Noninvasive Ventilation for Patients Presenting With Acute Respiratory Failure: The Randomized Controlled Trials

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Summary

Noninvasive ventilation (NIV) in patients with acute respiratory failure (ARF), which was originally described decades ago, underwent a rebirth after reports of successful use in 1989. Over the following 18 years the literature on NIV has grown substantially. This paper summarizes the randomized controlled trials (RCTs) on NIV for acute respiratory failure. We conducted an extensive literature search and selected RCTs from that search. The results are presented primarily by etiology of respiratory failure, but we also include a short section on NIV for ARF in immunocompromised patients. The latter studies included patients with various etiologies of respiratory failure but with the common comorbidity of immunocompromise. Most of the RCTs have studied NIV for exacerbation of chronic obstructive pulmonary disease (COPD) or cardiogenic pulmonary edema. In general the RCTs have been small and used endotracheal intubation or NIV failure rate as primary outcomes. We conclude that NIV for ARF is supported by strong evidence from patients with COPD, but there is only weak support for NIV in other patient groups, such as immunocompromised patients. For other groups, such as patients with asthma, pneumonia, or acute lung injury, RCT-level evidence is lacking or does not suggest benefit. Clearly, major gaps remain in our evidence base. Key words: noninvasive ventilation, NIV, acute respiratory failure, chronic obstructive pulmonary disease, COPD, cardiogenic pulmonary edema, intubation, immunocompromise, asthma, pneumonia, acute lung injury, acute respiratory distress syndrome, ARDS. [Respir Care 2009;54(1):116–124. © 2009 Daedalus Enterprises]

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Introduction

Over the last 20 years we have seen the use of noninvasive ventilation (NIV) flourish in the treatment of acute respiratory failure (ARF). Meduri and colleagues were among the first to describe the modern-day use of mask ventilation to obviate endotracheal intubation.\(^1,2\) The literature on NIV has evolved from case series to randomized controlled trials (RCTs). The RCTs have differed in patient populations, interventions applied, sample size, definition of treatment-failure, and options available for patients who failed their assigned treatment arm.

This paper summarizes the published evidence on NIV for ARF. We will briefly review etiologies of ARF; discuss general concerns with the literature and some points to consider when reading RCTs on NIV; review the available RCTs and group them by patient population; and then summarize the evidence and highlight NIV uses we believe have sufficient support, and uses that deserve further research. NIV for ARF in patients with acute cardiogenic pulmonary edema and after extubation is discussed in other papers in this conference.\(^3,4\)

We searched PubMed with the terms “noninvasive ventilation,” “non-invasive ventilation,” “noninvasive positive-pressure ventilation,” “non-invasive positive-pressure ventilation,” “nasal ventilation,” “BiPAP,” and “continuous positive airway pressure.” We also scanned the bibliographies of selected papers and reviewed our personal files. We conduct ongoing literature searches on NIV in MEDLINE, EMBASE, and the Cochrane database. In this review we restrict our consideration to RCTs. Studies of other designs were considered for background only. We did not include trials that have only been published in abstract form.

Acute Respiratory Failure

Though ARF can be defined in various ways, for the purposes of this review we will begin by dividing ARF into 2 groups (Fig. 1): hypoxemic, and hypercapnic, although individual patients may present with elements of both. Hypoxemic respiratory failure arises from a mismatch of ventilation and perfusion, most often as a result of fluid filling the alveoli. Hypercapnic respiratory failure arises when there is a decrease in the drive to breathe, a problem with the neuromuscular axis of breathing, or an increase in the work of breathing, usually due to airway obstruction. Table 1 summarizes the RCTs.

Issues to Consider When Reading RCTs on NIV

On reviewing the published RCTs of NIV for ARF, we made several observations. First, the etiology of the ARF strongly influences the likelihood of success, so we did not include trials that included patients with heterogeneous causes of ARF that did not report separate results for the different ARF etiologies.\(^5-8\) We did include trials that enrolled heterogeneous patient groups that did report outcome by ARF etiology.\(^9,11\)

Second, most trials were investigator-initiated, and the number of patients was small, particularly compared to the large multicenter trials with critically ill patients with sepsis or acute respiratory distress syndrome (ARDS). Reasonable sample size calculations are variably reported, leading to the potential for these trials to be underpowered, and it is only by systematically reviewing and summarizing all the literature for a specific patient group that we can get the best appreciation of the potential benefits of NIV in ARF.

Patient outcomes reported in trials usually focus on the need for endotracheal intubation, as NIV has overwhelmingly been studied as a means to avoid endotracheal intubation in the earlier stages of ARF. Other outcomes reported include mortality and success versus failure of NIV. Failure is generally defined by gas exchange and physiologic variables such as respiratory rate and level of consciousness. Though the failure/success rates may appear to be consistent with the criteria for endotracheal intubation, patients who fail their

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**Fig. 1.** Etiologies of acute respiratory failure. CNS = central nervous system. COPD = chronic obstructive pulmonary disease.
assigned treatment (NIV or standard treatment) are handled differently, both within and among studies. Patients who fail in their assigned treatment arm may be intubated if they require ventilation. Mortality rate also depends on the whether the study includes do not-intubate patients, the patients’ severity of illness, and whether patients who fail standard therapy are allowed to cross over to NIV.

In summary, though hospital mortality would generally be considered the most important outcome to the patient and success/failure rate the “softest” outcome, in some studies the success/failure rate may actually be a better indicator of the effectiveness of NIV. Reported outcomes must be interpreted in the context of the patients included and the study design, especially the permission to cross over.

Table 1. Randomized Controlled Trials of Noninvasive Ventilation for Acute Respiratory Failure, by Etiology

<table>
<thead>
<tr>
<th>Etiology</th>
<th>RCTs (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemic Acute Respiratory Failure</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary edema</td>
<td>Not covered in this review</td>
</tr>
<tr>
<td>ALI/ARDS</td>
<td>3 NIV</td>
</tr>
<tr>
<td>Severe community-acquired or hospital-acquired pneumonia</td>
<td>2 NIV</td>
</tr>
<tr>
<td>Chest trauma</td>
<td>1 NIV</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>1 CPAP</td>
</tr>
<tr>
<td>Acute on chronic respiratory disease (eg, interstitial lung disease)</td>
<td>0</td>
</tr>
<tr>
<td>Hypercapnic Acute Respiratory Failure</td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>17 NIV</td>
</tr>
<tr>
<td>Asthma</td>
<td>2 NIV</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>0</td>
</tr>
<tr>
<td>Primary central nervous system</td>
<td>0</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial
ALI = acute lung injury
ARDS = acute respiratory distress syndrome
NIV = noninvasive ventilation
CPAP = continuous positive airway pressure

Hypoxic Respiratory Failure

Acute Lung Injury/Acute Respiratory Distress Syndrome

Table 2 summarizes the 4 RCTs with patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). One study was designed to determine the effectiveness of continuous positive airway pressure (CPAP) in patients with acute hypoxic respiratory failure.12 Though none of those patients were thought to present primarily with cardiogenic pulmonary edema, results were provided for subgroups with and without a cardiac history, and only data from the latter subgroup are included in Table 2. Delclaux and coworkers12 found no benefit from CPAP in patients with or without a cardiac history, and they observed more adverse events, the most concerning of which was cardiac arrest (n = 4) related to CPAP mask dislodgment or removal for endotracheal intubation. Based on the potential for harm identified in that study, we do not recommend CPAP for patients with ALI/ARDS. The harm is probably related to delay of endotracheal intubation, during which the underlying disease process progresses and reduces oxygen reserve.

No RCTs have been specifically designed to determine the effectiveness of NIV in patients with ALI/ARDS. Auriant and colleagues reported the use of NIV in a selected population of patients who developed post-lung-resection hypoxic respiratory failure.13 NIV was highly effective in preventing endotracheal intubation, and this translated into a mortality benefit. Though it was a single-center study with a small number of patients, the impressive results suggest that NIV may benefit post-lung-resection patients in hypoxic respiratory failure.

Two studies9,10 that enrolled various types of patients included patients with ALI/ARDS and reported their results by subgroups. The number of patients in both studies was extremely small (7 and 15, respectively), and no signal suggested NIV effectiveness. Despite an interesting recent cohort study that suggested that NIV can be safe in selected patients with ALI/ARDS,14 to date we lack properly powered RCT evidence, so we cannot currently recommend routine use of NIV for patients with ALI/ARDS.

Community-Acquired Pneumonia

Immunocompetent patients with severe community-acquired pneumonia frequently require ventilatory support. Two RCTs have been published: one that included a subgroup of patients with severe community-acquired pneumonia and reported the results of that subgroup,10 and one that focused specifically on patients with severe community-acquired pneumonia.11 Confalonieri and associates enrolled patients with severe community-acquired
pneumonia and found significantly less need for intubation and shorter ICU stay. However, those effects were due entirely to the subset of patients with chronic obstructive pulmonary disease (COPD) and community-acquired pneumonia; there was no benefit in patients without underlying COPD (Fig. 2). Conversely, in a study by Ferrer and coworkers, in the subgroup of patients with severe community-acquired pneumonia and hypoxemic respiratory failure, NIV was associated with significantly lower intubation rate and ICU mortality.10

The small number of studies and patients, and the inconsistency of those studies’ results preclude a recommendation for NIV in immunocompetent patients with severe community-acquired pneumonia.

Chest Trauma

Patients with severe chest trauma, determined by the presence of multiple rib fractures and various degrees of pulmonary contusion, frequently require immediate endotracheal intubation and mechanical ventilation because of the severity of the thoracic injuries or the presence of associated injuries such as traumatic brain injury. A subset of patients with chest trauma who present with initially stable or milder derangements of gas exchange may be considered at high risk for respiratory deterioration because of their injuries. Though no RCTS have evaluated NIV for preventing endotracheal intubation in these patients, 2 trials compared NIV or CPAP as alternatives to endotracheal intubation and conventional mechanical ventilation.15,16

Bolliger and colleagues compared NIV with epidural analgesia to endotracheal intubation, conventional ventilation, and systemic analgesia. NIV had shorter ICU and hospital stay and fewer complications.15 More recently, Gunduz and associates compared CPAP to endotracheal intubation and conventional ventilation in patients with flail chest, all of whom received systemic rather than epidural analgesia.16 There was a trend toward shorter ICU stay and, most impressively, a lower hospital mortality. These studies suggest that patients with chest trauma who do not require immediate intubation should not be intu-

![Fig. 2. Summary of the results of the subgroups in 2 studies10,11 of patients with severe community-acquired pneumonia who did not have associated chronic obstructive pulmonary disease (COPD), treated with or without noninvasive ventilation (NIV).]
<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>NIV Interface, Mode, Ventilator</th>
<th>Number of NIV Patients</th>
<th>Number of Control Patients</th>
<th>NIV Group Intubation/ Failure Rate</th>
<th>Control Group Intubation/ Failure Rate</th>
<th>( P ) (NIV vs Control Intubation/ Failure Rate)</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bott(^{15})</td>
<td>1993</td>
<td>Nasal mask, volume-cycled, portable ventilator</td>
<td>30</td>
<td>30</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Mortality (3/30 vs 9/30), breathlessness, and arterial blood gases all favored NIV.</td>
</tr>
<tr>
<td>Brochard(^{16})</td>
<td>1995</td>
<td>Face mask, pressure support, ICU ventilator</td>
<td>43</td>
<td>42</td>
<td>11</td>
<td>31</td>
<td>&lt;.001</td>
<td>Mortality, encephalopathy score, arterial blood gases, and duration of stay all favored NIV.</td>
</tr>
<tr>
<td>Kramer(^{17})</td>
<td>1995</td>
<td>Nasal or face mask, pressure support, portable ventilator</td>
<td>11</td>
<td>12</td>
<td>1</td>
<td>8</td>
<td>.02</td>
<td>Mortality, stay, costs similar. Oxygenation, respiratory rate, and heart rate improved faster in the NIV group.</td>
</tr>
<tr>
<td>Angus(^{18})</td>
<td>1996</td>
<td>Nasal mask, pressure support, portable ventilator</td>
<td>9</td>
<td>8</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Mortality not significantly different, but only patient in control arm died. More rapid increase in ( P_{aO_2} ) with NIV.</td>
</tr>
<tr>
<td>Barbe(^{19})</td>
<td>1996</td>
<td>Nasal mask, pressure support, portable ventilator</td>
<td>14</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>No difference in mortality, stay, or arterial blood gases. Milder-illness population treated on the ward.</td>
</tr>
<tr>
<td>Avdeev(^{20})</td>
<td>1998</td>
<td>Nasal or face mask, pressure support, portable ventilator</td>
<td>29</td>
<td>29</td>
<td>3</td>
<td>8</td>
<td>.18</td>
<td>Mortality, stay, breathlessness, and arterial blood gases all better in NIV group.</td>
</tr>
<tr>
<td>Celikel(^{21})</td>
<td>1998</td>
<td>Face mask, pressure support, ICU ventilator</td>
<td>15</td>
<td>15</td>
<td>1</td>
<td>6</td>
<td>&lt;.05</td>
<td>Mortality not different. Stay and arterial blood gases favored NIV group.</td>
</tr>
<tr>
<td>Confalonieri(^{19})</td>
<td>1999</td>
<td>Face mask, pressure support, ICU ventilator</td>
<td>12</td>
<td>11</td>
<td>0</td>
<td>6</td>
<td>&lt;.005</td>
<td>2-month mortality and ICU stay favored NIV group.</td>
</tr>
<tr>
<td>Plant(^{22})</td>
<td>2000</td>
<td>Nasal or face mask, pressure support, portable ventilator</td>
<td>118</td>
<td>118</td>
<td>18</td>
<td>32</td>
<td>.02</td>
<td>Mortality, arterial blood gases, and respiratory rate favored NIV group. No difference in stay.</td>
</tr>
<tr>
<td>Zhou(^{23})</td>
<td>2001</td>
<td>Face mask, pressure support, portable ventilator</td>
<td>30</td>
<td>30</td>
<td>7</td>
<td>17</td>
<td>&lt;.05</td>
<td>Arterial blood gases favored NIV group. No mortality or stay data.</td>
</tr>
<tr>
<td>Dickensoy(^{24})</td>
<td>2002</td>
<td>Face mask, pressure support, portable ventilator</td>
<td>17</td>
<td>17</td>
<td>2</td>
<td>7</td>
<td>&lt;.05</td>
<td>Arterial blood gases, respiratory rate, heart rate, and stay favored NIV group. No difference in mortality.</td>
</tr>
<tr>
<td>Castillo(^{25})</td>
<td>2003</td>
<td>Nasal or face mask, pressure support, portable ventilator</td>
<td>20</td>
<td>21</td>
<td>1</td>
<td>3</td>
<td>NS</td>
<td>Arterial blood gases, respiratory rate, heart rate, and stay favored NIV group. No difference in mortality.</td>
</tr>
<tr>
<td>Liao(^{26})</td>
<td>2004</td>
<td>Nasal mask, pressure support, portable ventilator</td>
<td>20</td>
<td>20</td>
<td>1</td>
<td>3</td>
<td>NS</td>
<td>Arterial blood gases, respiratory rate, heart rate, and stay favored NIV group. No difference in mortality.</td>
</tr>
<tr>
<td>Dhamija(^{27})</td>
<td>2005</td>
<td>Nasal or face mask, pressure support, portable ventilator</td>
<td>14</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>NS</td>
<td>Arterial blood gases, respiratory rate, heart rate and stay favored NIV group. No difference in stay or mortality.</td>
</tr>
<tr>
<td>Keenan(^{28})</td>
<td>2005</td>
<td>Nasal or face mask, pressure support, portable ventilator</td>
<td>25</td>
<td>20</td>
<td>2</td>
<td>5</td>
<td>.42</td>
<td>Trends towards faster reduction in dyspnea and stay with NIV. No difference in mortality.</td>
</tr>
<tr>
<td>Wang(^{29})</td>
<td>2005</td>
<td>Face mask, pressure support, portable ventilator</td>
<td>171</td>
<td>171</td>
<td>8</td>
<td>26</td>
<td>.002</td>
<td>No difference in arterial blood gases, mortality, or stay.</td>
</tr>
<tr>
<td>Matzanka(^{30})</td>
<td>2006</td>
<td>Face mask, pressure support, portable ventilator</td>
<td>30</td>
<td>30</td>
<td>3</td>
<td>10</td>
<td>.03</td>
<td>No difference in arterial blood gases, mortality, or stay. Less breathlessness at 1 h in NIV group.</td>
</tr>
</tbody>
</table>

\( \text{NIV} = \text{noninvasive ventilation} \)
\( \text{COPD} = \text{chronic obstructive pulmonary disease} \)
\( \text{ND} = \text{no data given} \)
\( \text{ICU} = \text{intensive care unit} \)
\( \text{NS} = \text{difference not significant} \)
bated prophylactically; NIV or CPAP appears to be a better alternative. However, these studies did not include control groups that received systemic or epidural analgesia alone. We also lack studies of the effectiveness of NIV as a rescue therapy in patients with chest trauma who develop delayed ARF.

**Hypercapnic Respiratory Failure**

The hypercapnic ARF category includes patients with COPD, asthma, neuromuscular disease, and primary central-nervous-system disorders. No RCTs have been published on NIV in patients with neuromuscular disease and primary central-nervous-system disorders (see Table 1).

**Chronic Obstructive Pulmonary Disease**

Excluding studies that have only been published in abstract form, 17 RCTs have compared NIV to standard therapy in patients with COPD exacerbations (Table 3).11,17-32 These trials represent international experience, were conducted in various settings (ICUs, emergency departments, and hospital wards), and included patients with a wide range of illness severity. Though only 9 of the 16 studies found a lower failure rate with NIV than with standard therapy,11,18,19,23-26,31,32 and only 3 of the trials reported lower hospital mortality,18,22,24 our systematic and critical review found some consistency in the findings. NIV appears to offer the greatest absolute reduction in failure rate, intubation rate, and hospital mortality in patients with more severe COPD exacerbations. There is also benefit for patients with milder COPD exacerbations, although the evidence is not as strong and is of a lesser degree (lower absolute risk difference). Overall, the evidence for benefit of NIV in patients with COPD exacerbations is strong, and we recommend that NIV be considered first-line therapy for patients who present with respiratory distress and respiratory acidosis. Future research on this topic should focus on optimizing the intervention, such as determining the best mode or interface for these patients. It is also important to note that all the trials excluded patients with the most severe COPD exacerbations (patients with decreased consciousness). Case series that described the use of NIV in patients with decreased consciousness suggest potential benefit33 and an RCT in this setting for patients who decline intubation would be of interest.

**Asthma**

Only 2 small trials have been conducted on NIV in patients with asthma. In a single-center trial with 30 patients, Soroksky and colleagues randomized patients who presented to their emergency department with asthma exacerbation to either NIV or sham NIV.34 The sham NIV was accomplished with a nasal mask but with holes cut in the tubing, and patients were encouraged to breathe through the mouth. Sorosky et al reported less need for hospital admission and more rapid improvement in FEV1 in the patients treated with NIV. The second trial was stopped early because of a recognized marked bias in recruitment, which precluded study completion and validity.35 The authors found only trends toward benefit from NIV in that setting. The evidence for NIV in patients with asthma remains weak.

**Impact of Other Patient-Specific Variables**

We believe that the etiology of the ARF is the most important variable that determines NIV effectiveness. However, other variables (eg, a do-not-intubate order) may contribute to the decision to use NIV or CPAP, regardless of the ARF etiology. There have been no RCTs of NIV in patients with do-not-intubate orders, and considerable ethical barriers may preclude such an RCT.

One patient-specific variable that has been studied is altered immune status. Two studies have evaluated NIV in immunocompromised patients with ARF (Fig. 3).9,36
In both studies the patients had heterogeneous etiologies of ARF, including cardiogenic pulmonary edema, pneumonia, and ARDS. In patients who had undergone solid-organ transplants and developed ARF, Antonelli and coworkers found a lower intubation rate and a strong trend toward lower ICU mortality. Hilbert and colleagues found significantly less endotracheal intubation, ICU mortality, and hospital mortality in immunocompromised patients with ARF and bilateral pulmonary infiltrates who were treated with NIV. Immunocompromised patients who undergo endotracheal intubation and mechanical ventilation tend to have very poor outcomes. Though more recent studies suggest that the prognosis of intubated patients may not be as dismal, we still recommend that NIV be considered for immunocompromised patients developing ARF. Clearly, the ARF etiology also impacts outcome, and these patients require close monitoring and early intervention if they deteriorate.

**Summary**

Over the past decade there have been numerous RCTs on NIV, and, to a lesser extent CPAP, for ARF. However, we still have large gaps in our knowledge. A tally of the RCTs discussed in this paper and in the forthcoming paper from this conference on NIV in patients with acute cardiogenic pulmonary edema reveals that more than 80% of the trials were conducted in patients with COPD or pulmonary edema. With the exception of a few trials, most of the studies were small and many did not include power calculations. Though we can confidently recommend NIV for COPD exacerbation, recommendations on NIV for other ARF etiologies are necessarily weaker.
mised patients should be considered for a trial of NIV, but there are not enough data to recommend NIV for patients with ALI/ARDS, severe community-acquired pneumonia, asthma, or chest trauma (Table 4).

We need larger RCTs, powered to detect clinically important differences in important outcomes, and to enroll patients with specific ARF etiologies. The necessary sample size will depend on the patient group studied, because it depends on both the baseline rate of the primary outcome and what is considered a clinically important difference in that outcome. We believe there is a pressing need to study the role of NIV in patients with asthma, community-acquired and hospital-acquired pneumonia, and ALI/ARDS.

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Discussion

Mehta: The results from the trials have been so heterogeneous. I would challenge you on one thing, and that is whether intubation is an objective outcome. I think it’s not an objective outcome, because it is most often based on a very subjective assessment. As you said, some people who need intubation don’t get intubated, and some people who don’t need intubation do get intubated, because of the intubation criteria. I think that’s one of the biggest problems with all of the NIV trials.

Keenan: By a “hard” outcome I meant one that can be clearly defined. I agree that there can be a bias in intubation rates, and I sometimes wonder whether patients who met intubation criteria and were intubated actually required it. I think the studies that have compared standard invasive ventilation to NIV also raise questions as to whether everybody had to get intubated.

Hill: Evidence-based medicine purists gag when they see these data. After the international consensus conference in 2000 a well-known clinical trialist on the jury said to me, “I can’t believe you people are presenting this as evidence: the numbers are so small!” The cardiologists turn up their noses as evidence: the numbers are so small!

The results from the trials that we actually looked for and documented in our study. Where our study differed was from people who said “You had all these people outside your study,” but we looked for it. We had some flak because in our study we were clearly choosing not to enrol patients with SAPS II scores of 35, but they had mortality of about 50%. I think patients with SAPS II of about 35, but they had mortality of about 50%. I think patients with SAPS II scores of 35 have
a predicted mortality below 20%. With these patients with ARDS, they kept them on NIV from 8 to 24 hours before intubating. It seemed like it was more than one study that found that, which is very concerning.


Keenan: There have been unrandomized studies that looked at patient variables that suggested bad outcomes with NIV. They included patients in shock. I think Antonelli’s study1 of NIV in hypoxic respiratory failure had a very good approach to selecting patients; they excluded patients in shock or with 2-organ failure, I believe. That study found that people who did okay with NIV had a low mortality rate, but those who failed NIV had a higher mortality rate. What that study design does, in effect, is to take a large group and separate them according to whether they can tolerate NIV. It remains unclear whether NIV helps these patients or whether tolerating it is a marker that the patient is going to do better.

I also think that experienced centers may be able to treat sicker patients successfully with NIV than those with less experience. Where I work we probably not treat patients with NIV that Stefano [Nava] would consider reasonable candidates, and his center would obtain good results with those patients. As you get better at it, you can probably try to extend it to people who are more sick, as long as they don’t have a lot of comorbidities.

Epstein: I agree with your concern about the high mortality rate. Part of it is that when you put a mask on these patients, you have a much higher $F_{IO_2}$ [fraction of inspired oxygen], and they have what looks to be an improvement in their $P_{A_{O_2}}$ even though their underlying process hasn’t changed and has probably deteriorated. I think we get fooled a lot.

Kallet: In one of Antonelli’s studies1 they found that patients who ultimately ended-up intubated had $P_{A_{O_2}}/F_{IO_2}$ ratio less than 175 mm Hg after 1 hour of NIV. The hospital mortality rate of those patients was quite high: something like 50%. Most of those patients were intubated within 8 to 12 hours for hypoxemia and dyspnea. So it might just be that we should have a shorter cut-off time for NIV in those patients whose oxygenation doesn’t improve very quickly.


Nava: I think that in 2 studies by Antonelli,1,2 the cut-off was after 1 to 2 hours, not 8 to 12 hours. So if you check blood gases after 1 or 2 hours and the $P_{A_{O_2}}/F_{IO_2}$ ratio does not improve to over 146 mm Hg, NIV failure is very likely. But I agree with Scott [Epstein] that one of the main problems is how do you measure $F_{IO_2}$ in those patients? It is not really easy, especially when you compare different patients.

You said that the patients who fail NIV and have hypoxic respiratory failure may have a higher mortality rate. That is not true of COPD patients. NIV failure is a mortality risk factor for patients with hypoxic respiratory failure, but not for those with COPD. That is a critically important message.


Kacmarek: Nick, I think the studies you mentioned are not RCTs. I agree with Stefano that they had very strict criteria for intubation. There are a lot of case series where NIV has been started for hypoxic respiratory failure and the $P_{A_{O_2}}$ increase, but clinically the patient looks horrible and nothing’s changed; they’re still working as hard, they’ve still got the same respiratory rate, tidal volume, et cetera. I tend to agree with Stefano [Nava]; it seems like we should make a stronger statement, based on the literature, regarding the potential danger of NIV in patients with acute hypoxic respiratory failure. I don’t see anything in the literature that strongly supports the use of NIV in those patients, and I see a ton of stuff that indicates that NIV does them a disservice.

Benditt: Bob, I agree entirely. To me it makes physiologic sense, because the main function of NIV is to reduce work of breathing, and that’s not the critical problem in patients with acute hypoxic respiratory failure. Hypoxemia can be dealt with in various ways; so I agree, it’s a chimera.

Kallet: I agree that clinically we put somebody on NIV, their blood gases improve slightly, the respiratory rate comes down a little bit, and the clinicians tend to say, “We’ll keep them there; we won’t intubate them just now.” I think it can really lull clinicians into a false sense of security with somebody whose lung injury is rapidly progressing.
Keenan: If you buy into the idea of the benefit of low tidal volume in acute lung injury, I wonder how well this can be applied with NIV. In the study by Antonelli the protocol had a tidal volume of 6 mL/kg. However, people who are failing NIV tend to work harder and breathe at greater tidal volumes, which makes me wonder if they're at risk of greater lung injury and whether patients that are not doing well with NIV may be at risk of harm, because there is that physiologic reason they could do worse. You may cause more lung injury in that short period of time that they're on NIV and not intubated.

Doyle: Regarding the patients with hypoxemic respiratory failure who had to be intubated, does the data include the starting required PEEP [positive end-expiratory pressure] when they were intubated? Because it's likely the intubated PEEP was much higher than they were receiving on NIV. It seems there's a lot of work to be done to determine the appropriate PEEP to make sure that the alveoli do not de-recruit when intubated. The average PEEP on NIV is often 5 cm H₂O, whereas 10 minutes after intubation the PEEP may be 10 to 16 cm H₂O.

Kacmarek: As far as I know, those data are not in those trials. They only recorded when and how many patients were intubated. From practical experience, you are correct; PEEP is much higher after intubation than during NIV, but you also sedate them and take over ventilation. It's a much different set of circumstances after intubation.

Hill: I was going to say the same thing. It's extremely difficult to give PEEP higher than about 8 cm H₂O in an acute setting, because patients don't tolerate it well, especially when you have to increase inspiratory pressure by an equal amount to maintain the same level of pressure support. When you intubate, you can increase PEEP because you don’t have the same limitations. Also we need to acknowledge that we don’t know the ideal PEEP.

Epstein: Sean, you showed 16 studies on COPD. Do you think this is a topic on which we can stop doing randomized controlled trials?

Keenan: Yes, definitely. Though it is gratifying to see a large number of RCTs on this NIV topic over the last 10 years, almost all were on pulmonary edema or COPD. We need to concentrate on other questions about NIV now.


Doyle: We may not be protecting them from de-recruitment if we’re start at 5 or 6 cm H₂O, because of limitations with NIV.

Hill: But we don’t know if higher PEEP improves outcomes more than lower PEEP.

Nava: I have a provocative question. How far can you go? Do you have firm limits to intubating a patient? The average pH in the RCTs in patients with COPD has been about 7.28, I think. If you consider patients with pH of 7.20 to 7.25, do you think we do not need to know more, to get information about very sick patients? It’s not likely to prevent further intervention.

Keenan: OK, I think I can buy that. Some case series have suggested that NIV can rescue patients who are comatose with COPD exacerbation. One issue will be whether you would restrict an RCT on patients with exacerbations of COPD, low pH, and decreased consciousness to those who have elected not to be intubated. There may be ethics problems with using NIV in patients with decreased consciousness and who do wish to be intubated if necessary.