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

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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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Dr Keenan has had a relationship with Respironics. The authors report no other conflicts of interest related to the content of this paper.

Dr Keenan presented a version of this paper at the 42nd Respiratory Care Journal Conference, "Noninvasive Ventilation in Acute Care: Controversies and Emerging Concepts," held March 7-9, 2008, in Cancún, México.

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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.

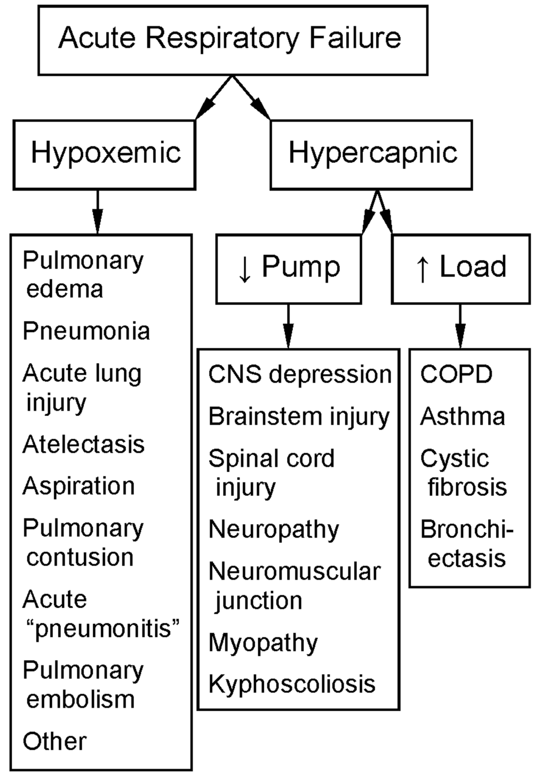

Fig. 1. Etiologies of acute respiratory failure. CNS = central nervous system. COPD = chronic obstructive pulmonary disease.

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

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

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

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

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, may cross over to NIV, or may continue with standard therapy alone. Trials that do not report specific success/failure criteria generally report endotracheal intubation criteria, so endotracheal intubation rate is the implicit success/failure rate for that study.

Interpreting intubation rates across studies or pooling these rates in meta-analyses must be done cautiously. Studies that allow crossover to NIV or include patients not to be intubated would report a lower rate of intubation in the control arm failure than those that only enroll patients that are to 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.

Hypoxemic 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 hypoxemic 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 coworkers[12] 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 dislodgement 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 hypoxemic 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 hypoxemic respiratory failure.

Two studies[9,10] 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

Table 2. Trials of NIV or CPAP in Patients With Acute Lung Injury/Acute Respiratory Distress Syndrome

First Author Year	Types of NIV, Interface, Mode, Ventilator	Number of CPAP or NIV Patients	Number of Control Patients	NIV Group Intubation/ Failure Rate (%)	Control Group Intubation/ Failure Rate (%)	*P* (NIV vs Control Intubation/ Failure Rate)	Other Outcomes
Delclaux[10] 2000 (ARDS subgroup)	CPAP vs standard therapy CPAP 7.5–10 cm H_2O	40	41	15	18	.18	No difference in mortality, stay. More adverse events in CPAP group.
Auriant[11] 2001	NIV vs standard therapy Nasal mask, pressure support, portable ventilator	24	24	5	12	.04	Mortality, heart rate, respiratory rate better with NIV. No difference in stay.
Ferrer[8] 2003 (ARDS subgroup)	NIV vs standard therapy Face mask, pressure support, portable ventilator	7	8	6	8	.47	No difference in mortality or stay.
Antonelli[7] 2000 (ARDS subgroup)	NIV vs standard therapy Face mask, pressure support, ICU ventilator	5	2	2	2	.28	No differences in mortality or stay.

NIV = noninvasive ventilation
CPAP = continuous positive airway pressure
ARDS = acute respiratory distress syndrome
ICU = intensive care unit

pneumonia and found significantly less need for intubation and shorter ICU stay.[11] 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-

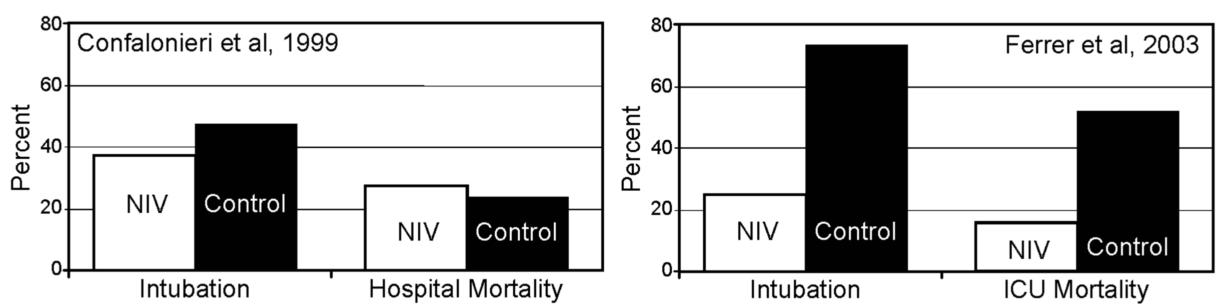

Fig. 2. Summary of the results of the subgroups in 2 studies[10,11] of patients with severe community-acquired pneumonia who did not have associated chronic obstructive pulmonary disease (COPD), treated with or without noninvasive ventilation (NIV).

Table 3. Randomized Trials That Compared NIV to Standard Therapy in Patients With COPD Exacerbation

First Author Year	NIV Interface, Mode, Ventilator	Number of NIV Patients	Number of Control Patients	NIV Group Intubation/ Failure Rate	Control Group Intubation/ Failure Rate	*P* (NIV vs Control Intubation/ Failure Rate)	Other Outcomes
Bott[15] 1993	Nasal mask, volume-cycled, portable ventilator	30	30	ND	ND	ND	Mortality (3/30 vs 9/30), breathlessness, and arterial blood gases all favored NIV.
Brochard[16] 1995	Face mask, pressure support, ICU ventilator	43	42	11	31	< .001	Mortality, encephalopathy score, arterial blood gases, and duration of stay all favored NIV.
Kramer[17] 1995	Nasal or face mask, pressure support, portable ventilator	11	12	1	8	.02	Mortality, stay, costs similar. Oxygenation, respiratory rate, and heart rate improved faster in the NIV group.
Angus[18] 1996	Nasal mask, pressure support, portable ventilator	9	8	ND	ND	ND	Mortality not significantly different, but only patient in control arm died. More rapid increase in P_{aO_2} with NIV.
Barbe[19] 1996	Nasal mask, pressure support, portable ventilator	14	10	0	0	NS	No difference in mortality, stay, or arterial blood gases. Milder-illness population treated on the ward.
Avdeev[20] 1998	Nasal or face mask, pressure support, portable ventilator	29	29	3	8	.18	Mortality, stay, breathlessness, and arterial blood gases all better in NIV group.
Celikel[21] 1998	Face mask, pressure support, ICU ventilator	15	15	1	6	< .05	Mortality not different. Stay and arterial blood gases favored NIV group.
Confalonieri[9] 1999	Face mask, pressure support, ICU ventilator	12	11	0	6	< .005	2-month mortality and ICU stay favored NIV group
Plant[22] 2000	Nasal or face mask, pressure support, portable ventilator	118	118	18	32	.02	Mortality, arterial blood gases, and respiratory rate favored NIV group. No difference in stay.
Zhou[24] 2001	Face mask, pressure support, portable ventilator	30	30	7	17	< .05	Arterial blood gases favored NIV group. No mortality or stay data.
Dickensoy[24] 2002	Face mask, pressure support, portable ventilator	17	17	2	7	< .05	Arterial blood gases, respiratory rate, heart rate, and stay favored NIV group. No difference in mortality.
Castillo[25] 2003	Nasal or face mask, pressure support, portable ventilator	20	21	1	3	NS	Arterial blood gases, respiratory rate, heart rate, and stay favored NIV. No difference in mortality.
Liao[26] 2004	Nasal mask, pressure support, portable ventilator	20	20	1	3	NS	Arterial blood gases, respiratory rate, heart rate, and stay favored NIV group. No difference in mortality.
Dhamija[27] 2005	Nasal or face mask, pressure support, portable ventilator	14	15	0	1	NS	Arterial blood gases, respiratory rate, and heart rate favored NIV group. No difference in stay or mortality.
Keenan[28] 2005	Nasal or face mask, pressure support, portable ventilator	25	29	2	5	.42	Trends towards faster reduction in dyspnea and stay with NIV. No difference in mortality.
Wang[29] 2005	Face mask, pressure support, portable ventilator	171	171	8	26	.002	No difference in arterial blood gases, mortality, or stay.
Matuska[30] 2006	Face mask, pressure support, portable ventilator	30	30	3	10	.03	No difference in arterial blood gases, mortality, or stay. Less breathlessness at 1 h in NIV group.

NIV = noninvasive ventilation
COPD = chronic obstructive pulmonary disease
ND = no data given
ICU = intensive care unit
NS = difference not significant

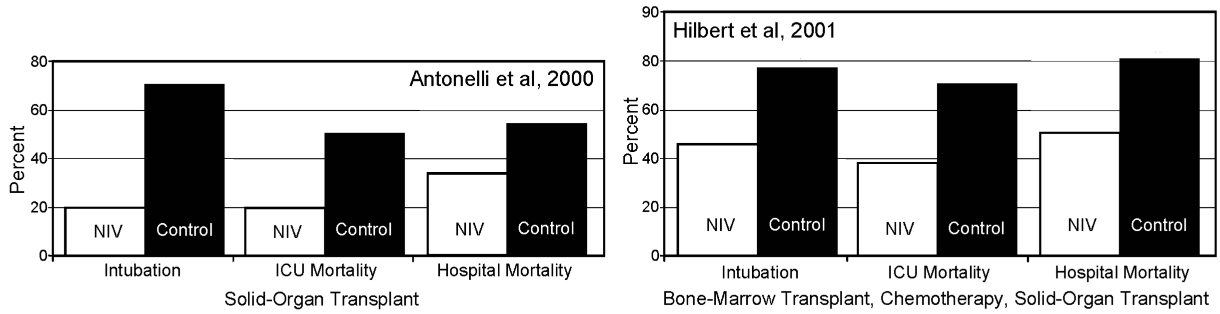

Fig. 3. Summary of the outcomes of 2 studies[9,36] of immunocompromised patients with acute respiratory failure treated with or without noninvasive ventilation (NIV).

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 benefit[33] 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 FEV_1 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]

Table 4. Summary of Evidence on Noninvasive Ventilation for Acute Respiratory Failure

Patient Population	Evidence	Intubation Benefit	Mortality Benefit	Possibility of Harm
Hypoxemic Respiratory Failure				
Acute lung injury/ARDS				
CPAP	1 RCT	No	No	Possible*
NIV	3 RCTs Small subgroups	Possible benefit for post-lung-resection patients Other patients: insufficient evidence	Possible benefit for post-lung-resection patients Other patients: insufficient evidence	Unclear†
Community-acquired pneumonia				
CPAP	No RCTs	Unclear	Unclear	Unclear
NIV	2 RCTs subgroups	Unclear: conflicting study results	Unclear: conflicting study results	Unclear
Chest Trauma				
CPAP	No RCTs‡	Unclear	Unclear	Unclear
NIV	No RCTs‡	Unclear	Unclear	Unclear
Hypercapnic Respiratory Failure				
COPD				
CPAP	No RCTs	Unclear	Unclear	Unclear
NIV	17 RCTs	Yes	Yes	Minimal§
Asthma				
CPAP	No RCTs	Unclear	Unclear	Unclear
NIV	2 RCTs	Unclear	Unclear	Unclear
Immunocompromised Patients				
CPAP	No RCTs	Unclear	Unclear	Unclear
NIV	2 RCTs	Probable‖	Probable	Unclear

* "Possible" implies some evidence in support.
† "Unclear" implies no evidence in support.
‡ The randomized controlled trials (RCTs) in patients with chest trauma (one study with continuous positive airway pressure [CPAP], one with noninvasive ventilation [NIV]) were not designed to test either intervention as a means of preventing intubation compared to epidural analgesia alone. Both CPAP and NIV appear to be better than intubating all patients with chest trauma.
§ "Minimal" implies that the evidence does not suggest harm other than pressure ulcers.
‖ "Probable" implies supporting evidence but small numbers of trials and patients.
COPD = chronic obstructive pulmonary disease

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.[9] 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.[36] Immunocompromised patients who undergo endotracheal intubation and mechanical ventilation tend to have very poor outcomes.[37] Though more recent studies suggest that the prognosis of intubated patients may not be as dismal,[38-40] 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[3] 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. Immunocompromised 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.

REFERENCES

1. Meduri GU, Conoscenti CC, Menashe P, Nair S. Noninvasive face mask ventilation in patients with acute respiratory ventilation. Chest 1989;95(4):865-870.
2. Meduri GU, Abou-Shala N, Fox RC, Jones CB, Leeper KV, Wunderink RG. Noninvasive face mask mechanical ventilation in patients with acute hypercapnic respiratory failure. Chest 1991;100(2):445-454.
3. Mehta S, Al-Hashim AK, Keenan SP. Noninvasive positive pressure ventilation in patients with acute cardiogenic pulmonary edema. Respir Care 2009 (in press).
4. Epstein SK. Noninvasive ventilation to shorten the duration of mechanical ventilation. Respir Care 2009;54(2):(in press).
5. Martin TJ, Hovis JD, Costantino JP, Bierman MI, Donahoe MP, Rogers RM, et al. A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. Am J Respir Crit Care 2000;161(3 Pt 1):807-813.
6. Wysocki M, Tric L, Wolff MA, Gertner H, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure. Chest 1993;103(3):907-913.
7. Thys F, Roeseler J, Reynaert M, Liistro G, Rodenstein DO. Noninvasive ventilation for acute respiratory failure: a prospective randomized placebo-controlled trial. Eur Respir J 2002;20(3):545-555.
8. Wood KA, Lewis L, Von Harz B, Kollef MH. The use of noninvasive positive pressure ventilation in the emergency department: results of a randomized clinical trial. Chest 1998;113(5):1339-1346.
9. Antonelli M, Conti G, Bufi M, Costa MG, Lappa A, Rocco M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. JAMA 2000;283(2):235-241.
10. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive ventilation in severe acute hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med 2003; 168(12):1438-1444.
11. Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Meduri GU. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med 1999;160(5 Pt 1):1585-1591.
12. Delclaux C, L'Her E, Alberti C, Mancebo J, Abroug F, Conti G, et al. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: a randomized controlled trial. JAMA 2000; 284(18):2352-2360.
13. Auriant I, Jallot A, Herve P, Cerrina J, Ladurie FLR, Fournier JL, et al. Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. Am J Respir Crit Care Med 2001; 164(7):1231-1235.
14. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, et al. A multiple-center survey of the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med 2007;35(1):18-25.
15. Bolliger CT, Van Eeden SF. Treatment of multiple rib fractures. Randomized controlled trial comparing ventilatory with nonventilatory management. Chest 1990;97(4):943-948.
16. Gunduz M, Unlugenc H, Ozalevii M, Inanoglu K, Akman H. A comparative study of continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) in patients with flail chest. Emerg Med J 2005;22(5):325-329.
17. Bott J, Carroll MP, Conway JH, Keilty SE, Ward EM, Brown AM, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet 1993;341(8860):1555-1557.
18. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1995;333(13):817-822.
19. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 1995;151(6):1799-1806.
20. Angus RM, Ahmed MM, Fenwick LJ, Peacock AJ. Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chroninc obstructive pulmonary disease. Thorax 1996;51(10):1048-1050.
21. Barbé F, Togores B, Rubí M, Pons S, Maimó A, Agustí AG. Noninvasive ventilatory support does not facilitate recovery from acute respiratory failure in chronic obstructive pulmonary disease. Eur Respir J 1996;9(6):1240-1245.
22. Avdeev SN, Tret'iakov AV, Grigor'iants RA, Kutsenko MA, Chuchalin AG. [Study of the use of noninvasive ventilation of the lungs in acute respiratory insufficiency due to exacerbation of chronic obstructive pulmonary disease.] Anesteziol Reanimatol 1998;(3):45-51. *Article in Russian.*
23. Celikel T, Sungur M, Ceyhan B, Karakurt S. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. Chest 1998; 114(6):1636-1642.
24. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomized controlled trial. Lancet 2000;355(9219):1931-1935.
25. Zhou R, Chen P, Luo H, Xiang X. [Effects of noninvasive positive pressure ventilation on gas exchange and patients' transformation in chronic obstructive pulmonary disease and respiratory failure.] Hunan Yi Ke Da Xue Xue Bao 2001;26(3):261-262. *Article in Chinese.*
26. Dikensoy O, Ikidag B, Feliz A, Bayram N. Comparison of noninvasive ventilation and Standard medical therapy in acute hypercapnic respiratory failure: a randomized controlled study at a tertiary health centre in SE Turkey. Int J Clin Pract 2002;56(2):85-88.
27. del Castillo D, Barrot E, Laserna E, Otero R, Cayuela A, Castillo Gómez J. [Noninvasive positive pressure ventilation for acute respiratory failure in chronic obstructive pulmonary disease in a general respiratory ward.] Med Clin (Barc) 2003;120(17):647-651. *Article in Spanish.*
28. Liao X, Li Q, Lin K, et al. Noninvasive positive pressure ventilation for early treatment of respiratory failure due to exacerbation of chronic obstructive pulmonary disease: a random controlled trial. Acta Academiae Medicinae Militaris Tertiae 2004;26:739-741.

29. Dhamija A, Tyagi P, Caroli R, Ur Rahman M, Vijayan VK. Noninvasive ventilation in mild to moderate cases of respiratory failure due to acute exacerbation of chronic obstructive pulmonary disease. Saudi Med J 2005;26(5):887-890.
30. Keenan SP, Powers CE, McCormack DG. Noninvasive positive-pressure ventilation in patients with milder chronic obstructive pulmonary disease exacerbations: a randomized controlled trial. Respir Care 2005;50(5):610-616.
31. Collaborative Research Group of Noninvasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease. Early use of noninvasive positive pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease: a multicentre randomized controlled trial. Chin Med J (Engl) 2005;118(24):2034-2040.
32. Matuska P, Pilarová O, Merta Z, Skricková J. [Non-invasive support in patients with acute exacerbation of chronic obstructive pulmonary disease.] Vnitr Lek 2006;52(3):241-248. *Article in Czech.*
33. Díaz GG, Alcaraz AC, Talavera JC, Pérez PJ, Rodriguez AE, Cordorba FG, Hill NS. Noninvasive positive-pressure ventilation to treat hypercapic coma secondary to respiratory failure. Chest 2005;127(3): 952-960.
34. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. Chest 2003;123(4):1018-1025.
35. Holley MT, Morrissey TK, Seaberg DC, Afessa B, Wears RL. Ethical dilemmas in a randomized trial of asthma treatment: can Bayesian statistical anlyasis explain the results? Acad Emerg Med 2001; 8(12):1128-1135.
36. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 2001;344(7):481-487.
37. Kress JP, Christiansen J, Pohlman AS, Linkin DR, Hall JB. Outcomes of critically ill cancer patients in a university hospital setting. Am J Respir Crit Care Med 1999;160(6):1957-1961.
38. Depuydt PO, Benoit DD, Vandewoude KH, Decruyenaere JM, Colardyn FA. Outcome in noninvasively and invasively ventilated hematologic patients with acute respiratory failure. Chest 2004;126(4): 1299-1306.
39. Azoulay E, Thiéry G, Chevret S, Moreau D, Darmon M, Bergeron A, et al. The prognosis of acute respiratory failure in critically ill cancer patients. Medicine (Baltimore) 2004;83(6):360-370.
40. Adda M, Coquet I, Darmon M, Thiéry G, Schlemmer B, Azoulay E. Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. Crit Care Med 2008; 36(10):2766-2772.

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 because they're used to trials that enroll thousands. Also, the issue of blinding has always been a big bugaboo in NIV trials, because with use of a sham, it's usually obvious which group a patient is in. And, depending on how you set it up, the sham might actually make breathing worse than no mask at all and contribute to worse outcomes.

You also alluded to the problem of "cherry-picking," when patients are enrolled (or not) into trials, which drives us all crazy. It's been a major problem. That was a big problem, I think, in Esteban's post-extubation trial.[1] With an enrollment consisting of only 10% COPD patients, investigators were clearly choosing not to enroll COPD patients in the trial because they didn't want to subject them to the possibility of invasive mechanical ventilation. I don't think there's any way of getting around these problems. This illustrates some of the major limitations of evidence-based medicine. I think we do the best we can, but we all have to acknowledge that, according to the standards of evidence-based medicine purists, our trials are far from ideal.

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.

Keenan: I'm glad you brought up cherry-picking, because in our study we looked for it. We had some flak from people who said "You had all these people outside your study," but I don't think that was unique to our study. Where our study differed was that we actually looked for and documented NIV use outside the study.

Kallet: I just read a paper on NIV for patients with ARDS, and I was struck by the mortality of the NIV group.[1] The patients had a SAPS II [Simplified Acute Physiology Score 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.

1. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med 2007;35(1):18-25.

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 study[1] of NIV in hypoxemic 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 would 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.

1. Antonelli M, Pennisi MA, Conti G. New advances in the use of noninvasive ventilation for acute hypoxaemic respiratory failure. Eur Respir J 2003;42(Suppl):65S–71S.

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_{aO_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 studies[1] they found that patients who ultimately ended-up intubated had P_{aO_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.

1. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med 2007;35(1):18-25.

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_{aO_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 hypoxemic respiratory failure, but *not* for those with COPD. That is a critically important message.

1. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med 2007; 35(1):18-25.
2. 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 multi-center study. Intensive Care Med 2001;27(11):1718-1728.

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 hypoxemic respiratory failure and the P_{aO_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 hypoxemic 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 hypoxemic 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.[1] 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.

1. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med 2007; 35(1):18-25.

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:* 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 H_2O, whereas 10 minutes after intubation the PEEP may be 10 to 16 cm H_2O.

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 H_2O 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.

Doyle: We may not be protecting them from de-recruitment if we're start at 5 or 6 cm H_2O, 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.

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