. I don't think we're doing this routinely, although we've done it in some patients. I think if somebody wanted to continue to study this topic, they should refine the predictive criteria, because there are some differences between Stefano's and Ferrer's studies.

Mehta: We do it in certain patients too, but not in patients whose only risk factor is age. There have to be other factors.

Epstein: Yes, I would probably never use age as the sole factor.

Kacmarek: I think that's a little misleading, because their unit is primarily a pulmonary unit, not a general ICU, so almost everybody admitted to it has comorbidities such as COPD or congestive heart failure. I think age is a secondary issue.