CRITICAL CARE ALERT®

A monthly update of developments in critical care and intensive care medicine

Thomson American Health Consultants Home Page— www.ahcpub.com

CME for Physicians— www.cmeweb.com; CE for Nurses— www.ceweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Higher vs Lower PEEP in ARDS

ABSTRACT & COMMENTARY

Synopsis: *In patients with acute lung injury or ARDS, the addition of higher PEEP levels to the strategy of a low tidal volume does not improve clinical outcomes.*

Source: The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. *N Engl J Med*. 2004;351:327-336.

THE AIM OF THE STUDY CARRIED OUT BY THE ARDS CLINICAL Trials Network investigators was to determine whether the use of higher levels of positive end-expiratory pressure (PEEP) would improve clinical outcomes among patients with acute lung injury or acute respiratory distress syndrome (ARDS) who were receiving mechanical ventilation with lower tidal volumes (6 mL per kilogram of predicted body weight) and inspiratory airway pressure (inspiratory plateau pressure 30 cm H_2O or less). The primary outcome measure was the proportion of patients who died before they were discharged home while breathing without assistance. Secondary outcome variables included the number of ventilator-free days (the number of days a patient breathed without assistance for at least 48 consecutive hours from day 1 to day 28), the number of days a patient was not in the ICU from day 1 to day 28, and the number of days without organ failure from day 1 to day 28.

This trial was conducted from October 1999 through February 2002 at 23 hospitals of the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. During this period, patients who were intubated and mechanically ventilated were eligible if there was a sudden decrease in the ratio PaO_2/FiO_2 to 300 mm Hg or less, a recent appearance of bilateral pulmonary infiltrates consistent with the presence of edema, and no clinical evidence of left atrial hypertension. These patients were randomly assigned to receive lower or high PEEP levels, adjusting PEEP and FiO_2 in discrete steps to maintain a SaO_2 (measured by pulse oximetry) of 88 to 95% or a PaO_2 of 55 to 80 mm Hg. The lower-PEEP strategy was the same used by the ARDS Clinical Trials Network investigators in their previous trial comparing ventilator strategies involving traditional and lower tidal volumes.[1] (*See Figure 1.*)

The higher-PEEP strategy was designed to use PEEP levels that were similar to those used in a previous trial in which higher PEEP levels and smaller tidal volumes were associated with better survival.[2] (*See Figure 1.*) Moreover, patients randomized to the higher PEEP group were required to have a PEEP of at least 12 cm H_2O for at least 12 hours after randomization to be included in that group. However, after 171 patients had been enrolled in the trial, the difference in mean PEEP levels between study groups on days 1 through 7 was less than the difference in the previous study that tested the effects of higher PEEP levels and smaller tidal volumes.[2] Then, to approximate more closely the separation in PEEP between study groups as in this previous trial, the steering committee (without knowledge of the clinical outcome data) decided to modify the higher-PEEP strategy by eliminating the steps with a PEEP of less than 12 cm H_2O and requiring a minimum PEEP of 14 cm H_2O for the first 48 hours (*see Figure 1*).

Figure 1

Allowable Combinations of PEEP and FiO_2

Lower-PEEP group														
FiO2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24
Higher-PEEP group														
FiO2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5-0.8	0.8	0.9	1.0	
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22-24	
Higher-PEEP group (after protocol's change)														
FiO2	0.3	0.3	0.4	0.4	0.5	0.5	0.5-0.8	0.8	0.9	1.0				
PEEP	12	14	14	16	16	18	20	22	22	22-24				

Adapted from: *ARDS Network. N Engl J Med. 2004;351:327-336.*

The study did not show that the use of higher PEEP resulted in a statistically significant clinical outcome benefit. Mean (± SD) PEEP values on days 1 through 4 were 8.3 ± 3.2 cm H_2O in the lower-PEEP group and 13.2 ± 3.5 cm H_2O in the higher-PEEP group ($P < 0.001$). The rates of death before hospital discharge were 24.9 % and 27.5 %, respectively ($P = 0.48$; 95 % CI for the difference between groups, -10.0 to 4.7 %) (*see Figure 2*). From day 1 to day 28, breathing was unassisted for a mean of 14.5 ± 10.4 days in the lower-PEEP group and 13.8 ± 10.6 days in the higher-PEEP group ($P = 0.50$). There were no significant differences in the numbers of ventilator-free and ICU-free days. There were no significant differences in the number of days without circulatory, coagulation, hepatic, or renal failure or in the incidence of barotraumas. Changes in plasma levels of interleukin-6, surfactant protein D, and intercellular adhesion molecule 1 from day 0 to day 3 did not differ significantly between study groups.

It is worthy of note that the data and safety board stopped the trial after 549 patients had been enrolled. At this time it was calculated that if the study had continued to the planned maximal enrollment of 750 patients, the probability of demonstrating the superiority of the higher-PEEP strategy was less than 1% under the alternative hypothesis based on the unadjusted mortality difference. However, although most of the baseline characteristics of the 2 study groups were similar, in the higher-PEEP group, the mean age was significantly higher

Critical Care Alert, ISSN 1067-9502, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

MANAGING EDITOR: Robert Kimball.

ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Critical Care Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Back issues: $40.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issues date.

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail Address: customerservice@ahcpub.com

Editorial E-Mail Address: robert.kimball@thomson.com

World Wide Web: http://www.ahcpub.com

Subscription Prices

United States

1 year *with* free AMA Category 1 credits: $269

(Student/Resident rate: $120)

Multiple Copies

Documents are available for multiple subscriptions. For pricing information, please call Steve Vance at (404) 262-5511.

Canada

Add GST and $30 shipping.

Elsewhere

Add $30 shipping.

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

This CME activity was planned and produced in accordance with the ACCME Essentials.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

AHC is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation. Provider approved by the California Board of Registered Nursing, Provider Number CEP 10864, for approximately 16 contact hours.

This CME activity is intended for the critical care physician. It is in effect for 36 months from the date of publication.

THOMSON AMERICAN HEALTH CONSULTANTS

Questions & Comments

Please call **Robert Kimball,** Managing Editor, at (404) 262-5413 or e-mail at robert.kimball@thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Ms. Ball serves as a consultant to Steris Corp, IC Medical, and AMT-Coherent (Canada), is a stockholder of Steris and SLT, and is on the speaker's bureau of AORN. Dr. Pierson is on the speaker's bureau of GlaxoSmithKline, Boehringer-Ingelheim, 3-M, Bayer, and Astra Zeneca. Dr. Rubenfeld is a consultant to Eli Lilly and is involved in research with the National Institutes of Health. Drs. Baigorri, Durbin, Hess, Hoffman, Johnson, and O'Keefe report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Drs. Crawford, Gladwin, Nanavaty, and Takezawa did not return a 2004 financial disclosure form. Thomson American Health Consultants accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that must meet all ACCME and ANCC requirements.

Figure 2

PEEP Levels and Mortality Rates Before and After the Higher-PEEP Protocol was Modified to Use Higher Levels of PEEP

		Lower-PEEP group	Higher-PEEP group	P value
Patients enrolled before modification of the higher-PEEP protocol	N	85	86	
	PEEP (cmH_2O)	8.4 ± 2.9	12.2 ± 3.5	< 0.001
	Mortality (%)	14.1	19.8	0.32
	Adjusted mortality (%)	16.4	17.5	0.83
Patients enrolled after modification of the higher-PEEP protocol	N	188	190	
	PEEP (cmH_2O)	8.2 ± 3.3	13.6 ± 3.5	< 0.001
	Mortality (%)	29.8	31.1	0.79
	Adjusted mortality (%)	32.8	28.3	0.29
Total	N	273	276	
	PEEP (cmH_2O)	8.3 ± 3.2	13.2 ± 3.5	< 0.001
	Mortality (%)	24.9	27.5	0.48
	Adjusted mortality (%)	27.5	25.1	0.47

Values of PEEP represent means (± SD). Mortality rates were adjusted for differences between the study groups at baseline in covariates that predict mortality.

Adapted from: *ARDS Network. N Engl J Med. 2004;351:327-336.*

(54 ± 17 vs 49 ± 17; $P = 0.004$) and the mean initial PaO_2/FiO_2 was significantly lower (151 ± 67 vs 165 ± 77; $P = 0.03$).

On the other hand, the authors also analyzed separately the results for the first 171 patients, studied before the modification of the higher-PEEP protocol, and the results for the subsequent 378 patients. Notably, the overall mortality rate among the first 171 patients was lower than that among the subsequent 378 patients (*see Figure 2*). This difference in overall mortality was associated with significant differences in several baseline characteristics that predict mortality. The authors assert that there was no apparent reason for these differences in baseline characteristics in the 2 phases of the trial other than chance variation. Baseline variables, main outcomes, and changes in plasma levels of interleukin-6, surfactant protein D, and intercellular adhesion molecule 1 from day 0 to day 3 were not significantly different between study subgroups in either the first 171 patients or the subsequent 378 patients.

Figure 3

Ventilatory Strategies to Optimize the Cardiovascular Status

Minimize detrimental hemodynamic effects of ventilation

- Prevent hyperinflation
  - "Least" PEEP
  - Prolonged expiratory time
  - Increased inspiratory flow rate
- Keep peak and mean airway pressure low
  - Promote spontaneous inspiratory efforts
  - Decrease inspiratory flow rate
- Keep the swings in intrathoracic pressure to a minimum
- Decrease the work-cost of breathing (in spontaneously breathing patient)
  - Match machine ventilatory pattern to patient's ventilatory pattern
  - Decrease inspiratory trigger threshold for assisted breath
  - Offset Auto-PEEP with extrinsic PEEP

Maximize beneficial hemodynamic effects of ventilation

- Maintain end-expiratory lung volume near functional residual capacity
  - Prevent hyperinflation in obstructive lung disease
  - Give minimal level of PEEP in hypoxemic respiratory failure
- Prevent large negative swings in intrathoracic pressure
  - Decrease inspiratory pressure threshold
  - Increase CPAP or PEEP to offset inspiratory effort
  - Decrease extrinsic airway resistance
- Add increased intrathoracic pressure only when venous return is adequate
  - Fluid resuscitation and inotropic support as necessary
  - Allow for spontaneous respiratory efforts with assisted breaths

Adapted from: *Pinsky M. Heart-Lung Interactions. In: Pathophysiological foundations of critical care. Pinsky M, Dhainaut J, eds. Baltimore, Md: Williams & Wilkins, 1993: 472-490.*

COMMENT BY FRANCISCO BAIGORRI, MD, PhD

I began my training in critical care a few years after Dr. Suter published, also in the *New England Journal of Medicine*, his study entitled "Optimum end-expiratory airway pressure in patients with acute pulmonary failure," showing that the end-expiratory pressure resulting in maximum oxygen transport (cardiac output times arterial oxygen content) and the lowest dead-space fraction both resulted in the greatest total static compliance.[3] It was then clear to me

that cardiovascular and respiratory systems work together to supply adequate amounts of O_2 to the tissues and that understanding heart-lung interaction is central to the management of critically ill patients. It is particularly important when mechanical ventilation is used to support our patients.

I also remember when I stopped hearing the prominent sound of ventilators cyclically inducing tidal air movement into patients' lungs. This happened after the article of Dr. Hickling,[4] by the end of the 1980s, alerted us about the risk of high inspiratory pressure. It was then suggested that it may be very important to limit inspiratory pressure by reducing tidal volume, even if this results in hypercapnia and a deterioration of oxygenation in the short term.

Altogether, our ventilatory strategies evolved guided by the principles of maximize beneficial hemodynamic effects of ventilation and minimize its detrimental effects, as summarized by Dr. Pinsky in the early nineties (*see Figure 3*).[5]

Recent data confirmed a significant survival benefit among patients who received a low tidal volume.[1] The present ARDS Clinical Trials Network study (despite its complicated methodology and difficult interpretation of the results) suggests that higher PEEP levels do not improve clinical outcomes among patients with acute lung injury or ARDS who are receiving mechanical ventilation with lower tidal volumes and inspiratory airway pressures. It would appear, then, that the more than 10 years old aforementioned principles of—maximize beneficial hemodynamic effects of ventilation and minimize its detrimental effects (*see Figure 3*)—should still guide our ventilatory strategies.[5]

This history raises in my mind the question of what should be the evidence needed for guiding our therapy. At this regard, a recent editorial of Intensive Care Medicine entitled "Searching for evidence: don't forget the foundations"[6] dealt with the issue of how to integrate the whole trail of research in a field and translate it into a usable product for the care of patients. In this editorial, a single, but striking, example of the importance of studies judged to have a low scientific value when compared with large randomised controlled trials is the first description of ARDS by Ashbaugh, Bigelow, Petty, and Levine.[7] It was a small case series. The editorial says: "The report would never qualify as an important contribution to current practice according to the criteria employed in an EBM [evidence-based medicine] search. This 1967 report described the basic characteristics of ARDS and the effects of PEEP on oxygenation. No clinical study has since proposed that patients with ARDS should be ventilated without PEEP. The report of Ashbaugh et al. still constitutes the basis for ventilator management of patients with ARDS." It seems there is not an easy answer. Ultimately, then, we can fall back on a perfectly rational and morally defensible principle of moral prudence. ■

References

1. Acute Respiratory Distress Syndrome network. *N Engl J Med.* 2000;342:1301-1308.
2. Amato BMP, et al. *N Engl J Med*. 1998; 338:347-354.
3. Suter PM, et al. *N Engl J Med*. 1975;292:284-289.
4. Hickling KG. *Intensive Care Med*. 1990;16:219-226.
5. Pinsky MR. Heart-lung interactions. In: *Pathophysiological Foundations of Critical Care*. Pinsky MR, Dhainaut JFA, eds. Baltimore, Md:Williams & Wilkins, 1993; 472-490.
6. Brochard L, et al. *Intensive Care Med*. 2003;29: 2109-2111.
7. Ashbaugh, DG, Bigelow DB, Petty TL, Levine BE. *Lancet*. 1967; 2:319-323.

Special Feature

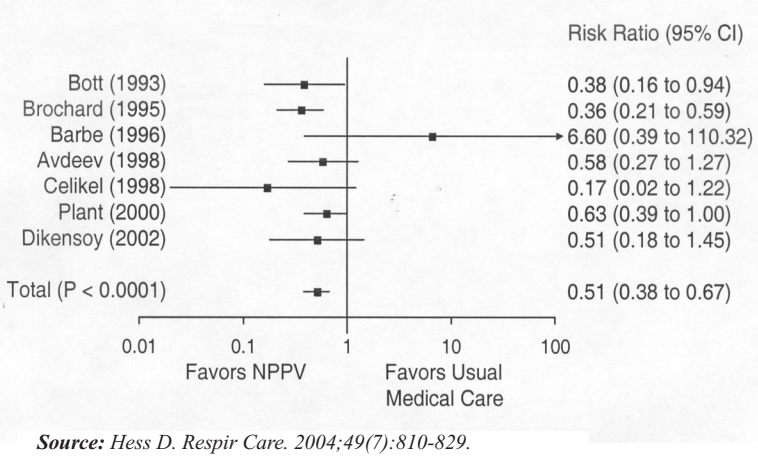
Noninvasive Positive-Pressure Ventilation: Current Evidence Supporting Practice

By Dean R. Hess PhD RRT

THERE CURRENTLY EXISTS MUCH EVIDENCE TO direct the application of noninvasive positive pressure ventilation (NPPV). NPPV for the treatment of patients with acute respiratory failure has generated several meta-analyses and systematic reviews,[1-4] including a recent one by me.[5] A prospective survey[6] for 3 weeks in 42 intensive care units found that NPPV was used as first-line therapy in 16% of mechanically ventilated patients. The first meta-analysis of NPPV was published by Keenan et al and concluded that the use of NPPV in acute respiratory failure affords a beneficial effect on survival and decreases the need for endotracheal intubation. Moreover, the survival advantage was greatest in patients presenting with an exacerbation of chronic obstructive pulmonary disease (COPD). Peter et al,[2] in their meta-analysis, concluded that there was a substantial reduction in mortality and the need for intubation with NPPV in acute respiratory failure—especially in the COPD subgroup. Lightowler et al[3] conducted a systematic review and meta-analysis

Figure 2

Pooled Analysis for Studies of the Use of NPPV to Treat Patients with Acute Hypoxemic Respiratory Failure. A:



Source: *Hess D. Respir Care. 2004;49(7):810-829.*

restricted to the use of NPPV for COPD exacerbation and reported that NPPV significantly reduced the risk of mortality, the risk of endotracheal intubation, complications of treatment, and length of stay in hospital (*Figure 1*). In another meta-analysis by Keenan et al,[4] they concluded that patients with severe COPD exacerbations benefit from the addition of NPPV to standard therapy.

NPPV for COPD Exacerbation

The strongest evidence for use of NPPV is for patients with COPD exacerbation.[5] A number of studies reported the use of NPPV only in patients with COPD and report benefit in this patient population with the exception of those with mild exacerbation. The use of NPPV for patients with COPD exacerbation is now considered a standard of care, the evidence for which is established in 2 meta-analyses.[3,4]

NPPV for Acute Asthma

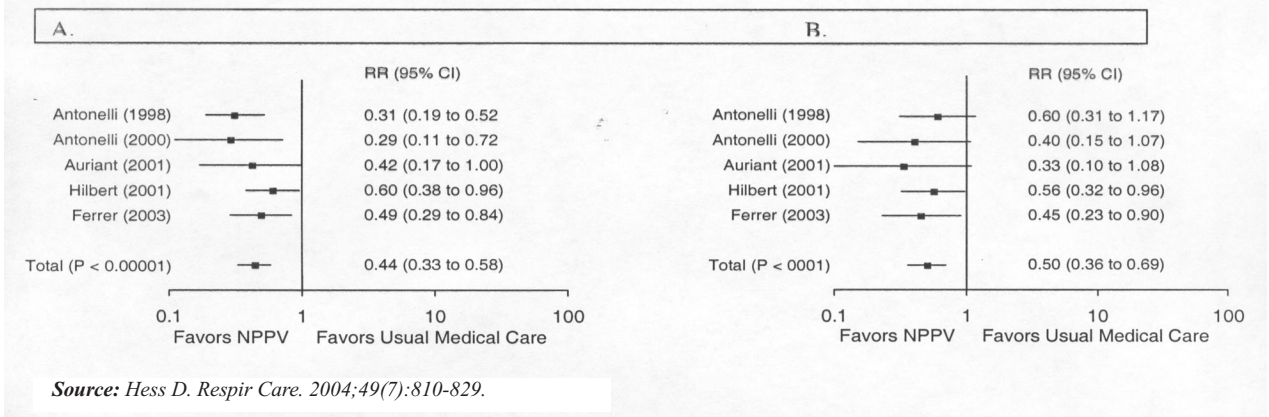
Compared to COPD, considerably less evidence exists for the use of NPPV in patients with asthma. Soroksky et al[7] reported the results of a randomized, controlled trial of NPPV for asthma exacerbation. Hospitalization was required for 3 of 17 patients (17.6%) randomized to NPPV compared to 10 of 16 patients (62.5%) in the control group ($P = 0.01$). Soroksky et al concluded that, in selected patients with a severe asthma, the addition of NPPV to conventional treatment can improve lung function, alleviate the exacerbation faster, and reduce the need for hospitalization. Before recommendations can be made regarding the use of NPPV in the treatment of asthma exacerbation, additional studies will be needed with larger sample sizes.

NPPV for Hypoxemic Respiratory Failure

An area of considerable controversy is the role of NPPV in patients with hypoxemia who are not hypercapnic. Unlike COPD, hypoxemic respiratory failure is a heterogeneous group of diagnoses. Five randomized controlled trials have reported success with the use of NPPV in patients with acute hypoxemic respiratory failure.[5] Evolving evidence supports the use of this therapy in such patients, albeit with evidence less compelling than that for COPD. As shown in Figure 2, intubation rate and mortality were lower in the patients receiving NPPV in each study evaluating its use in patients with acute hypoxemic respiratory failure.

Figure 2

Pooled Analysis for Studies of the Use of NPPV to Treat Patients with Acute Hypoxemic Respiratory Failure. A: Requirement for Intubation. B: Mortality.



Source: *Hess D. Respir Care. 2004;49(7):810-829.*

Cardiogenic Pulmonary Edema

Another area of controversy is the use of NPPV in the treatment of patients with acute cardiogenic pulmonary edema (CPE). Pang et al[8] conducted a systematic review of continuous positive airway pressure (CPAP) on mortality and the need for intubation in cardiogenic pulmonary edema. CPAP was associated with a decreased need for intubation (risk difference 26%; 95% confidence interval, 13 to 38%) and a trend towards a decreased hospital mortality (risk difference, 6.6%; 95% confidence interval, 3 to 16%) compared with standard therapy. Evidence was also lacking on the potential for harm associated to the use of CPAP in this patient population.

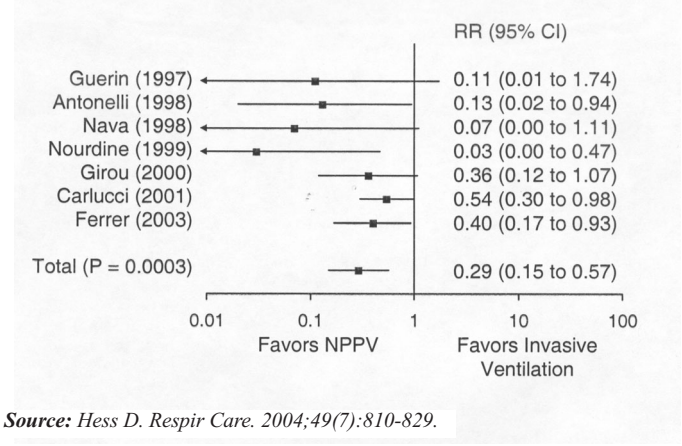
In contrast to the situation with CPAP, insufficient high-level evidence exists to allow recommendation of NPPV in the treatment of patients with acute CPE. Of concern is the risk for harm, with 2 studies reporting significantly greater rates of myocardial infarction in patients treated with NPPV.[9,10] Moreover, there is no clear evidence of benefit in terms of intubation rate or mortality with the use of NPPV. Subgroup analysis, however, suggests a benefit for the use of NPPV in hypercapnic patients with acute CPE.[11] Given the high level of evidence supporting the use of CPAP in this patient population, it seems reasonable to recommend the use of CPAP in hypoxemic patients with acute CPE, and to reserve NPPV for those who are also hypercapnic.

Peri-Extubation

The role of NPPV in the peri-extubation period remains to the determined. Only 4 randomized, controlled trials evaluated the role of NPPV to allow earlier extubation and only 2 of those were positive.[5] The positive trials might relate to their enrollment of patients with COPD. Thus, one might consider the use of NPPV to facilitate earlier extubation of patients with COPD. Both randomized trials of NPPV for patients who failed planned extubation were negative,[12,13] suggesting a limited role of NPPV in this setting. In the most recent study[13] examining the role of NPPV in patients with failed extubation, the mortality rate was higher among patients assigned to NPPV than among those assigned to standard medical therapy, and the interval from the development of respiratory failure to reintubation was significantly longer with NPPV than with standard therapy.

Figure 3

Pooled Analysis for Studies that Compared the Rate of Nosocomial Pneumonia for NPPV and for Invasive Mechanical Ventilation.



Source: *Hess D. Respir Care. 2004;49(7):810-829.*

Noninvasive Ventilation and Nosocomial Pneumonia

It is now well accepted that nosocomial pneumonia in mechanically ventilated patients is due to aspiration of pharyngeal secretions rather than to what is breathed from the ventilator. It follows that the risk of nosocomial pneumonia should be decreased if mechanical ventilation is provided with NPPV rather than through an endotracheal tube. The incidence of nosocomial pneumonia with NPPV has been compared with invasive mechanical ventilation in 7 studies and every one of them reported that the rate of nosocomial pneumonia was lower with NPPV. The combined risk of pneumonia is significantly reduced with the use of NPPV (*see Figure 3*).

Predictors of Success

NPPV is not universally successful in the avoidance of intubation. Although reported success rates vary, 25% or more of patients with acute respiratory failure who receive NPPV require intubation. It is useful to identify patients who have a higher likelihood for NPPV failure so that this may be anticipated and endotracheal intubation performed promptly if necessary. Predictors of NPPV failure include higher APACHE score, lower level of consciousness, lower pH, more air leak around the interface, greater quantity of secretions, poor initial response of NPPV, and the presence of pneumonia.[5] NPPV may be least likely to be successful in patients who are most sick. This should not dictate that some patients should not receive a trial of NPPV, but should provide a lower threshold for intubation knowing that these patients have a high likelihood to failure of NPPV.

The Interface for NPPV

Both nasal and oronasal interfaces have been applied successfully in randomized controlled trials. An oronasal interface may be more effective and better tolerated than the nasal interface for patients with acute respiratory failure.[14] An issue related to the interface and headgear is facial skin breakdown. The use of a mask of proper size, avoiding placing the headgear too tightly, and the use of wound-care tape on the bridge of the nose are important considerations to avoid facial skin breakdown.

A relatively new interface for application of NPPV is the helmet, which fits over the entire head of the patient and fits snugly around the neck.[15] Potential advantages of this design include ability of the patient to interact with the environment, a fixation system that should have a lower risk of skin breakdown, and it can be applied to any patient regardless of facial contour. Concerns with this interface include the risk for rebreathing, and effective triggering and cycling of the ventilator. Until these issues are resolved, the helmet cannot be recommended for the treatment of hypercapnic respiratory failure with NPPV.

The Ventilator for NPPV

Although any ventilator can be used to provide NPPV, the most commonly used are the bilevel or BiPAP® ventilators. These ventilators are designed to operate in the presence of a leak. They typically apply an inspiratory positive airway pressure (IPAP) and an expiratory positive airway pressure (EPAP). Breaths are triggered by the patient and the difference between the IPAP and EPAP is the level of pressure support. They are blower devices that use a single limb circuit. There is no exhalation valve, with the fixed leak in the circuit serving as the exhalation port. The available evidence suggests that these ventilators trigger and cycle as well as, and sometimes better than, critical care ventilators.[5]

An issue that has received considerable attention with the portable pressure ventilators is the potential for rebreathing.[16] Although a potential for rebreathing is present with bilevel ventilators, this can be minimized if the leak port is in the mask rather than the hose, if oxygen is titrated into the mask rather than the hose, if a higher level of EPAP is used, and with the use of a plateau exhalation valve. Anything that increases the leak increases the flow through the hose and more effectively flushes the hose and decreases the amount of rebreathing.

Most bilevel ventilators, however, do not have an oxygen control and thus supplemental oxygen is usually administered by adding it into the mask or the circuit. When administering oxygen with a portable pressure ventilator that does not have an oxygen blender, the delivered oxygen concentration is affected by oxygen flow, the site where oxygen in added into the circuit, the position of the leak port, the type of leak port, the amount of leak (intentional and non-intentional), and the IPAP and EPAP settings.[17] Due to the complex interaction between these variables, pulse oximetry should be used to monitor oxygenation when using this therapy in patients with acute respiratory failure.

There is controversy related to the need for humidification during NPPV. Unlike invasive mechanical ventilation, the upper airway is not bypassed with NPPV. When a bilevel ventilator is used, much of the delivered gas is from the surrounding room (except for the supplemental oxygen) and should thus have the same humidity content that the patient would breathe if not receiving NPPV. Anecdotally, I have found greater patient comfort, greater compliance, and less upper airway drying when NPPV is used with a humidifier. Aerosolized bronchodilators can be effectively delivered during NPPV and thus there is no need to temporarily interrupt NPPV to administer these. The evidence for use of MDI during NPPV is not as strong as that for use of nebulizer, but the available evidence suggests that MDI can be used effectively during NPPV.[5]

Several studies have evaluated the combination of heliox with NPPV in patients with COPD.[5] However, further work is needed before a recommendation can be made regarding heliox administration during NPPV. Several short-term studies suggest physiologic benefit when heliox is combined with NPPV in patients with COPD exacerbation.[18] But there is only one randomized controlled study that assessed outcomes such an intubation rate and mortality and the results of that study were inconclusive. Of concern is the potential for ventilator malfunction when used with heliox.

Clinical Application

Incorporation of NPPV into usual clinical practice requires a concerted effort by physicians, respiratory therapists, and nurses. A suggested approach to initiation of NPPV is as follows:

- Determine that patient is a good candidate for NPPV (eg, COPD exacerbation);
- Choose a ventilator capable of meeting patient needs;
- Choose the correct interface; avoid mask that is too large;

- Explain therapy to the patient;
- Silence alarms and choose low settings;
- Initiate NPPV while holding mask in place;
- Secure mask, avoiding a tight fit;
- Titrate pressure support (IPAP) to patient comfort;
- Titrate FIO_2 to SpO_2 > 90%
- Avoid peak inspiratory pressure > 20 cm H_2O
- Titrate PEEP (CPAP/EPAP) per trigger effort and SpO_2
- Continue to coach and reassure patient; make adjustments to improve patient compliance

Summary

High-level evidence exists for the use of NPPV in patients with COPD exacerbation. This form of ventilatory support has also been used successfully in selected patients with acute hypoxemic respiratory failure and to allow earlier extubation of mechanically ventilated patients following COPD exacerbation. The role of NPPV in patients with acute cardiogenic pulmonary edema is inconclusive. Both nasal and oronasal interfaces have been used successfully with NPPV, although the oronasal interface is often preferred for acute respiratory failure. Bilevel ventilators with the pressure support mode are most commonly used for NPPV, although any ventilator and mode can be used successfully. NPPV can be combined with inhaled bronchodilators and heliox. ■

References

1. Keenan SP, et al. *Crit Care Med*. 1997; 25:1685.
2. Peter JV,et al. *Crit Care Med*. 2002; 30:555.
3. Lightowler et al. *BMJ*. 2003; 326:185.
4. Keenan SP, et al. *Ann Intern Med*. 2003; 138:861.
5. Hess DR. *Respir Care*. 2004;49(7):810-29.
6. Carlucci A, et al. *Am J Respir Crit Care Med*. 2001;163:874.
7. Soroksky A, et al. *Chest*. 2003;123:1018.
8. Pang D, et al. *Chest*. 1998;114:1185.
9. Mehta S, et al. *Crit Care Med*. 1997;25:620.
10. Sharon A, et al. *J Am Coll Cardiol*. 2000;36:832.
11. Nava S, et al. *Am J Respir Crit Care Med*. 2003;168:1432.
12. Keenan SP, et al. *JAMA*. 2002; 287:3238.
13. Esteban, et al. *N Engl J Med*. 2004;350;24.
14. Kwok H, et al. *Crit Care Med*. 2003;31:468.
15. Antonelli M, et al. *Anesthesiology*. 2004;100:16.
16. Ferguson GT, et al. *Am J Respir Crit Care Med*. 1995;151:1126.
17. Schwartz AR, et al. *Respir Care*. 2004;49:270.
18. Hotchkiss JR, et al. *Am J Respir Crit Care Med*. 2001;163:374.

CME / CE Questions

22. The use of higher PEEP levels in patients with acute lung injury or ARDS who are receiving mechanical ventilation with lower tidal volumes and inspiratory airway pressure is associated with:

a. a significant decrease in plasma levels of interleukin-6.
b. no significant differences in survival nor in the numbers of ventilator-free and ICU-free days.
c. no significant differences in numbers of ventilator-free and ICU-free days but an increment in the incidence of barotrauma.
d. a significant improvement of survival but no changes in organ failure.
e. no significant differences in survival but a significant reduction in plasma levels of surfactant protein D.

23. For which of the following diagnoses has NPPV been shown to have the greatest success?

a. COPD
b. Acute cardiogenic pulmonary edema
c. Extubation failure
d. Asthma
e. Cystic fibrosis

24. Which of the following ventilator modes is most commonly used for NPPV?

a. Volume-controlled ventilation
b. Pressure-controlled ventilation
c. Pressure support ventilation
d. Volume support ventilalation
e. Airway pressure-release ventilation

Answers: 22 (b); 23 (a); 24 (c)

CME / CE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

In Future Issues: **Colloid or Crystalloid?**

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

New Clinical Guidelines on Cholesterol Management

The National Cholesterol Education Program (NCEP), a product of a collaboration of the National Heart, Lung, and Blood Institutes, the American College of Cardiology, and the American Heart Association, has updated its clinical practice guideline on cholesterol management. Based on several recent studies, that suggest that aggressive lowering of LDL cholesterol benefits high-risk patients, the new guidelines recommend aggressive treatment for patients who are at risk for coronary artery disease. Specifically, patients who are defined as "very high-risk" should be considered for aggressive treatment. Very high-risk patients are defined as those who have cardiovascular disease together with multiple risk factors (especially diabetes), severe and poorly controlled risk factors (such as continued smoking), or metabolic syndrome. The guideline had previously recommended drug therapy in these patients only if the LDL cholesterol was greater than 130 mg/dL, with a goal of 100 mg/dL. The new guideline recommends a treatment threshold of 100 mg/dL, with a goal of 70 mg/dL. "High-risk patients" are defined as those who have coronary heart disease, cerebrovascular disease, peripheral vascular disease, diabetes, or 2 or more risk factors (such as smoking or hypertension) that give a greater than 20% chance of having heart attack within 10 years. The LDL goal for these patients remains 100 mg/dL or less, and the new guideline now recommends drug treatment for those high-risk patients with an LDL > 100 mg/dL. Moderately high-risk patients are defined as those with 2 or more risk factors for coronary heart disease and a 10-20% risk of heart attack within 10 years. For these patients, drug therapy is recommended to lower LDL cholesterol under 130 mg/dL, and the option is given to treat to levels under 100 kg/dL. For lower-risk patients, the guideline was not changed. Drug therapies recommended by the NCEP include statins, bile acid resins, nicotinic acid, and ezetimibe. As in previous NCEP guidelines, the role of lifestyle modification is stressed. The full guideline can be viewed in the July 13th issue of *Circulation*, and highlights can be reviewed on-line at www.nhlbi.nih.gov.

Hypothyroidism and Pregnancy

A new study clarifies thyroid replacement therapy during pregnancy. Researchers at Harvard followed 19 women with hypothyroidism through 20 pregnancies, of which 17 resulted in full-term births. Thyroid function, HCG levels, and estradiol were measured before conception, every 2 weeks for the first trimester, and monthly thereafter. Oral doses of levothyroxine were increased during pregnancy to maintain preconception levels. The mean levothyroxine requirements increased 47% during the first half of pregnancy, plateaued by week 16, and remained

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5416. E-mail: leslie.hamlin@ thomson.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

stable until delivery. The authors recommend that hypothyroid women, who become pregnant, should increase their levothyroxine dose by 30% as soon as pregnancy is confirmed, and should be monitored carefully throughout the duration of their pregnancy (*N Engl J Med*. 2004;351:241-249). Although simple in its design, this is an important study because it is estimated that 1 to 2% of all pregnant women are hypothyroid and need replacement therapy. Hypothyroidism during pregnancy is associated with poor fetal outcomes including impaired cognitive development and increased mortality. Clinicians now have a clear guide to levothyroxine dosing changes during pregnancy.

Anti-Depressants and the Risk of Suicide

The risk of suicidal behavior is relatively high after starting anti-depressants, however, there is no statistical difference between anti-depressants used, according to a new study. Researchers reviewed data from the UK General Practice Research Database from 1993 to 1999, and compared nearly 160,000 users of 4 anti-depressant drugs, 2 SSRIs and 2 tricyclics; fluoxetine, paroxetine, amitriptyline, and dothiepin (a trycyclic anti-depressant not marketed this country). The outcome was first-time non-fatal suicidal behavior, or suicide in treated patients vs comparable patients who did not exhibit suicidal behavior. The relative risks for non-fatal suicidal behavior were 0.83 for amitriptyline (95% CI, 0.61-1.13), 1.16 for fluoxetine (95% CI, 0.90-1.50), and 1.29 for paroxetine (95% CI, 0.97-1.70), compared to those using dothiepin. Perhaps the most startling finding in this study was the 4.07 relative risk for suicidal behavior within 9 days of starting any anti-depressant (95% CI, 2.89-5.74), compared to patients prescribed an anti-depressant 90 days or more before their suicidal behavior. Even more concerning, was a relative risk for fatal suicide among new users of anti-depressants of 38.0 (95% CI, 6.2-231). The authors found no significant associations between use of the various anti-depressants and the risk of suicide (*JAMA.* 2004;292:338-343, ed 379-380). The accompanying editorial points out the timeliness of the study, with regard to current congressional hearings in the use of anti-depressants in young adults. The authors point out that the data on patients aged 10 through 19 is limited however, and further study may be needed in this group.

FDA Actions

The FDA has approved acamprosate (Campral-Merck) for the maintenance of abstinence in patients in alcohol recovery programs. The drug, which has been available in Europe for several years, may not work if patients are still drinking or abusing other drugs when initiating therapy. Acamprosate's mechanism of action is unknown, but it appears to act in the central nervous system. Common side effects include diarrhea, nausea, vomiting, and abdominal pain.

The FDA has approved Merck and Schering-Plough's Vytorin for the treatment of hypercholesterolemia. The drug combines Merck's simvastatin (Zocor) with the jointly developed ezetimibe (Zetia), and is touted to be as potent as the so-called "super statins" atorvastatin (Lipitor) and rosuvastatin (Crestor). The new drug, which is expected to garner a hefty market share, will be priced at $2.30 a pill and should be available this fall.

Imiquimod (Aldera-3M) has received the expanded indication for treatment of superficial basal cell carcinoma. The drug, which is a topical immune modulator, was recently approved for treatment of actinic keratosis, and was initially approved for the treatment of venereal warts.

Brief Notes

The over-the-counter cough medications, dextromethorphan and diphenhydramine, are no better than placebo in suppressing cough in children (*Pediatrics.* 2004;114:e85-e90).

Many women are turning to phytoestrogens in lieu of hormone replacement therapy. The most commonly used of these, isoflavone soy protein, does not improve cognitive function, bone mineral density, or plasma lipids in healthy postmenopausal women (*JAMA.* 2004;292:65-74).

Ginseng reduces the effectiveness of warfarin in healthy volunteers. Patients on warfarin should be questioned as to their herbal supplement use (*Ann Intern Med.* 2004;141:23-27).