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SPECIAL FEATURE

Noninvasive Positive Pressure Ventilation in Acute Respiratory Failure

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Dr. Thompson reports no financial relationships relevant to this field of study.

The use of noninvasive positive pressure ventilation (NPPV) has been studied since the 1930s, and it has been in common use for sleep-disordered breathing, chronic respiratory failure, and acute respiratory failure (ARF) for the past few decades.[1] In that time, advances in technology and the data supporting its use in various clinical settings have evolved. The term NPPV typically refers to the use of expiratory positive airway pressure (EPAP) with a higher inspiratory positive airway pressure (IPAP), together referred to as bilevel positive airway pressure (BPAP, also commonly referred to as BiPAP). However, the use of continuous positive airway pressure (CPAP) also must be considered in the discussion of these devices, as the two different modalities have been used and often compared in the treatment of the various causes of ARF. In this article, the two modes of therapy will be referred to as NPPV and CPAP. It is the goal of this review to summarize the data supporting the use of NPPV and CPAP in the setting of acute hypoxic and hypercapnic respiratory failure, and to provide a practical approach to the use of this technology in the acute care setting. Its use for chronic restrictive lung disease and sleep-disordered breathing also has evolved but is beyond the scope of this review.

INDICATIONS SUPPORTED BY STRONG EVIDENCE

The two indications for use of NPPV or CPAP in the setting of ARF supported by extensive data are severe acute exacerbation of COPD (AECOPD) and cardiogenic pulmonary edema (CPE).[2] In AECOPD with relative hypercarbia and respiratory acidosis (typically pH < 7.35), NPPV has been shown to improve hospital mortality, $PaCO_2$, dyspnea scores, and length of hospital stay and de-

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This issue is dedicated to noninvasive ventilation and how clinicians can best utilize this therapy in the management of acute respiratory failure, acute respiratory distress syndrome, and asthma.

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crease the need for intubation. Although CPAP has been found to improve survival and rate of hospitalization when used chronically to treat COPD-obstructive sleep apnea (OSA) overlap syndrome,[3] it has not been studied enough to support or refute its usefulness in the setting of AECOPD.

Similarly, the use of NPPV and CPAP is supported in the setting of acute CPE as a means of improving oxygenation and hospital mortality and decreasing intubation rates.[4] Early studies suggested a higher risk of myocardial infarction with NPPV compared to CPAP, but more recent studies have not confirmed this risk. Thus, both NPPV and CPAP can be considered. Many will use CPAP starting near 10 cm H_2O for patients without hypercarbia but prefer use of NPPV when hypercarbia is a component of the ARF. Notably, there are insufficient data to support the use of either mode of therapy when respiratory failure is accompanied by either shock or acute coronary syndrome requiring urgent revascularization.

INDICATIONS SUPPORTED BY LIMITED EVIDENCE

Some data supporting the use of NPPV are available for many other indications, which include immunosuppressed patients in the setting of transplantation or chemotherapy for malignancy with chiefly hypoxic ARF or respiratory distress.[5,6] For these patients, in whom ARF is associated with particularly high mortality, NPPV can reduce the need for intubation as well as improve mortality and ICU length of stay. However, predictors of failure in hematologic malignancy include high respiratory rate on NPPV, need for vasopressors, need for dialysis, acute respiratory distress syndrome (ARDS), and delay between admission to initiation of NPPV.[7] In addition, recent studies, while somewhat underpowered and criticized for methodologic issues, have proposed that oxygen therapy (especially high-flow oxygen) may be equally efficacious or better than NPPV in the treatment of hypoxic respiratory failure in immunocompromised patients.[8-10]

Limited evidence backs the use of CPAP in those suffering from ARF after abdominal surgery and the use of NPPV for ARF after lung resection surgery. NPPV also has been used successfully, mostly in the setting of COPD, to facilitate liberation from the ventilator in those presenting with risk factors for re-intubation, which include age > 65 years, cardiac failure as the cause of intubation, APACHE II score > 12 at the time of intubation, AECOPD, and chronic hypercapnia.[11] In these patients, it is important to institute NPPV soon after extubation and not wait until evidence of recurrent respiratory failure develops. No study has shown an improvement in rate of re-intubation; one study demonstrated an increase in ICU mortality among patients with established respiratory failure and for whom re-intubation was delayed by the use of NPPV.[2,12]

Additionally, there is growing interest but limited data in the use of NPPV in palliative care settings.[13,14] As noted by Curtis et al,[13] it is important to discuss the goals of NPPV therapy with patients and family in advance to clearly outline whether NPPV is being used to avoid intubation in patients who have no preset limits on advanced life support, as a substitute for intubation for those who have declined advanced life support, or as a means of palliating dyspnea.

INDICATIONS SUPPORTED BY WEAK OR NO EVIDENCE

Although NPPV and CPAP have been used in a number of settings, insufficient literature exists to support or refute its use in several clinical scenarios. These include acute asthma exacerbation, for which only small studies in relatively mild exacerbations exist,[15] and severe community-acquired pneumonia, in which those who benefit most appear to be those with known COPD. Other indications for which there are insufficient data include patients presenting with chest trauma, hypoxemic patients undergoing bronchoscopy, and patients suffering from acute rapidly progressive neuromuscular disorders.

INDICATIONS WITH EVIDENCE AGAINST THE USE OF NPPV/CPAP

Worse outcomes are associated with the

Table 1: Contraindications to NPPV/CPAP

- Respiratory arrest
- Medical instability
- Acute respiratory distress syndrome
- Inability to protect airway
- Excessive secretions
- Uncooperative or agitated patient
- Inability to fit a mask
- Upper airway trauma or burns
- Recent upper airway surgery
- Severe upper gastrointestinal bleed

use of NPPV in established ARF after extubation as noted above. Minimal data support NPPV in the setting of ARDS. However, available evidence would suggest not using CPAP in the setting of ARDS in that it has not been shown to improve rate of intubation or mortality but actually may produce more adverse events.[16] The recent study by Frat et al[9] also suggested that high-flow oxygen through nasal cannula in hypoxemic respiratory failure (mostly for pneumonia) might be as efficacious as NPPV at preventing intubation and result in lower mortality. However, it has been criticized for the little amount of time patients in the NPPV group spent on positive pressure treatment (median of eight hours per day), the uneven distribution of septic shock in the two groups, and for lack of power for the endpoint of mortality.

MANAGEMENT OF NPPV/CPAP IN ARF

Most of the information available indicating when to start NPPV comes from the COPD and acute CPE literature. One must first decide if the patient needs mechanical assistance, and then whether there are any contraindications to NPPV/CPAP that would dictate intubation and use of mechanical ventilation. Those who demonstrate elevated $PaCO_2$ > 45 mmHg in the setting of a low pH < 7.35 are likely candidates for NPPV or intubation. Other indications for mechanically assisted ventilation include tachypnea, use of accessory muscles, paradoxical breathing, and hypoxemia. Those with contraindications to NPPV/CPAP (*see Table 1*) should go on to intubation and mechanical ventilation, while those without contraindications can start on NPPV/CPAP.

For patients suffering from AECOPD, acclimation to the NPPV mask at low pressures (EPAP 4-5 cm H_2O, IPAP 8-12 cm H_2O) and potentially simply holding the mask to the face can be helpful. Pressures gradually increase as dictated by the patient's tolerance and by the measured tidal volumes and vital signs. Patients presenting with acute CPE often will do well starting CPAP near 10 and adjusting based on comfort, pulse oximetry, and vitals. Elevation of the head of the bed to > 30 degrees is recommended when possible. It is important to reassess the patient in one to two hours (*see Table 2*), as this typically is sufficient to gauge whether the patient will benefit from NPPV/CPAP or will need to go on to invasive mechanical ventilation. Failure rates of 5-40% have been reported.[17] Risk factors for failure, which may dictate elevated level of care for the patient, include agitation or diminished level of consciousness, pH < 7.2, asynchronous breathing, lack of adequate dentition, excessive air leak from the mask, excessive secretions, poor tolerance, diagnosis of ARDS or pneumonia, older age, metabolic acidosis, systolic blood pressure < 90 mmHg, and low PaO_2/FiO_2 ratio.[18] For those seeking more complete references for a practical approach to management of NPPV and CPAP in ARF and for establishing a noninvasive ventilation program, articles by Hess et al, Davidson et al, and the Royal College of Physicians are recommended.[19-21]

Although most studies have suggested that most mask types (nasal, oronasal, nasal pillow, total-face, helmet) are equally effective interfaces, some data suggest the oronasal mask may result in less leak and better tolerance in the setting of ARF; thus, it is typically recommended as the first choice of masks. However, one should have a low threshold for trying other masks based on patient comfort, especially if the patient already has experience with a particular mask. Mask fit also may be affected by patient dentition and may improve if dentures are left in place. Control of mask and mouth leak are key to optimal device triggering and cycling, making mask fit one of the most important aspects of care.

Patients often are kept *nil per os* until it is clear that they will not require intubation and that aerophagia will not be a significant problem. However, as dictated by their responses to NPPV/CPAP and underlying medical conditions, patients usually can be given progressively longer trials off the device with concurrent liberalization of their oral intake.

TROUBLESHOOTING

Patient-ventilator asynchrony in NPPV can affect dyspnea and patient tolerance of the device significantly. It is important to assess and correct early in the course of treatment.[22] Asynchrony usually centers

Table 2: Markers of Success After 1-2 Hours of Treatment

- Improvement in pH and $PaCO_2$
- Improvement in oxygenation
- Reduction in respiratory rate
- Reduction in heart rate
- Improvement in tidal volume

around the device threshold for initiating a breath (triggering) and terminating a breath (cycling). An asynchrony index (AI) can be calculated as the number of asynchrony events divided by the total number of breaths (including all asynchrony events), with an AI > 10% considered severe. Vignaux et al found an AI of > 10% in 43% of 60 patients, including ineffective triggering (8%), double-triggering (15%), auto-triggering (13%), premature cycling (12%), and delayed cycling (23%).[23] Asynchrony tends to correlate with magnitude of mask leak and level of pressure support (PS, the difference between IPAP and EPAP) and, thus, correction of mask leak is the first step in managing a high AI. Adjusting the sensitivity of the trigger to deliver the breath can reduce the number of missed, double, and auto-triggered breaths. Shortening the rise time, defined as the time to get from EPAP to IPAP, and increasing PS can improve dyspnea. Adjusting the cycle setting that turns off the breath, as well as adjusting the minimum and maximum inspiratory times, can improve comfort and asynchrony significantly.[11] For example, patients with severe obstructive lung disease often benefit from a shorter rise time, shorter maximum inspiratory time, and a cycle setting that turns off the delivered breath at 50% of peak inspiratory flow rather than the typical 25-30%. On the other hand, patients with neuromuscular weakness who experience a lower peak inspiratory flow may experience better outcomes using a longer rise time, more sensitive trigger setting (more easily triggering the breath), and less sensitive cycle setting (maintaining the breath until 10-15% of peak inspiratory flow occurs).

Another common mistake in patients with COPD-OSA overlap syndrome is to concentrate on the AECOPD and to neglect the OSA. In an attempt to improve ventilation, the pressure support will increase gradually at the exclusion of increasing EPAP. Typically, this will lead to cyclical pressurization of the oropharynx without adequate ventilation of the lower airways because the NPPV device is working against a closed upper airway. This also leads to inability of the device to sense respiratory effort and, thus, to patient-ventilator asynchrony. In short, "opening" the upper airway with adequate EPAP can improve ventilation and tidal volume, even if it results in a lower PS.

Once the settings have been optimized to improve patient comfort, if the patient still struggles with tolerance, entertain the question of sedation. Unfortunately, sedation is a double-edged sword, which by virtue of its potential to impair respiratory drive may exacerbate the patient's respiratory status and accelerate the failure of NPPV. As reviewed by Hess et al, use of analgesia, sedation, and restraints in this situation is quite variable from provider to provider.[19] Traditionally, sedation has consisted of benzodiazepines or opiates. Studies support the use of the short-acting agent remifentanil, although it is not FDA approved for this indication. Dexmedetomidine also has data to support its use with NPPV and offers the ability to provide sedation with minimal suppression of respiratory drive.

FUTURE DIRECTIONS

The use of NPPV and CPAP in the treatment of AECOPD and CPE is well established, to the point of representing standard of care in the appropriate clinical setting. However, there certainly is need for additional investigation on many of the other potential indications that currently have little to no literature to back the use of these modalities as a means of significantly improving patient outcomes. New areas ripe for further exploration include use of these devices in the field of palliative care and in those patients who have elected not to pursue intubation. Recent data also raise the possibility that newer technology in high-flow oxygen delivery may provide an alternative and potentially superior treatment option in hypoxic respiratory failure. Additionally, new modes of noninvasive ventilation (adaptive servo ventilation, volume-assured pressure support, neurally adjusted ventilator assist, proportional assist ventilation, and others) could lead to improved control over respiratory parameters and better patient tolerance. Until further information is available, it will remain unclear as to whether these newer technologies will offer any better outcomes. ■

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ABSTRACT & COMMENTARY

Noninvasive Ventilation Delivered Via Helmet May Decrease Intubation Rates in Acute Respiratory Distress Syndrome

By Betty Tran, MD, MSc, Editor

SYNOPSIS: In this single-center, randomized, clinical trial, among patients suffering from acute respiratory distress syndrome, the use of helmet noninvasive ventilation was associated with a reduction in intubation rates, ICU length of stay, and hospital and 90-day mortality.

SOURCE: Patel BK, Wolfe KS, Pohlman AS, et al. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA* 2016;315:2435-2441.

Previous work has shown a 51% failure rate of noninvasive ventilation (NIV) among patients suffering from acute respiratory distress syndrome (ARDS) who subsequently require endotracheal intubation.[1] This is thought to be related to the inability to deliver high levels of positive end-expiratory pressure (PEEP) with a face mask due to patient intolerance and mask leak. In this study from the University of Chicago, Patel et al sought to determine whether NIV delivered via a helmet interface, which allows for increased titration of positive airway pressure without substantial air leak and improved patient tolerability, could reduce the need for endotracheal intubation in addition to improving other patient outcomes.

In this single-center, randomized, clinical trial, consecutive patients admitted to the adult medical ICU were screened for eligibility. Patients > 18 years of age who met Berlin criteria for ARDS and who required face mask NIV for at least eight hours were eligible for enrollment. The primary outcome was the proportion of patients who required endotracheal intubation based on a priori criteria, which included: neurologic deterioration, persistent or worsening respiratory failure (e.g., oxygen satura-

tion < 88%, respiratory rate > 36 breaths/minute), intolerance of face mask or helmet, airway bleeding, or copious secretions. Secondary outcomes (which were considered exploratory) were 28-day invasive ventilation-free days, ICU and hospital length of stay, hospital and 90-day mortality, and adverse events.

Of the 740 patients admitted with acute respiratory failure requiring NIV, 83 were ultimately randomized: 39 to receive NIV via face mask and 44 to receive NIV via helmet. The authors ended the study early after meeting criteria for efficacy, but also based on work published at the time that suggested increased mortality among patients treated with face mask NIV compared to high-flow nasal cannula.[2] Median time on NIV to randomization was not significantly different between the two groups. The intubation rate in the face mask group was 61.5% vs. 18.2% in the helmet group (absolute difference -43.3%; 95% confidence interval [CI], -62.4% to -24.3%; $P < 0.001$). In the exploratory secondary analyses, the helmet group experienced more ventilator-free days (28 vs. 12.5 days; absolute difference, 8.4; 95% CI, 13.4-3.4; $P < 0.001$), shorter ICU length of stay (4.7 vs. 7.8 days; absolute difference, -2.76; 95% CI, -6.07 to 0.54; $P = 0.04$), and lower hospital and 90-day mortality (hazard ratio, 0.51; 95% CI, 0.23-0.99; $P = 0.047$). Adverse events were few; three patients in the face mask group developed a nose ulcer, and three patients in the helmet group developed neck ulcers.

■ COMMENTARY

Although it featured a small number of enrolled patients because it ended early, this study suggests that a change in delivery interface could significantly influence the effect of NIV in patients with ARDS. Compared to patients receiving NIV via face mask, those randomized to NIV via helmet had higher median sustained PEEP levels (8.0 cm H_2O vs. 5.1 cm H_2O; $P = 0.006$) and were less tachypneic after randomization (24.5 breaths/min vs. 29.1 breaths/min; $P < 0.001$). The most common reason for intubation among patients in the face mask group was respiratory failure; in the helmet group, it was neurologic failure. The significant reduction in intubation rate among those receiving NIV via helmet and low rate of adverse events makes it an attractive option in this patient population. Although the study could not be blinded, use of a priori criteria to determine failure of NIV, as well as standard protocols to titrate and wean NIV, helped decrease bias.

There are a few other points worth mentioning. The study ended early and, as such, the magnitude of the effect seen may be exaggerated. Second, helmet delivery devices may not be available or commonly used in all hospitals, and proper training with regard to use and titration is needed to ensure the outcomes seen in this study can be reproduced. Finally, results from this study should not be used as overwhelming evidence for the role of NIV in ARDS. Enrollment of patients did not occur until they were receiving NIV for at least eight hours; although not reported by the authors, I suspect that a sizable number of patients admitted with acute respiratory failure due to ARDS were intubated before the eight-hour mark. Regardless, this study's outcomes are intriguing, and further multicenter trials should focus on whether these findings can be replicated. ■

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ABSTRACT & COMMENTARY

Noninvasive Ventilation in Asthma Exacerbation: Predictors of Use and Outcomes

By Betty Tran, MD, MSc, Editor

SYNOPSIS: In this large, retrospective cohort study, the use of noninvasive ventilation (NIV) as an initial mode of ventilation for patients with asthma exacerbation was common; those successfully treated with NIV experienced lower inpatient mortality and shorter lengths of stay, but were likely a carefully selected population.

SOURCE: Stefan MS, Nathanson BH, Lagu T, et al. Outcomes of noninvasive and invasive ventilation in patients hospitalized with asthma exacerbation. *Ann Am Thorac Soc* 2016;13:1096-1104.

Despite limited evidence for the use of noninvasive ventilation (NIV) in acute exacerbation of asthma, rates of NIV use for patients suffering from asthma have increased recently.[1] In this retrospective cohort study, Stefan et al used an electronic medical record database comprised of ICD-9 diagnoses, medication, laboratory, and clinical data from 125 hospitals to examine factors associated with the choice of ventilation in patients hospitalized with acute asthma exacerbation and the outcomes of NIV vs. invasive mechanical ventilation (IMV) in this patient population. The primary outcomes of the study were in-hospital case fatality and length of stay. Secondary outcomes included initial method of ventilation and rates and outcomes of NIV failure (defined as use of IMV after NIV).

A total of 13,930 admissions at 97 hospitals were included in the study, with 1,254 of the patients requiring mechanical ventilation; 556 (44.3% of ventilated patients) were given NIV initially, and 698 (55.7% of ventilated patients) were initiated on IMV. NIV failure was reported in 26 patients (4.7% of those treated with NIV initially). Compared to those initially ventilated with IMV, those treated initially with NIV demonstrated lower in-hospital case fatality rates (2.3% vs. 14.5%) and shorter median lengths of stay (4.1 days vs. 6.7 days). However, those who experienced NIV failure demonstrated the highest in-hospital case fatality rate at 15.4% and longest length of stay at 10.9 days. Patients who were older, those who previously received NIV, and those who had more than two prior admissions in the past 12 months were more likely to receive NIV initially. In contrast, higher acuity patients (based on the Laboratory Acute Physiology Score), those with concomitant pneumonia, status asthmaticus, prior IMV use, comorbid weight loss, and neurological disorders, were less likely to receive NIV. In addition, the hospital in which the patient was treated had a major association with the type of ventilation received.

Overall, use of NIV was associated with lower inpatient mortality (relative risk, 0.12; 95% confidence interval [CI], 0.03-0.51) and shorter length of stay (4.3 days less; 95% CI, 2.9-5.8). However, patients with NIV failure had slightly higher (albeit statistically not significant) mortality rates than patients treated with IMV initially (15.4% vs. 14.7%; $P = 0.92$) and longer median lengths of stay (10.9 days vs. 6.7 days; $P = 0.007$). Factors associated with NIV failure included admission for asthma within the prior 12 months, diabetes, and coexisting pneumonia.

■ COMMENTARY

This is the largest cohort of patients with asthma treated with mechanical ventilation to date. Although it is retrospective in design and much of the data are subject to limitations of ICD-9 coding, selection bias, and propensity matching in only 38% of patients treated with NIV, this study reveals that NIV is used in > 40% of patients suffering from asthma who are started on some form of ventilation, despite limited evidence for its use. Although the reasons for this are not explored in this study, the authors hypothesized that physicians may be more likely to use NIV in asthma patients because of the similarities in the pathophysiology of asthma vs. COPD exacerbations, given evidence favoring use of NIV in the latter and increasing familiarity and comfort with the use of NIV in general.

[Overall, this study is enlightening with regard to current practice patterns surrounding NIV in asthma, but its findings that NIV is associated with improved outcomes in patients with asthma should be regarded as hypothesis-generating rather than conclusive.]

The rate of NIV failure was low at 4.7%, suggesting that NIV use across hospitals likely was in a very selected group of patients with asthma, probably an overall low-acuity, low-risk group. The fact that patients who failed NIV had higher rates of in-hospital death and longer lengths of stay suggests these patients probably should not have been started on NIV to begin with, and this may have delayed intubation when it was warranted. Overall, this study is enlightening with regard to current practice patterns surrounding NIV in asthma, but its findings that NIV is associated with improved outcomes in patients with asthma should be regarded as hypothesis-generating rather than conclusive. For now, patients with more severe asthma exacerbations who have a history of prior asthma admission within the past 12 months, diabetes, or concomittant pneumonia should not be considered for NIV given the higher risk of NIV failure with subsequent increased mortality." ■

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CME/CE QUESTIONS

1. **As summarized in the Special Feature, strong evidence supports the use of NPPV/CPAP in:**
   a. early ARDS.
   b. cardiogenic pulmonary edema in the setting of shock.
   c. severe asthma exacerbation with elevated $PaCO_2$.
   d. COPD and cardiogenic pulmonary edema.

2. **Markers of adequate response to NPPV/CPAP after one to two hours include which of the following?**
   a. Lower blood pressure
   b. Lower pH and $PaCO_2$
   c. Lower respiratory rate
   d. Higher heart rate

3. **To improve comfort and NPPV synchrony in patients presenting with severe obstructive lung disease, one could consider:**
   a. lengthening the rise time.
   b. increasing the cycle setting from 25% to 50% of peak inspiratory flow.
   c. increasing the respiratory rate from 12 to 20.
   d. lengthening the maximum inspiratory time.

4. **In the study by Patel et al, NIV delivered via helmet was associated with:**
   a. higher rate of skin ulceration.
   b. lower ICU mortality.
   c. lower rate of endotracheal intubation.
   d. shorter hospital length of stay.

5. **Based on the study by Stefan et al, which of the following statements is true?**
   a. Patients who failed NIV had higher in-hospital mortality rates.
   b. Patients who were started on IMV had the shortest lengths of stay.
   c. Patients who were started on NIV had higher in-hospital mortality rates compared to those on IMV.
   d. Patients who were started on NIV tended to be younger.

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.