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Noninvasive Positive Pressure Ventilation in Critically Ill Patients: The Winds of Change?

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Although endotracheal intubation undoubtedly saves lives, it is also associated with significant morbidity and mortality. In short, while endotracheal intubation achieves definitive airway control, it can sacrifice natural airway defense mechanisms and increase infections. Endotracheal intubation often mandates medications and invasive devices, all of which have potential complications. This issue of *Critical Care Rounds* reviews the evidence supporting noninvasive positive pressure ventilation (NIPPV) in critically ill patients.

The basics of noninvasive ventilation

NIPPV can achieve many of the physiologic benefits that endotracheal mechanical ventilation (ETMV) has traditionally provided, including improved oxygenation and ventilation, respiratory muscle unloading, and symptomatic relief of dyspnea.¹ Masks comprise nasal pillows, mouth pieces, full-face devices, and even a full helmet system.² Poorly fitted masks may contribute to NIPPV failure; therefore, it may be necessary to try various masks before a successful one is found.

The simplest form of noninvasive ventilation is provided by continuous positive airway pressure (CPAP). A constant pressure delivered throughout the respiratory cycle prevents alveolar collapse, maintains functional residual capacity, improves lung compliance, and increases alveolar ventilation.^{3,4} Increased intrathoracic pressure resulting from CPAP reduces right ventricular preload and left ventricular wall tension, leading to some of its beneficial effects in congestive heart failure.³ The application of extrinsic positive end-expiratory pressure (PEEP) helps to decrease the inspiratory flow necessary for ventilator triggering, particularly in patients with airflow obstruction.³

An alternate mode, known as noninvasive pressure support ventilation, provides additional support during inspiration. This has been shown to decrease neuromuscular drive, inspiratory muscle effort, and work of breathing (WOB) when compared with CPAP.¹ Although pressure support ventilation has been postulated to improve oxygenation and ventilation by improving ventilation/perfusion (V/Q) matching, it is not well-supported by clinical studies. Instead, blood gas improvement following NIPPV appears to be from an increase in alveolar ventilation.⁴ Pressure support ventilation is often well-tolerated because the patient is able to trigger and control the duration of each supported breath. The ventilator is “cycled,” meaning that flow terminates when it falls below a specified threshold or when a prolonged time period has elapsed.

Portable ventilators, known as “bi-level” devices, can provide differing levels of pressure support during expiration and inspiration. In contrast to full-service ventilators, however, bi-level devices are smaller and, hence, can be used at home. Unfortunately, they may lack the sophisticated alarms and battery backup of their larger counterparts. Furthermore, while technology is rapidly improving, many bi-level devices cannot generate the pressures or oxygen concentrations required for critically ill patients.³

The terminology associated with bi-level ventilators also differs. Practitioners set the expiratory positive airway pressure (EPAP) – the physiologic equivalent to PEEP – and the inspiratory positive airway pressure (IPAP) – the equivalent of pressure support plus PEEP.



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The driving pressure, or amount of positive pressure support per breath, is determined by subtracting EPAP from IPAP. Adding to the confusion, the term “BiPAP” is often erroneously used interchangeably with “bi-level” when, in fact, “BiPAP” (an acronym of “bilevel positive airway pressure”) is the brand name of a specific bi-level ventilator.

Other modes of invasive ventilation, such as volume-limited ventilation, can also be administered noninvasively. In acute settings, however, these modes may be less able to compensate for air leaks and may require higher set tidal volumes, possibly rendering them too difficult for patients to tolerate.³ Novel modes of ventilation (eg, noninvasive proportional assist ventilation [PAV] and neurally adjusted ventilation [NAVA]) have met with some success, but are not yet widely adopted in Canada.⁵ PAV has theoretical benefits over pressure support ventilation because it allows the ventilator to dynamically adjust flow by monitoring the WOB.⁴ Instead of setting a fixed pressure (as in pressure limited ventilation), clinicians specify the proportion of the WOB they wish the ventilator to deliver.⁶ As a patient’s respiratory compliance and resistance changes, the amount of support changes. This may improve ventilator-patient synchrony and, hence, increase patient tolerance. Similarly, NAVA may also improve synchrony by adjusting triggering and flow, based on diaphragmatic electrical activity obtained via a nasogastric catheter.⁷ Since triggering is neither flow- nor pressure-based, NAVA may avoid the triggering problems that occur with traditional NIPPV from intrinsic PEEP or air leaks.

Benefits of NIPPV

Many of the benefits of NIPPV over ETMV stem from the avoidance of intubation and all that it entails (Table 1). ETMV is part of a package of interventions that include not only intubation, but also the administration of medications (eg, neuromuscular blocking agents, analgesics, and sedatives) and the placement of invasive devices (eg, venous catheters, nasogastric and tracheostomy tubes).

The etiology of ventilator-associated pneumonia is multi-factorial. However, two contributing mechanisms are the aspiration of accumulated oropharyngeal secretions from around the endotracheal tube (ET) cuffs and the generation of infected biofilms that subsequently coat the ET tubes.⁸ Attempts to counteract these problems include using ET tubes that have a subglottic suction port.⁹ In addition, some evidence supports early tracheostomy.¹⁰ Another solution, however, is simply to avoid endotracheal intubation wherever possible. In a retrospective case-control study comparing 50 patients managed with NIPPV to 50 patients managed with ETMV who were matched for diagnosis, Simplified Acute Physiology Score II, Logistic Organ Dysfunction score, age, and no contraindication to NIPPV. Rates of nosocomial infection (18% vs 60%), length of intensive care unit (ICU) stay (9 vs 15 days), and crude mortality (4% vs 26%), were lower in those receiving NIPPV.¹¹ A recent meta-analysis of 12

Table 1: Potential benefits of NIPPV

Physiologic

- Improved oxygenation and ventilation
 - alveolar recruitment
 - maintenance of functional residual capacity
 - improved lung compliance
 - increased alveolar ventilation
- Respiratory muscle unloading
- Reduced preload and afterload
- Decreased inspiratory flow necessary for triggering in patients with extrinsic PEEP

Clinical

- Decreased risk of pneumonia as compared with ETMV
- Decreased risk of mechanical complications (e.g. vocal cord damage, tracheal stenosis)
- Decreased use of medications (sedative agents, analgesics, and neuromuscular blocking agents)
- Decreased use of invasive devices (central venous catheters, nasogastric and tracheostomy tubes)
- Able to be rapidly stopped and started
- Preserve the ability to eat, speak, and think (less sedation necessary)

studies examining the risk of pneumonia in patients receiving NIPPV revealed a strong benefit of NIPPV in lowering the risk of pneumonia (relative risk [RR] 0.38; 95% confidence interval [CI], 0.20 to 0.73; $p=0.003$).¹²

In contrast to NIPPV, continuous infusions of sedative medications are often necessary during ETMV. This has been associated with increased lengths of stay in the ICU. While titration of medications using sedation scales, as well as daily interruptions in sedation, have been shown to significantly decrease complications,¹³ numerous potential mechanical complications, including vocal cord damage, laryngeal edema, and tracheal stenosis, may also be avoided by foregoing endotracheal intubation.³ There may also be increased WOB imposed by endotracheal tube resistance created by its relatively small diameter. In short, these complications are more related to endotracheal cannulation than to mechanical ventilation. This has prompted some authors to propose changes in nomenclature, referring to “tube-associated pneumonias” rather than “ventilator-associated pneumonias.”¹²

Besides the medical benefits of NIPPV, a noninvasive approach may increase ongoing quality-of-life and involvement in day-to-day care. For example, in contrast to invasive ventilation, NIPPV can help to preserve the ability to eat, speak, and think (less sedation necessary). In addition, NIPPV can be rapidly stopped or restarted at the patient’s request, thereby preserving patient control and autonomy.

Limitations of NIPPV

Despite the numerous putative benefits of NIPPV, important limitations do exist (Table 2). Patients normally require intubation and mechanical ventilation for 1 of 4 reasons:

Table 2: Evidence of benefit or harm of NIPPV in specific patient populations

- **Acute exacerbations of COPD**
 - Strong evidence of benefit in selected patients
- **Acute cardiogenic pulmonary edema**
 - Reasonable evidence supporting CPAP or non-invasive pressure support ventilation in selected patients
- **Hypoxemic respiratory failure**
 - Not enough evidence to support a general recommendation of NIPPV.
- **Aid to weaning and following extubation**
 - Limited studies available. Some evidence supporting immediate post-extubation NIPPV for patients failing weaning trials or at high risk of recurrent respiratory failure
 - Evidence of harm (increased mortality) when NIPPV applied following a delayed period in patients who develop post-operative respiratory failure.
- **Severe acute respiratory syndrome**
 - Although NIPPV has been used successfully, it should be avoided due to concern of co-infection

- failure of airway maintenance or protection
- anticipated future respiratory compromise (ie, likelihood of clinical deterioration)
- bronchial-pulmonary toilet
- failure of ventilation or oxygenation.

Patients who fulfill the first 3 conditions are often not candidates for NIPPV, and endotracheal cannulation would offer definitive airway protection in these cases. Furthermore, while NIPPV can improve ventilation and oxygenation, patients may not be able to tolerate the high levels of pressure due to mask discomfort, air leaks, or gastric distention. Specific modes of ventilation, such as inverse ratio pressure control ventilation, may not be feasible noninvasively. Air leaks around a mask or nasal cushions can cause not only local eye irritation, but also complicate ventilator management. As well, patients may simply not be able to tolerate a mask, whether nasal or full-face, due to confusion, anxiety, or a sense of claustrophobia.

Most importantly, use of NIPPV may delay the initiation of ETMV and definitive airway management. This has been associated with increased mortality in certain situations.¹⁴ Most studies have traditionally excluded patients with co-morbidities that are likely to be better managed with ETMV, such as those with hemodynamic instability, decreased level of consciousness, confusion or the inability to cooperate, poor airway protection, facial deformity or trauma, and cardiac or respiratory arrest. Careful selection of patients is necessary to determine which ones have the highest likelihood of benefiting from NIPPV versus ETMV. The remainder of this issue presents the evidence for NIPPV in specific patient populations.

Acute exacerbations of chronic obstructive pulmonary disease (COPD)

The use of NIPPV following acute exacerbations of COPD is supported by numerous randomized-controlled trials. A comprehensive meta-analysis by Keenan et al demonstrated substantial benefits of NIPPV when added to usual medical care, including decreased endotracheal intubation (risk reduction [RR] 28%; 95% CI, 15-40), decreased length of hospital stay (absolute RR 4.57 days; 95% CI, 2.30-6.83 days) and decreased in-hospital mortality (RR 10%; 95% CI, 5 -15).¹⁵ A recent Cochrane systematic review of 14 good-quality, randomized, controlled trials demonstrated decreased mortality (RR 0.52; 95% CI, 0.35-0.76), decreased need for intubation (RR 0.41; 95% CI, 0.33-0.53), and decreased length of hospital stay when NIPPV was compared with standard medical treatment.¹⁶

Unfortunately, not all patients with acute exacerbations of COPD benefited from the addition of NIPPV to standard medical care. Although pooled meta-analysis data suggest an overall benefit with NIPPV, subgroup analysis revealed a lack of benefit in nonsevere exacerbations – defined as those with a baseline pH >7.30 or an in-hospital mortality rate <10%. There was no detectable difference in hospital survival or intubation rate in these patients.¹⁵ As well, 2 randomized controlled trials, one by Keenan et al and another by Barbe et al, failed to show benefit of NIPPV in less severely ill patients with COPD who rarely required intubation.^{17,18} At the other extreme, patients with a decreased level of consciousness or hemodynamic instability may be too ill to benefit from NIPPV and are likely best managed with ETMV.

Ultimately, clinicians have to select patients who are severely ill enough to actually benefit from NIPPV, but not so severely ill that they will inescapably progress to ETMV.

Acute cardiogenic pulmonary edema (ACPE)

In a utilization review conducted in Hamilton, Ontario, the most common indication for NIPPV was pulmonary edema (49.4%), surpassing even COPD (24.2%).¹⁹ In a recent meta-analysis of 15 randomized trials, NIPPV significantly reduced the mortality rate in ACPE compared with standard therapy (RR 0.55; 95% CI, 0.40-0.78).²⁰ However, while studies support the use of NIPPV in ACPE, the data are not as robust as for COPD.²⁰

Both CPAP and bi-level noninvasive pressure support ventilation (NIPSV) have been studied in ACPE and the debate as to which is superior is ongoing. Both CPAP and NIPSV have been shown to reduce right and left ventricular preload. The addition of inspiratory pressure support in NIPSV, however, has been shown in physiologic studies to unload the respiratory muscles more effectively and ameliorate hypercapnea and vital signs more rapidly than CPAP.²¹ However, this theoretical advantage of NIPSV over CPAP has not consistently meant clinically significant differences.^{20,22} In another study, Mehta et al compared

CPAP and NIPSV and demonstrated a significantly higher level of myocardial infarctions in the NIPSV group (71% vs 31%).²³ However, more patients in the NIPSV group reported chest pain at the start of the study. A larger follow-up study did not reveal any differences in infarction rates, although it was not adequately powered to definitively answer this question.²⁴

From a practical standpoint, there is reasonable evidence supporting either CPAP or NIPSV in selected patients with ACPE since both prevent intubation and improve outcomes compared with conventional treatment. For the clinician, the choice may depend more on the available equipment rather than on conclusive scientific evidence.²²

Hypoxemic respiratory failure

Acute hypoxemic respiratory failure – defined as an arterial oxygen tension-to-inspired oxygen fraction ($\text{PaO}_2/\text{FiO}_2$) ratio of <200 – encompasses disorders that include interstitial lung disease, cardiogenic pulmonary edema, pneumonia, aspiration, and trauma. Several randomized trials have attempted to address the use of NIPPV in this state, but definitive conclusions are complicated by the heterogeneity of diseases and the high rate of patients eventually requiring ETMV.

In a prospective, randomized trial of 64 patients requiring mechanical ventilation for hypoxemic respiratory failure, NIPPV patients had significantly lower rates of pneumonia/sinusitis (31% vs 3%), shorter length of mechanical ventilation (3 ± 3 days vs 6 ± 5 days) and shorter ICU stay (6.6 ± 5 days vs 14 ± 13 days).²⁵ However, a sizable proportion (31%) of the NIPPV group eventually required intubation. Those intubations were significantly delayed by an average of 15 ± 7 hours. Given concerns suggesting increased mortality with late intubation, such delays may not be acceptable despite potential benefits of NIPPV.¹⁴

Honrubia et al also suggested benefits for NIPPV over ETMV in all-comers with acute hypoxemic respiratory failure. Intensive care unit mortality (23% vs 39%; $p=0.09$) and complications (52% vs 70%; $p=0.07$) were lower in the NIPPV group, but results did not reach statistical significance.²⁶ In addition, all of the patients in the subgroup with pneumonia that received NIPPV ultimately required ETMV. As such, this particular subgroup may be better managed with immediate tracheal intubation rather than NIPPV because NIPPV may simply delay the time to definitive airway management.

A recent systematic review of 8 randomized controlled trials suggests that NIPPV reduces the intubation rate (absolute RR 23%, 95% CI, 10-35), ICU length of stay (absolute RR 2 days, 95% CI, 1-3 days) and ICU mortality (absolute RR 17%, 95% CI, 8-26). However, the authors cautioned that significant

heterogeneity in the trial results made generalizations difficult and that subgroups of patients with hypoxemic respiratory failure may not benefit or may even be harmed by a noninvasive approach.²⁷ In short, although preliminary results are encouraging, there is currently inadequate evidence to recommend NIPPV for all patients with acute hypoxemic respiratory failure.

NIPPV to aid weaning from mechanical ventilation

Ferrer et al studied 43 mechanically-ventilated patients who had persistent weaning failure defined as 3 consecutive failed spontaneous breathing trials. In their small, but well-designed, randomized, controlled trial, patients who failed weaning were randomized to either extubation with immediate application of NIPPV or remained intubated with administration of conventional weaning techniques. The NIPPV group had a shorter period of invasive ventilation (9.5 days vs 20.1 days, $p=0.003$), less need for tracheostomy (5% vs 59%, $p<0.001$), a lower incidence of nosocomial pneumonia (24% vs 59%, $p=0.042$), and a trend towards improved 90-day survival (odds ratio 3.5; $p=0.018$).²⁸ Due to the positive results achieved in the NIPPV group, the trial was stopped early after interim analysis.

In contrast, however, significant concern was raised after NIPPV was associated with an increase in all-cause mortality in patients who developed respiratory failure after extubation. In contrast to the earlier work by Ferrer,²⁸ in another study, Esteban et al applied NIPPV to patients who had passed a spontaneous breathing trial, were then extubated, but who subsequently developed respiratory failure.¹⁴ In this study of 221 patients, there was no difference in the rate of reintubation (48% for both groups), but the rate of death in the NIPPV group was significantly higher (25% vs 14%; $p=0.046$, number needed to harm = 9).¹⁴ Median time to reintubation was much longer in the NIPPV group and this delay may have contributed to the increased mortality.

Timing of NIPPV after extubation may be a critical factor. For example, in a follow-up study, Ferrer et al identified patients who had passed a spontaneous breathing trial, but were at risk for requiring intubation²⁹ (eg, they were aged >65 years, had cardiac failure, or an APACHE-II score >12 on the day of extubation). In this way, NIPPV could be applied in those at highest risk immediately following extubation, without having to wait for overt respiratory failure. Respiratory failure after extubation was lower in the NIPPV group (33% vs 16%, $p=0.029$) and ICU mortality was lower (3% vs 14%, $p=0.41$) although 90-day mortality was not significantly different between the groups. As such, while enthusiasm must be tempered, NIPPV has the potential in the

“difficult-to-wean” patient and may decrease reintubation. However, in summary, there is no current data to support universal NIPPV in the post-extubation period.

Postoperative hypoxemia

An estimated 8% to 10% of patients develop postoperative respiratory failure following major abdominal surgery and traditionally receive ETMV.³⁰ Squadrone et al compared the effectiveness of CPAP versus standard oxygen therapy for patients who developed a PaO₂/FiO₂ of ≤300 during the first hour post-extubation.³⁰ Interim analysis revealed a lower intubation rate (1% vs 10%; p=0.05), a lower rate of pneumonia (2% vs 10%; p=0.02) and a lower rate of sepsis (2% vs 9%; p=0.03) for those receiving CPAP. Interestingly, CPAP was administered using a helmet, which may have increased patient tolerance. The success of this trial may also result from the early application of CPAP (within 1 hour of extubation) with interruption only when a prespecified oxygenation target was reached (mean 19 hours).

Special populations

NIPPV was reported to be successful in observational studies in China during the severe acute respiratory syndrome (SARS) crisis.³¹ While no clear evidence of cross-infection between healthcare workers was reported, NIPPV is typically forbidden in North American viral pandemic protocols due to concerns of dissemination.³² Barotrauma in SARS patients was noted with both NIPPV and conventional mechanical ventilation, suggesting the importance of a lung protective strategy, regardless of the ventilatory mode.

Patients who refuse invasive ventilation may still choose to accept NIPPV. In a proportion of these “do-not-intubate” patients, NIPPV can allow time to attempt reversal of acute respiratory failure. This may prevent or delay in-hospital mortality, particularly for those with a primary diagnosis of COPD or acute cardiogenic pulmonary edema (ACPE). However, NIPPV was not found to prevent in-hospital mortality in patients with acute hypoxemic respiratory failure or terminal cancer.³³ NIPPV may be desirable in these patients since they are often still able to eat and communicate during breaks from mask ventilation.

Factors predicting NIPPV failure

Even within rigorous trials under optimal conditions, a substantial proportion of patients fail NIPPV and require ETMV. Observational studies have provided clues about who fails NIPPV under real-world conditions. In a multi-centre cohort study in 354 ICU patients, NIPPV failed in 30% of patients. Failure was predicted by age >40 years, simplified acute physiology score (SAPS II) >35, the presence of acute

respiratory distress syndrome (ARDS) or pneumonia, and a PaO₂/FiO₂ <146 after 1 hour.³⁴ Using a cohort of 1033 patients with COPD exacerbation, Confalonieri et al devised a prediction chart.³⁴ Failure rates of >70% with NIPPV were predicted by a Glasgow Coma Scale (GCS) <11; an APACHE II score ≥29; RR ≥30 breaths per minute; and a pH at admission of <7.25. Similarly, an emergency department study of NIPPV identified GCS <13, RR ≥20, and pH ≤7.35 as predictors of failure.³⁵

Conclusion

In selected patient populations, NIPPV can mitigate many of the hazards associated with conventional endotracheal intubation. While we have attempted in this presentation to summarize the evidence, the successful application of NIPPV in individual patients remains an art, as well as a science.

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