Noninvasive Ventilation

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Introduction

Noninvasive ventilation (NIV) is defined as a method of delivering ventilatory support to a patient without the use of an invasive airway such as an endotracheal, nasotracheal, or tracheostomy tube. Noninvasive ventilation can be provided with negative or positive pressure. In the early twentieth century, negative pressure ventilation was the predominant modality [1]. These large, tank-style ventilators enclosed a patient's entire thorax and created a negative pressure to help passively expand the patient's chest wall and lungs. Due to increased experience with the technique as well as improved ventilator technology, noninvasive positive pressure ventilation (NPPV) has now become the preferred method of NIV.

NPPV has been shown to be effective in treating chronic conditions such as obstructive sleep apnea and chronic obstructive pulmonary disease (COPD). As the use of NPPV has become more widespread and understood, the technique has been applied to a much wider spectrum of respiratory conditions and clinical scenarios, including those commonly seen in the critical care setting. The use of NPPV has been described in acute hypoxemic/hypercapnic respiratory failure, post-extubation failure, patients who are difficult to wean from the ventilator, and even acute respiratory distress syndrome (ARDS).

The appeal of NPPV is self-descriptive; it is noninvasive in nature. Many complications are associated with invasive ventilation. These include but are not limited to increased rates of hospital-acquired pneumonia, hospital days, ICU days, and mortality. Intubation itself is not a benign procedure and can cause direct trauma to airways and the oropharynx. Furthermore, patients who are endotracheally or nasotracheally intubated lose the ability to communicate verbally and eat normally. If these potential complications and limitations of traditional invasive ventilation can theoretically be prevented by the use of NPPV without jeopardizing patient safety, then the decision on which modality to use becomes clearer. The question becomes how to identify the patients that will benefit most from NPPV.

This chapter will discuss the practical applications of NPPV in the critical care setting, including appropriate indications and contraindications for its use.

Mechanism of Action

The physiology and theory of NPPV will be briefly addressed here. The principle of applying NPPV is similar to that of invasive positive pressure ventilation. The positive airway pressure provided forces air into the airways with the result of opening collapsed airways and alveoli. This recruits areas of under-ventilated or collapsed lung helping to correct ventilation/perfusion (V/Q) mismatch, leading to improvement in oxygenation and lung compliance. Increased lung compliance reduces the work of breathing for the patient. The delivered positive pressure also off-loads the muscles of respiration, contributing to improvement in respiratory mechanics. Other purported benefits include improvement of cardiac function in patients with congestive heart failure (CHF). The proposed mechanism of this is due to the increased intrathoracic pressure caused by the positive pressure delivered via NPPV. This increased intrathoracic pressure helps to decrease the venous return to the heart (decreased preload) and augment the ejection of blood by the left ventricle (decreased afterload).

There are many different ways that NPPV can be delivered, but the process essentially is distilled down into positive airway pressure being applied during a respiratory cycle. The two most common methods of delivering NPPV are continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BPAP). Although some controversy exists as whether or not CPAP is truly a mode of NIV, for the purposes of this chapter, it will be included as such.

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CPAP is a constant pressure that is delivered throughout both the inspiratory and expiratory phase of the respiratory cycle. It is often used in the treatment of sleep apnea, where the constant pressure provided prevents the upper airways from collapsing during sleep. This is the most rudimentary form of NPPV and requires the patient to initiate all breaths. Because the pressure does not change between the inspiratory and expiratory phases, it does not augment tidal volumes (i.e., it provides no pressure support).

BPAP provides separate inspiratory and expiratory positive airway pressures during the respiratory cycle. The inspiratory pressure is set higher than the expiratory pressure, and the difference between these two values (pressure support) is what augments tidal volume. The expiratory positive airway pressure is analogous to setting the PEEP for invasive mechanical ventilation. BPAP is a much more versatile mode of NPPV and does not necessarily require patient-initiated breaths, as a set "backup" rate can be dialed in. BPAP is the most commonly used mode of NPPV, and due to its flexibility, it is the preferred modality in the ICU.

Patient Selection

While noninvasive ventilation is an attractive option to provide ventilatory support with many potential upsides, it should never replace traditional invasive ventilation when that is what the clinical situation calls for. Table 16.1 lists contraindications to NPPV.

Patient selection is of the utmost importance when the decision is made to initiate NPPV, particularly in the ICU setting. The role of NPPV in critical care is still not well defined. Specific applications will be discussed later in the chapter. In general however, patients with the following characteristics generally will have greater success with NPPV application [2]:

- A rapidly reversible cause of hypoxemia
- Mild to moderate respiratory acidosis (pH 7.1–7.35)
- Moderate to severe dyspnea
- Tachypnea (greater than 24 breaths per minute for COPD, greater than 30–35 breaths per minute for hypoxemic respiratory failure)

The decision to initiate NPPV should be made early once a patient starts showing initial signs or symptoms of impending respiratory failure. Early application of NPPV will yield the highest rates of success. Waiting until a patient becomes too unstable or requires more advanced airway management before considering NPPV wastes a potential opportunity to circumvent such a scenario from occurring.

Table 16.1 Contraindications to NPPV

Cardiopulmonary arrest	Severe hypoxemia
Inability to protect airway	Airway obstruction
Hemodynamic instability	Massive hematemesis/hemoptysis
Severe acidosis	Facial trauma/burns
Inability to fit NPPV apparatus	Patient noncompliance
Recent upper GI surgery	

Specific Conditions

Chronic Obstructive Pulmonary Disease (COPD) and Cardiogenic Pulmonary Edema

The vast majority of studies pertaining to the use of NPPV have been in the treatment of respiratory failure related to COPD exacerbation and cardiogenic pulmonary edema.

Multiple randomized controlled studies and meta-analyses have shown marked benefits when using NPPV (generally BPAP) in the treatment of COPD exacerbation when compared to standard oxygen therapy and invasive mechanical ventilation [3–7]. Significant reductions in mortality, rate of intubation, and hospital length of stay have been demonstrated, although long-term outcome improvement has yet to be shown. A recent meta-analysis of NPPV in the acute care setting showed that its use reduces morality by almost half when compared to standard treatments [8]. NPPV appears to be more beneficial in moderate to severe cases of COPD exacerbation (defined as a baseline pH of <7.3) and thus is an appropriate modality for use in ICU patients who are admitted with respiratory failure due to COPD. NPPV is considered a first-line therapy in this patient population, with strong data to support its use [3–8].

Similar data exists for those who have respiratory failure secondary to cardiogenic pulmonary edema. NPPV has been shown to decrease rates of intubation and improve respiratory mechanics in this subset of patients [9–13]. The data regarding mortality is somewhat less compelling than that for COPD, though several reviews concluded that the use of NIV for cardiogenic pulmonary edema does improve overall survival [8, 14, 15]. Regardless, NPPV is considered a viable, first-line treatment for respiratory failure in these patients with high-quality evidence to support its use. It should be noted that the majority of studies done examining the use of NPPV in patients with acute cardiogenic pulmonary edema were done using CPAP as the primary modality. One RCT comparing CPAP to BPAP in these patients showed a higher incidence of myocardial infarction in the BPAP arm, but this may have been due to patient selection issues. Overall mortality between the two groups was no different [16].

Weaning from the Ventilator and Post-extubation Respiratory Failure

Early liberation of patients from the ventilator remains a priority of ICU care. Although invasive mechanical ventilation is frequently lifesaving and unavoidable, it is not a benign intervention, and prolonged intubation can lead to many detrimental (and some would say preventable) consequences.

Traditionally, ventilator-weaning trials are performed while the patient is still intubated. This may involve spontaneous breathing trials, pressure support modes, synchronized intermittent mechanical ventilation (SIMV), or other techniques. Regardless of the method, the patient is monitored, and a decision is made on whether or not the patient is ready for extubation. If the patient fails, they are left intubated on the ventilator, often for at least another 24 h until a subsequent weaning trial is performed.

The concept of using NIV to wean patients from the ventilator has appeal because the process of weaning occurs after the patient has been extubated. This may be a difficult concept to grasp at first. Some might assume that extubation equates to liberation from the ventilator; however, it would be remiss to forget that NPPV is still mechanical ventilation, only delivered without an invasive airway in place.

A 2013 Cochrane review examining NPPV as a weaning strategy for intubated patients contained 16 trials deemed to be of "moderate to good quality" concluded that weaning strategies that included NPPV "may reduce rates of mortality and ventilator-associated pneumonia without increasing the risk of weaning failure or re-intubation" [17]. The majority of patients in these studies (approximately two thirds of the total study population) were COPD patients with respiratory failure, so these results may be limited when applied to a broader patient population. Regardless, data exists that shows that NPPV could be a viable option to get patients extubated sooner.

The use of NPPV in post-extubation respiratory failure at first might seem similar to its use as a strategy to wean patients from the ventilator. However the key difference is in how this population is defined. NPPV has been described for use in patients who develop respiratory failure after extubation, presumably after passing a weaning trial while intubated, or immediately after extubation to circumvent the development of post-extubation respiratory failure. It is important to make this distinction because the data differs between these two groups.

A meta-analysis of 10 trials containing 1382 patients done in 2014 examined the efficacy of using NPPV to manage post-extubation respiratory failure. It concluded that in the subgroup of patients who developed respiratory failure after extubation, NPPV did not reduce the rate of re-intubation, nor did it reduce mortality [18]. In fact, there was a trend toward worse outcomes in this group. For those patients deemed to be at "high risk" for post-extubation respiratory failure (but are able to successfully pass a SBT during invasive ventilation), early application of NIV seems to show some benefit by reducing rates of re-intubation and mortality. The definition of "high risk" however is not uniform and subject to interpretation. Given the current evidence, the use of NPPV for the management of post-extubation failure should be done judiciously and only by clinicians with experience using it in the ICU setting. It should never delay re-intubation if clinically indicated.

Table 16.2 Risk factors for postoperative respiratory failure

Abdominal aortic aneurysm repair	Thoracic surgery
Neurosurgery	Upper abdominal surgery
Peripheral vascular surgery	Neck surgery
Emergent surgery	Albumin level < 30 g/L
Blood urea nitrogen level > 30 mg/dL	Dependent functional status
COPD	Age

Postoperative Respiratory Failure

Postoperative respiratory failure is a similar but distinct entity to post-extubation respiratory failure. It is defined as the continued need for mechanical ventilation immediately postoperatively or the need for re-intubation after postoperative extubation. Postoperative respiratory failure differs from other causes of respiratory failure in several ways. Surgery and general anesthesia lead to dysfunction of respiratory muscles, especially the diaphragm, resulting in impaired respiratory mechanics, atelectasis, hypoxia, hypoventilation, and the potential for subsequent respiratory failure. Additionally, the type of surgery and patient comorbidities often will contribute to the constellation of factors that lead to postoperative respiratory failure. A large multicenter Veterans Affairs (VA) study developed a model, which identified risk factors for postoperative respiratory failure (Table 16.2) [19].

A recent randomized clinical trial published in 2016 examined the effect of NIV on rates of tracheal re-intubation in patients with postoperative hypoxemic respiratory failure after undergoing abdominal surgery [20]. NIV was compared to oxygen delivered by mask at up to 15 L/min to maintain adequate saturation. NIV was shown in this population to significantly decrease the rates of re-intubation, ventilator days, and rates of nosocomial infection. No mortality benefit was observed. These results are similar to those found in a previous review on the subject, which included surgical patients of all disciplines and was not limited only to those receiving abdominal surgery [21].

The available data suggests that NIV may be a useful adjunct as both a prophylactic and therapeutic treatment for

patients presenting with postoperative respiratory failure. Unfortunately many of the available studies are of low quality, and further research is required in order to make a stronger recommendation on its use in this specific population.

Hypoxemic Respiratory Failure

Hypoxemic respiratory failure encompasses a very large, heterogeneous population of patients, as the causes of this condition are numerous and varied. The definition of hypoxemic respiratory failure is not uniform but has been defined as hypoxemia ($SpO_2 < 90\%$ or PaO_2/FiO_2 ratio < 200) while breathing 50% supplemental oxygen via venturi mask [22, 23].

Many of the large meta-analyses that have been done reviewing the use of NPPV in the acute care setting include studies examining its use to treat respiratory failure from acute lung injury, trauma, ARDS, pneumonia, and other etiologies as well as the previously described conditions of COPD and cardiogenic pulmonary edema. The analyses conclude that overall in adult patients with acute respiratory failure, NPPV led to a lower intubation rate, shorter ICU length of stay, and lower rates of mortality when compared to conventional therapy [8, 18, 24].

The data supporting the use of NPPV for patients with respiratory failure due to COPD or cardiogenic pulmonary edema is quite robust. Fewer studies exist that have examined NPPV for treating hypoxemic respiratory failure in the absence of these two conditions. Data does exist however showing that NPPV can be effective in managing these patients. One study assigned patients with hypoxemic respiratory failure to receive either conventional invasive mechanical ventilation or NPPV via a standardized protocol. It was found that NPPV improved gas exchange just as effectively as invasive mechanical ventilation, measured as an improvement in the PaO_2/FiO_2 ratio. The NPPV arm also had significantly shorter stays in the ICU and fewer serious complications [22].

A randomized trial was subsequently done by a separate group examining the use of NPPV as a primary treatment for severe hypoxemic respiratory failure (the mean PaO_2/FiO_2 ratio of the study population was approximately 100 mmHg) and its effect on both survival and need for intubation [23]. Patients were randomized to receive either NPPV or high-concentration oxygen therapy. The study demonstrated that overall, patients treated with NPPV had a significantly lower need for intubation and had improved ICU and 90-day survival. These benefits were especially pronounced in patients with pneumonia. Conversely, in the subgroup of patients with respiratory failure due to ARDS, NPPV did not decrease rates of intubation or improve 90-day survival [23].

In 2013, an observational cohort study was published that looked to identify predictors of NPPV failure in patients with hypoxemic respiratory failure and determine the rates of failure when NPPV was used as a first-line treatment [24]. The patients included had hypoxemic respiratory failure in the absence of COPD and cardiogenic pulmonary edema. The study population was then divided into those who met clinical criteria for ARDS and those who did not. The ARDS group was further subdivided into those with mild, moderate, and severe ARDS based on the Berlin criteria. Similar to what was observed in the previously mentioned study, patients with ARDS had a significantly higher rate of intubation than those who did not. However those with no ARDS or mild ARDS had no difference in rates of intubation. Mortality was also higher in patients with ARDS. The authors identified that patients with active cancer, lower GCS scores, shock, moderate or severe ARDS, and lower levels of PEEP while on NPPV were predictive of failure [24].

It appears that NPPV does have a role in the treatment of hypoxemic respiratory failure not due to COPD or cardiogenic pulmonary edema and is especially effective for patients with pneumonia. Those with more severe disease such as ARDS or presenting in shock are still better served by invasive mechanical ventilation. The data seems to show that NPPV can be an effective strategy for hypoxemic respiratory failure, but selecting the appropriate patient will be a large determinant of its success.

Trauma

Respiratory failure in trauma patients is frequently multifactorial. Patients may have injuries to the chest wall such as rib fractures or sternal fractures that make breathing painful and alter respiratory mechanics, pulmonary contusions that cause impairment in gas exchange at the alveolar level, pneumothoraces, and other injuries that cause overall deconditioning of the patient. Because of this, trauma patients are a heterogeneous population by definition, and the use of NPPV is difficult to apply broadly. In 2002 the British Thoracic Society Standards of Care Committee gave a grade C (low) recommendation on the use of NPPV for patients with chest wall trauma who remain hypoxic despite the use of oxygen therapy and adequate analgesia, citing a lack of evidence [14]. Since this guideline was published, several studies and meta-analyses have been performed which suggest that in patients who have suffered chest trauma, NPPV can reduce rates of intubation, ICU length of stay, mortality, and overall complications when compared with high-flow oxygen therapy and invasive ventilation. It should be noted however, that many of these studies contain small sample sizes, the number of studies themselves is small, and the quality of the evi-

dence is of low to moderate quality (few randomized controlled trials). A more recent clinical practice guideline published in 2011 by the Canadian Critical Care Society gave no recommendations on the use of NPPV in patients with chest trauma, citing a lack of strong evidence [15].

Given the lack of quality evidence to support the application of NPPV in trauma patients with hypoxemic respiratory failure, it is difficult to give a broad recommendation on its use in this population. NPPV should be used on a case-by-case basis for in appropriately selected trauma patients. Further studies on the use of NPPV in the trauma population are needed to better delineate the subset of patients that would benefit most from this modality.

Application of Noninvasive Ventilation

Once a patient has been identified that is a suitable candidate for NPPV, the next step is to initiate treatment as soon as possible. Early application of NPPV is one of the keys to its success.

NPPV is administered by face mask, and the two most common types are nasal masks and full face masks. Nasal masks are triangular-shaped devices that fit over the nose and form a seal over the face with an inflated cuff. The nasal mask is better tolerated over long periods of time due to a decreased sensation of claustrophobia and the ability to eat and converse normally. Nasal masks are more suited for chronic conditions. Full face masks are the preferred interface for delivering NIV in the acute setting [15]. They consist of a mask that covers both the nose and mouth, which leads to less air leakage through the mouth. A good mask fit is very important to the successful implementation of NPPV. Excessive air leak, especially when using ventilators that cannot compensate for it, will lead to suboptimal ventilatory support. If a mask is uncomfortable or a poor fit, patients will be less likely to tolerate noninvasive therapy and may require invasive mechanical ventilation.

There are many types of ventilators from different manufacturers that use proprietary nomenclature, but for all intents and purposes, BPAP is our preferred modality of NPPV for use in the critical care setting. Once the appropriate patient has been selected and a good mask fit established, initial ventilator settings are then selected. Selecting ventilator settings for NPPV is similar to doing so for invasive ventilation. An initial inspiratory positive airway pressure (IPAP) of 10 cm H_2O and an expiratory positive airway pressure (EPAP or PEEP) of 5 cm H_2O are a good starting point for most patients. FiO_2 is set at 100% and titrated down to the lowest number that provides the desired oxygen saturation on pulse oximetry. After a period of observation, adjustments can be made to achieve appropriate clinical endpoints. In general a tidal volume of 6–8 ml/kg should be targeted while watching the patient's respiratory rate. If desired, a backup respiratory rate can be dialed in for patients who have difficulty initiating spontaneous breaths. A summary of adjustments to the initial ventilator settings based on clinical picture can be found in Table 16.3.

Table 16.3 NIV adjustments

Hypercapnia	Increase IPAP in increments of 1–2 (max 25 cm H_2O)
Dyspnea	Increase IPAP in increments of 1–2 (max 25 cm H_2O)
Hypoxia	Increase EPAP in increments of 1–2 (max of 10–15 cm H_2O)

Once NPPV has been started, patients should be continuously monitored for clinical improvement and tolerance of the treatment. Blood gasses can be drawn as needed to track changes in gas exchange. Signs of recovery in respiratory status within 1–2 h after initiation of treatment tend to be predictive of success. If the patient does not appear to be improving and the clinician is confident that the interface is working appropriately and ventilator settings have been optimized, converting to traditional invasive ventilation should be strongly considered. Failure to do so can lead to unnecessary complications and even death.

Summary

Noninvasive ventilation provides many of the same benefits as traditional invasive ventilation while potentially mitigating the negatives that come with having an intubated patient. Thus it is understandable why there is so much interest in applying NIV to a broader spectrum of respiratory disorders. NIV has been proven in the literature to be extremely effective for the treatment of COPD exacerbation and respiratory failure attributed to cardiogenic pulmonary edema and should be considered a first-line strategy for these specific respiratory disorders.

What is less clear is the role of NIV in treating or preventing other causes of respiratory failure encountered in the critical care setting. The available data is promising and should encourage clinicians to incorporate it into their armamentarium for treatment of respiratory conditions they might encounter. The challenge at this moment appears to be identifying the patients will benefit the most from NIV and applying it early to get maximum benefit from its use. More high-quality studies will need to be done to help clarify this picture going forward.

References

1. Hill NS. Clinical applications of body ventilators. Chest. 1986;90(6):897–905.
2. McNeill GBS, Glossop AJ. Clinical applications of non-invasive ventilation in critical care. Contin Educ Anaesth Crit Care Pain. 2011;12(12):33–7.
3. Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive pulmonary disease. Lancet. 1993;341:1555–7.
4. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333:817–22.
5. Collaborative Research Group of Noninvasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease. Early use of non-invasive positive pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease: a multicenter randomized controlled trial. *Chin Med J*. 2005;118:2034–40.
6. Ram FSF, Picot J, Lightowler J, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2004;3:CD004104.
7. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. Chest. 2008;133:756–66.
8. Cabrini L, Landoni G, Oriani A, et al. Noninvasive ventilation and survival in acute care settings: a comprehensive systematic review and Metaanalysis of randomized controlled trials. Crit Care Med. 2015;43(4):880–8.
9. Masip J, Betbese AJ, Paez J, et al. Non-invasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: a randomized trial. Lancet. 2000;356:2126–32.
10. Levitt MA. A prospective, randomized trial of BiPAP in severe acute congestive heart failure. J Emerg Med. 2001;21:363–9.
11. Kelly CA, Newby DE, McDonagh TA, et al. Randomised controlled trial of continuous positive airway pressure and standard oxygen therapy in acute pulmonary oedema. Eur Heart J. 2002;23:1379–86.
12. Nava S, Carbone G, DiBattista N, et al. Noninvasive ventilation in cardiogenic pulmonary edema: a multicenter, randomized trial. *Am J Resipr*. Crit Care Med. 2003;168:1432–7.
13. Park M, Sangean MC, Volpe M, et al. Randomized, prospective trial of oxygen, continuous positive airway pressure, and bilevel positive airway pressure by face mask in acute cardiogenic pulmonary edema. Crit Care Med. 2004;32:2407–15.
14. British Thoracic Society Standards of Care Committee. Noninvasive ventilation in acute respiratory failure. Thorax. 2002;57:192–211.
15. Keenan SP, Sinuff T, Burns KE, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ. 2011;183:E195–214.
16. Mehta S, Jay GD, Woolard RH, et al. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. Crit Care Med. 1997;25:620–8.
17. Burns KEA, Meade MO, Premji A, et al. Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure. Cochrane Database Syst Rev. 2013;12:CD004127.
18. Lin C, Yu H, Fan H, et al. The efficacy of noninvasive ventilation in managing postextubation respiratory failure: a meta-analysis. Heart Lung. 2014;43(2):99–104.
19. Arozullah AM, Daley J, Henderson WG, et al. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Ann Surg. 2000;232:242–53.
20. Jaber S, Lescot T, Futier E. Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery. JAMA. 2016;315(13):1345–53.
21. Chiumello D, Chevallard G, Gregoretti C. Non-invasive ventilation in postoperative patients: a systematic review. Intensive Care Med. 2011;37:918–29.
22. Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med. 1998;339:429–35.
23. Ferrer M, Esquinas A, Leon M, et al. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med. 2003;168(12):1438–44.
24. Thille A, Contou D, Fragnoli C, et al. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. Crit Care. 2013;17:R269.