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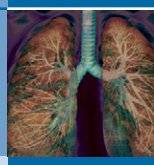

Chapter 33
Noninvasive Mechanical Ventilation

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Noninvasive ventilation (NIV) is mechanical ventilatory support delivered to the airways in the absence of invasive devices such as an endotracheal tube or tracheotomy cannula. The most common devices used to establish the ventilator-patient interface are nasal, oronasal, and full face masks, along with nasal pillows and helmets. The role of NIV has grown steadily in recent years, and in expert hands, it now represents an extremely valuable tool for the management of acute respiratory failure (ARF). The key factors in successful use of NIV are proper patient selection and a high level of competence and experience in both medical and adjunctive personnel on the respiratory care team. It has been shown that in the appropriate setting, NIV is effective in improving gas exchange and alveolar ventilation, as well as in avoiding intubation in patients with ARF. A role for this ventilatory mode also has been proposed in the management of chronic hypercapnic respiratory failure in chronic obstructive pulmonary disease (COPD), although its use is associated with more controversial results.

In general, the main goal of NIV is to provide adequate ventilatory support while avoiding the risks related to tracheal intubation (laryngeal and tracheal damage, lower-airway infections, accidental extubation, higher risk of barotrauma, and volutrauma), as well as sparing the patient the level of pharmacologic sedation commonly required for intubation. In addition, NIV can be performed outside the intensive care unit (ICU)—for example, in step-down units or the emergency department, or on respiratory care wards. On the other hand, it is obvious that NIV cannot guarantee the level of airway control provided by invasive ventilation in terms of leak avoidance, effective delivery of flow and pressure to the airways, and control of minute ventilation. Accurate positioning of the interface device is crucial to minimize air leaks, and patients should be constantly monitored for timely detection of signs of worsening that may necessitate a prompt switch to invasive ventilation.

INDICATIONS FOR IMPLEMENTATION OF NONINVASIVE VENTILATION

In general, NIV is indicated in patients showing clinical and functional signs of acute respiratory distress, in particular:

- Poor alveolar gas exchange level (as indicated by PaO_2/FIO_2 less than 200 mm Hg)
- Ventilatory pump failure with hypercapnia and respiratory acidosis ($PaCO_2$ greater than 45 mm Hg and pH below 7.35)
- Severe dyspnea accompanied by use of accessory respiratory muscles
- Tachypnea (with respiratory rate greater than 24 breaths/minute)

These signs indicate a combination of increased work of breathing and decline in respiratory pump efficiency and point to the need for ventilatory support to relieve the rapidly worsening inspiratory muscle fatigue and to restore acceptable levels of gas exchange and alveolar ventilation. In the presence of these conditions, NIV should be initiated as soon as possible.

It also is important to bear in mind the conditions that preclude use of NIV and dictate prompt intubation with no delay—severely impaired neurologic state as evidence by a Kelly score (a scale specifically devised to assess patient responsiveness) higher than 4, respiratory arrest, shock, severe cardiovascular instability, and presence of excessive airway secretions. Facial lesions that prevent the fitting of nasal or facial masks also will prevent the use of NIV.

MODES

This chapter focuses exclusively on positive-pressure ventilation, which can be broadly defined as the intermittent delivery of pressure to the airways by means of a machine connected to the airway opening. The modes more frequently used for noninvasive ventilation are pressure support ventilation (PSV) and proportional assist ventilation (PAV), often with the addition of extrinsic positive end-expiratory pressure (PEEP); the use of continuous positive airway pressure (CPAP) in the acute setting is confined mainly to the treatment of hypoxemic respiratory failure, especially if the cause is related to cardiogenic pulmonary edema.

EQUIPMENT

VENTILATORS

A simple, informal way of classifying mechanical ventilators on the basis of their performance distinguishes three main types:

1. *Typical ICU ventilators*, powered by compressed gas, usually from wall outlets, and interfaced to the patient exclusively by means of a double circuit, with separate inspiratory and expiratory limbs. These systems are equipped with a screen to allow complete monitoring of ventilatory parameters and graphic display of flow, volume, and pressure curves. They typically are used for invasive ventilation. When set for pressure ventilation, they function on the PSV/PEEP algorithm, in which, as mentioned, the PSV level is superimposed on

the PEEP, with total inspiratory pressure thus resulting from the sum of PSV and PEEP.

2. *Portable home ventilators* (bilevel ventilators), electrically powered and providing only a single circuit for both inspiration and expiration. These machines are used exclusively for noninvasive ventilatory support. They function on the IPAP/EPAP algorithm, in which the inspiratory positive airway pressure (IPAP) is not superimposed on the expiratory pressure (EPAP).
3. *"Hybrid" ventilators,* usually powered by electricity, allowing both single- and double-circuit options. They use the PSV/PEEP algorithm. They can be used for both invasive as well as noninvasive ventilation.

INTERFACES

Patient-circuit interfaces for NIV can be nasal (nasal mask or nasal pillows or plugs), oral (mouthpiece), or facial (oronasal mask, full face mask, helmet). The choice of the appropriate interface is crucial to ensure the success of the treatment and patient compliance. In general, the nasal mask is better tolerated by patients, because it allows expectoration and creates less overall discomfort and is associated with less subjective claustrophobia. In acutely ill patients, face masks usually are preferred over nasal masks by most clinicians, because they provide better control of air leaks, especially in view of the difficulty of breathing exclusively through the nose for patients with acute respiratory failure. In fact, leak control is a key determinant of success for NIV, because it has been shown that air leaks represent the single most important cause of patient-ventilator asynchrony, even when such leaks are relatively modest. On the other hand, placement of nasal or oronasal masks should never be too tight, to prevent development of severe pressure skin lesions, especially frequent across the bridge of the nose, and to improve tolerability. The marked difference in internal volume associated with different interfaces does not usually affect NIV outcome in terms of clinical response and gas exchange variables, when the treatment is delivered by an experienced staff, as shown by a randomized prospective study that compared full face masks, oronasal masks of various sizes, and mouthpieces.

CLINICAL INDICATIONS

In the past decade, the role of NIV has steadily grown, so that it has now become a first-line intervention in a number of clinical conditions. In particular, on the basis of solid evidence gathered over the past 2 decades, NIV has been established as a first-choice intervention in the treatment of acute respiratory failure in the setting of COPD exacerbations and cardiogenic pulmonary edema. The role of NIV also appears to be well established in the management of respiratory failure developing in immunocompromised patients. Finally, NIV has been used as a weaning strategy and to reduce extubation failure.

EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Acute respiratory failure frequently complicates COPD exacerbations for a number of reasons deeply rooted in the pathophysiology of the disease. In particular, a combination of airway disease and loss of elastic recoil contributes to the generation of airflow limitation, which in turn can lead to air trapping and lung hyperinflation. As a consequence, the diaphragm is flattened, with loss of optimal length of its muscle fibers and diminished contractile efficiency. Moreover, intrinsic positive end-expiratory pressure (PEEPi) often is present, as a result of the nonreversible airflow limitation. PEEPi places a further burden on inspiratory muscles, because it has to be overcome before a negative alveolar pressure, necessary to the initiation of inspiratory airflow, can be generated.

The contraction of the diaphragm initially is isometric, and only after PEEPi has been counterbalanced can chest expansion begin. The combined effect of increased work of breathing and loss of contractile efficiency places the diaphragm at risk for development of fatigue, a precursor to acute alveolar hypoventilation with hypercapnia and respiratory acidosis. The first studies on the role of noninvasive ventilation in patients with COPD experiencing acute hypercapnic respiratory failure were conducted in the late 1980s. Since then, several controlled randomized studies have shown that NIV added to standard medical treatment is effective in reducing mortality, avoiding intubation, relieving dyspnea, and reducing length of hospital stay in patients with COPD with acute respiratory failure when compared with medical management plus oxygen therapy alone.

A randomized controlled study conducted on 236 patients showed that the rate of success with NIV was especially high in subjects with mild acidosis (pH greater than 7.30), whereas patients with more severe acidosis did not fare equally well and were more likely to require intubation. These findings point to the need for an early and accurate differentiation between patient subgroups on the basis of severity of illness, to allow prompt initiation of the most effective treatment. Patients with mild to moderate acidosis can receive NIV in hospital units outside the ICU, so long as they are staffed with trained personnel. More severely affected patients can still undergo a NIV trial, but only under strict management in an ICU setting, where they can be intubated with no delay in case signs of failure become apparent. Patients treated with NIV, irrespective of their initial severity status, had lower rates of infectious complications (ventilator-associated pneumonia, sepsis). A recent prospective study conducted in the United Kingdom in 9716 inpatients with COPD exacerbation and ARF managed in general clinical practice showed an overall mortality rate of 25% for patients receiving NIV—significantly higher than rates reported in the randomized controlled trials (RCTs). The study pointed to several potential explanations, including inaccurate selection of candidate patients for NIV, including, in some cases, patients with mixed acidosis or prevailing metabolic acidosis; the use of NIV as a "ceiling" of treatment in subjects with very severe disease; and substantial delays in initiating the ventilatory treatment. In addition, patients with mild acidosis (those in which the effectiveness of NIV is higher) appeared to be a minority among the overall group and often do not receive NIV at all. These results highlight the need for better implementation, in general clinical practice, of proper use of NIV in accordance with the evidence gathered from the RCTs.

CARDIOGENIC PULMONARY EDEMA

Cardiogenic pulmonary edema is a consequence of left ventricular failure. It frequently leads to a reduction in lung compliance, with decreased functional residual capacity, regional atelectasis, ventilation-perfusion mismatch and poor gas exchange, resulting in lung failure with hypoxemic respiratory failure. The latter condition is characterized by Pa_{O_2}/Fi_{O_2} of less than 300. Treatment with CPAP has long been known to

improve survival rate and to lower the need for intubation in patients with cardiogenic pulmonary edema, compared with those receiving conventional medical treatment plus oxygen therapy.

CPAP has the advantage of being practical and relatively easy to use; in most cases treatment with CPAP is administered directly in the emergency department.

In hypoxemic patients, conventional NIV has not produced significant improvements over those achieved with CPAP, although it can be effective in patients with cardiogenic pulmonary edema exhibiting hypercapnia. These data were recently questioned by a multicenter trial comparing oxygen therapy alone, CPAP, and NIV. The investigators concluded that with NIV, the physiologic improvements were faster than with oxygen alone, but without any significant effect on intubation or mortality rates. However, the very low intubation rate in this study (less than 3%) raises questions regarding whether the patient population was comparable to that of other studies.

RESPIRATORY FAILURE IN IMMUNOCOMPROMISED PATIENTS

An immunocompromised status, irrespective of its specific cause (hematologic neoplasms, use of immunosuppressant drugs, AIDS) often leads to lung infections of serious entity which may result in severe hypoxemic respiratory failure. Immunocompromised patients can potentially benefit significantly from NIV, especially because they are particularly at risk for infectious complications related to endotracheal intubation and invasive ventilation. In fact, it has been shown that NIV, especially when applied early, can significantly ameliorate the respiratory symptoms of these patients and reduce need for intubation and overall mortality. According to Principi and colleagues, NIV can even be administered to these patients, by trained personnel, outside the ICU, so as to avoid the risks related to exposure to the ICU environment. These data provide a rationale for a timely use of NIV as an effective means of treatment for respiratory failure in these patients.

ROLE OF NONINVASIVE VENTILATION IN HYPOXIC PATIENTS

One of the major confounders of these studies was the marked variability of the case mix; patients with different underlying disorders and pathophysiologic pathways were included under the same generic definition of having hypoxemia. Confalonieri and associates evaluated NIV in patients with ARF (PaO_2/FIO_2 below 250) consequent to community-acquired pneumonia, including both those with and those without COPD. Compared with standard treatment alone, NIV produced a significant reduction in respiratory rate, need for endotracheal intubation, and ICU stay. A subgroup analysis, however, showed that the benefits of NIV occurred only in those patients with COPD.

Antonelli and co-workers compared NIV with conventional ventilation provided using an endotracheal tube in selected patients with hypoxemic ARF. Sixty-four consecutive patients were enrolled. After 1 hour of mechanical ventilation, the PaO_2/FiO_2 ratio had improved in both groups. Ten patients in the NIV group required intubation. Patients randomized to receive conventional ventilation more frequently developed serious complications and, in particular, infections secondary to endotracheal intubation. Among survivors, the duration of mechanical ventilation and ICU stay were shorter in patients randomized to receive NIV. It should be kept in mind, however, that this single study was conducted in selected patients in one well-experienced center.

A study performed in three European ICUs with considerable expertise with NIV clarifies the issue of "real-life" use of NIV in this setting. This study showed that only 16.5% of patients admitted with ARDS can be successfully treated with this technique. In two years' time, 479 patients were hospitalized for this disorder, a large majority of whom (69%) were already intubated at admission, so that only 147 were eligible for the study. NIV improved gas exchange and avoided intubation in 54% of this subset of patients, for an overall success rate of less than 20%. In these patients NIV was associated with less ventilator-associated pneumonia and a lower ICU mortality rate (6% versus 53%). It should be noted, however, that the study was conducted in three ICUs with solid expertise with NIV. In summary, the use of NIV as an alternative to invasive ventilation in severely hypoxemic patients generally is not advisable and should be limited to hemodynamically stable patients who can be closely monitored in an ICU.

Major surgery is sometimes complicated by the occurrence of atelectasis and pneumonia, which lead to hypoxemia and respiratory distress during the early postoperative period.

One randomized study showed that nasal CPAP delivered through a helmet decreased atelectasis and prevented pneumonia more effectively than did standard therapy alone during an episode of mild respiratory failure after upper abdominal surgery. In another study, NIV significantly ameliorated gas exchange and pulmonary function abnormalities after gastroplasty in obese patients.

NIV may be used in the early treatment of ARF secondary to lung resection, a fatal complication in up to 80% of cases. Auriant and colleagues showed that NIV is safe and effective for reducing the need for intubation and improving survival.

The use of NIV for severe acute respiratory syndrome (SARS) and other airborne diseases has generated debate. Two observational studies from China found no evidence of viral spread to caregivers who took appropriate precautions. In the event of a bird flu pandemic, ventilator resources are likely to be severely strained, and NIV may offer a means of supporting some of the afflicted, mainly those with initial respiratory failure. Some investigators, however, consider NIV to be contraindicated in respiratory failure from communicable respiratory airborne diseases unless it is used in a negative-pressure isolation room and strict precautions are taken against pathogen transmission.

In conclusion, the outcome of NIV in patients with hypoxemic ARF for whom endotracheal intubation is not mandatory yet depends primarily on the type and evolution of the underlying disorder. The high rate of failure of NIV in community-acquired pneumonia and acute respiratory distress syndrome suggests that for patients with these disorders, a cautious approach consisting of early treatment and avoidance of delay of needed intubation is advisable, and patients should be monitored in an ICU setting to assess progression toward the need for invasive ventilation.

ROLE OF NONINVASIVE VENTILATION IN THE PREVENTION OF POSTEXTUBATION FAILURE

Postextubation failure occurs in a percentage of patients varying from 2% to 20%. Necessity for reintubation usually becomes apparent 48 to 72 hours after extubation and is associated with a high mortality rate, as well as a high risk for lower respiratory tract infections. NIV has been applied as a mean of preventing

extubation failure with a variable degree of success, depending on the nature and severity of the underlying disease. Recently an RCT conducted on 106 patients with chronic pulmonary disease and hypercapnic respiratory failure who were treated either with NIV for 24 hours after extubation or with oxygen therapy alone, showed a significant effect of NIV in reducing the incidence of postextubation respiratory failure, the need for reintubation, and the overall 90-day mortality. This study seems to confirm a potential role for early NIV treatment in the prevention and treatment of post-extubation failure, at least in patients with chronic respiratory disease.

NONINVASIVE VENTILATION AND WEANING

The first randomized controlled study of an NIV strategy was performed in severely ill patients with COPD ventilated through an endotracheal tube. Patients who failed the T-piece trial were randomized to undergo either extubation, with immediate application of NIV, or continued weaning with the endotracheal tube in place. The study showed that the likelihood of weaning success is increased, while the duration of mechanical ventilation and ICU stay are decreased, when NIV is used as a weaning technique.

A second randomized controlled study was conducted in patients with chronic respiratory disorders, intubated for an episode of ARF. This study also found a shorter duration of invasive mechanical ventilation in the group weaned noninvasively, although no differences were found in ICU or hospital stay or 3-month survival rate.

In a third randomized controlled trial, patients who failed spontaneous breathing trials on three consecutive days were randomized to be extubated and receive NIV or to remain intubated and continue a conventional weaning protocol. Most of the patients were affected by hypercapnic respiratory failure. The duration of conventional mechanical ventilation, time spent in the ICU, and duration of hospitalization were significantly reduced in the NIV group. Patients treated with NIV also had lower rates of nosocomial pneumonia and septic shock and better 90-day survival.

In a recent report, unselected patients who failed trials with a spontaneous-breathing T-piece were randomized either to undergo extubation and NIV or to attempt a traditional weaning trial during invasive ventilation. The percentage of complications in the NIV group was lower, with lower frequency of pneumonia and tracheotomy. Length of stay in the intensive care unit and mortality were not statistically different between the groups. Further studies are clearly needed to assess the real benefits of NIV in weaning with other forms of respiratory failure, such as acute respiratory distress syndrome, postsurgical complications, or cardiac impairment.

In conclusion, in accord with the results of a recent meta-analysis, NIV may be safely and successfully used in the ICU setting to shorten the process of liberation from mechanical ventilation in clinically stable patients recovering from an episode of hypercapnic ARF who had previously failed a weaning trial.

PHYSIOLOGIC EFFECTS OF NONINVASIVE VENTILATION

NIV has been proved to achieve a variety of effects in patients with ARF, largely irrespective of the ventilator mode (PSV or PAV). In particular, in patients with hypercapnia, NIV can restore acceptable levels of alveolar ventilation, significantly reducing $PaCO_2$ and decreasing respiratory acidosis. Alveolar gas exchange also is significantly improved, as evidenced by an increase in PaO_2, which appears to be more rapid and dramatic in patients with cardiogenic pulmonary edema. The improvement in gas exchange seems to involve multiple mechanisms: increased functional residual capacity (FRC) with positioning of the lung volume along the linear part of the pressure-volume curve, facilitating the distensibility of lung parenchyma, and rendering areas of atelectasis or dystelectasis more accessible to ventilation; more uniform overall ventilation with improvement in the ventilation-perfusion ratio; and a higher alveolar pressure opposing fluid extravasation from the capillary bed.

A variable degree of inspiratory muscle rest also usually is obtained, although total diaphragm rest is almost never achieved with NIV because the required inspiratory pressure level would be too high, leading to excessive air leaks and gastric overdistention. Work of breathing is almost constantly reduced, as signaled by a marked reduction in the amplitude of esophageal pressure inspiratory shift (ΔPes). Diaphragmatic rest during noninvasive ventilation is also shown by a reduction in the pressure-time product and of diaphragm electrical activity as measured by electromyography.

Amelioration of diaphragm fatigue and improvement in alveolar ventilation as indicated by reduction in the level of hypercapnia are associated with a more normal breathing pattern, with reduction in breathing frequency. In patients with COPD, NIV increases dynamic compliance (usually decreased in this condition as a consequence of ventilation inhomogeneity and pendelluft), thus allowing a more uniform distribution of ventilation.

Moreover, NIV effectively prevents the increase in $PaCO_2$ often induced by oxygen therapy in ARF due to COPD exacerbations.

In addition to these favorable effects on respiratory mechanics and gas exchange, the potential for unfavorable hemodynamic effects also should be considered. In particular, even in normal persons, positive pressure, especially when applied throughout the entire ventilatory cycle, can reduce venous return to the heart, resulting in reduction in cardiac output. This effect has been demonstrated both in patients with "stable" COPD and during COPD exacerbations.

FUTURE DIRECTIONS

As reviewed in this chapter, the accumulating evidence seems to point to a number of more specific indications for the use of NIV. Several RCTs favor the use of this mode of ventilation. Smaller observational and pilot studies suggest the benefit of NIV in certain disease states; however, further large-scale trials are needed to confirm these findings. In certain geographic areas, old age is considered a barrier to ICU admission. Among patients older than 75 years, the use of NIV rather than standard therapy has been shown to significantly reduce mortality rate.

Some observation studies also have demonstrated that NIV may be successfully used to treat, rather than prevent, an episode of overt respiratory failure during exacerbations of a neuromuscular disease, cystic fibrosis, trauma, obesity-associated hypoventilation, and pancreatitis and eventually as a bridge to lung transplantation.

Indeed, other investigations suggested that NIV may be used in the weaning process in hypoxic patients, and in the treatment of postextubation failure in the subset of hypercapnic patients.

CONTROVERSIES AND PITFALLS

Despite the growing evidence for a role for NIV in the management of ARF, still unresolved are a few questions concerning its optimal utilization in clinical practice. The main controversy concerns the safety of NIV when applied outside the ICU setting, specifically in emergency departments and on regular wards. Although some evidence shows that NIV can be performed with good results in regular respiratory wards, the limiting factor for its success is the availability of specifically trained staff (doctors, nurses, and respiratory therapists). Such availability is far from consistent across hospitals and countries, so the experiences of different groups often are difficult to compare and to generalize. Availability of skilled and experienced staff is obviously crucial for proper patient selection and monitoring, appropriate handling of the equipment, and timely recognition of signs of worsening that might require escalation to invasive ventilation.

The same observations apply in the emergency department, where most patients with ARF who could potentially benefit from NIV initially are evaluated. In fact, many of these patients, for logistical reasons (such as shortage of ICU beds), first receive NIV in this setting, where monitoring is critical for ensuring success, because a delay in switching from noninvasive to invasive ventilation when necessary may result in increased mortality. Accordingly, knowledge and proper evaluation of the predictors of NIV outcome are extremely important.

As indicated by the foregoing considerations, the effectiveness of NIV is strictly dependent on location of implementation, timing, and staff training. Its success or failure will therefore depend on careful, case-by-case judgment that is firmly rooted in the reality of the available resources.

CONCLUSIONS

In summary, the past 2 decades have witnessed a dramatic increase in the use of NIV, which has become a clear-cut first-line treatment in the management of ARF in conditions as diverse as COPD and cardiogenic pulmonary edema and, in many instances, in immunocompromised patients. Moreover, NIV is no longer confined to the ICU, but in expert hands, it has crossed ever more often into the regular ward, thus broadening the spectrum of options available for the treatment of respiratory failure. Current research is focusing on improving the quality and safety of the devices and establishing new ventilatory modes to extend even further the indications for use of NIV, as well as improving its rate of success.

SUGGESTED READINGS

Ambrosino N, Nava S, Torbiki A, et al: Haemodynamic effect of pressure support and PEEP ventilation by nasal route in patients with stable chronic obstructive pulmonary disease, *Thorax* 48:523–528, 1993.

Antonelli A, Conti G, Esquinas A, et al: A multiple-center survey of the use in clinical practice of non invasive ventilation as a first line intervention for acute respiratory distress syndrome, *Crit Care Med* 35:18–25, 2007.

Antonelli M, Conti G, Rocco M, et al: A comparison of non-invasive positive pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure, *N Engl J Med* 339:429–435, 1998.

Auriant I, Jallot A, Hervé P, et al: Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection, *Am J Respir Crit Care Med* 164:1231–1235, 2002.

Beltrame F, Lucangelo U, Gregori D, Gregoretti C: Noninvasive positive pressure ventilation in trauma patients with acute respiratory failure, *Monaldi Arch Chest Dis* 54:109–114, 1999.

Bott J, Carrol MP, Conway JH, et al: Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease, *Lancet* 341:1555–1557, 1993.

Brochard L, Isabey D, Piquet J, et al: Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask, *N Engl J Med* 323:1523–1530, 1990.

Burns KE, Adhikari NK, Keenan SP, Meade M: Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: meta-analysis and systematic review, *BMJ* 338:b1574, 2009.

Celikel T, Sungur M, Cayhan B, Karakurt S: Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure, *Chest* 114:1636–1642, 1998.

Cheung TM, Yam LY, So LK, et al: Effectiveness of non-invasive positive pressure ventilation in the treatment of acute respiratory failure in severe acute respiratory syndrome, *Chest* 126:670–674, 2004.

Collins SP, Mielniczuk LM, Whittingham HA, et al: The use of non-invasive ventilation in emergency department patients with acute cardiogenic pulmonary edema: a systematic review, *Ann Emerg Med* 48:260–269, 2006.

Confalonieri M, Potena A, Carbone G, et al: Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of non invasive ventilation, *Am J Respir Crit Care Med* 160:1585–1591, 1999.

Crimi C, Noto A, Princi P, et al: A European survey of non-invasive ventilation practice, *Eur Respir J* 36:362–369, 2010.

Diaz O, Iglesia R, Ferrer M, et al: Effects of noninvasive ventilation on pulmonary gas exchange and hemodynamics during acute hypercapnic exacerbations of chronic obstructive pulmonary disease, *Am J Respir Crit Care Med* 156:1840–1845, 1997.

Dikensoy O, Ikidag B, Filiiz A, Bayram N: Comparison of non-invasive ventilation and standard medical therapy in acute hypercapnic respiratory failure: a randomised controlled trial at a tertiary health centre in SE Turkey, *Int J Clin Pract* 56:85–88, 2002.

Elliott MW: *European Respiratory Society Interactive course on non-invasive positive pressure ventilation: consensus, controversies and new horizons*, Hanover, Germany, February 12–14, 2009.

Fauroux B, Burgel PR, Boelle PY, et al: Chronic Respiratory Insufficiency Group of the French National Cystic Fibrosis Federation: Practice of noninvasive ventilation for cystic fibrosis: a nationwide survey in France, *Respir Care* 53:1482–1489, 2008.

Fernandez R, Blanch LP, Valles J, et al: Pressure support ventilation via face mask in acute respiratory failure in hypercapnic COPD patients, *Intensive Care Med* 19:456–461, 1993.

Ferrer M, Esquinas A, Arancibia F, et al: Noninvasive ventilation during persistent weaning failure: a randomized controlled trial, *Am J Respir Crit Care Med* 168:70–76, 2003.

Ferrer M, Valencia M, Carrillo A, et al: Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomized controlled trial, *Lancet* 374:1082–1088, 2009.

Ferrer M, Valencia M, Nicolas JM, et al: Early non-invasive ventilation averts extubation failure in patients at risk. A randomized trial, *Am J Respir Crit Care Med* 173:164–170, 2006.

Fraticelli AT, Lellouche F, L'her E, et al: Physiological effects of different interfaces during noninvasive mechanical ventilation for acute respiratory failure, *Crit Care Med* 37:939–945, 2009.

Girault C, Daudenthun I, Chevron V, et al: Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure: a prospective, randomized controlled study, *Am J Respir Crit Care Med* 160:86–92, 1999.

Gray A, Goodacre S, Newby DE, et al: Noninvasive ventilation in acute cardiogenic pulmonary edema, *N Engl J Med* 359:142–151, 2008.

Han F, Jiang YY, Zheng JH, et al: Noninvasive positive pressure ventilation treatment for acute respiratory failure in SARS, *Sleep Breath* 8:94–106, 2004.

Hess DR, Pang JM, Camargo CA Jr: A survey of the use of noninvasive ventilation in academic emergency departments in the United States, *Respir Care* 54:1306–1312, 2009.

Hilbert G, Gruson D, Vargas F, et al: Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever and acute respiratory failure, *N Engl J Med* 344:481–487, 2001.

Jaber S, Chanques G, Sebbane M, et al: Noninvasive positive pressure ventilation in patients with respiratory failure due to severe acute pancreatitis, *Respiration* 73:166–172, 2006.

Joris JL, Sottiaux TM, Chiche JD, et al: Effect of bi-level positive airway pressure (BiPAP) nasal ventilation on the postoperative pulmonary restrictive syndrome in obese patients undergoing gastroplasty, *Chest* 111:665–670, 1997.

Kallet RH, Diaz JV: The physiologic effects of noninvasive ventilation, *Respir Care* 54:102–114, 2009.

Kroschinsky F, Weise M, Illmer T, et al: Outcome and prognostic features of intensive care unit treatment in patients with hematological malignancies, *Intensive Care Med* 28:1294–1300, 2002.

Masip J, Rocha M, Sanchez B, et al: Non invasive ventilation in acute pulmonary edema. Systematic review and meta-analysis, *JAMA* 294:3124–3130, 2005.

Meduri GU, Conoscenti CC, Menashe P, Nair S: Noninvasive face mask ventilation in patients with acute respiratory failure, *Chest* 95:865–870, 1989.

Nava S, Ambrosino N, Clini E, et al: Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial, *Ann Intern Med* 128:721–728, 1998.

Nava S, Carbone G, Dibattista N, et al: Noninvasive ventilation in cardiogenic pulmonary edema: a multicenter, randomized trial, *Am J Respir Crit Care Med* 168:1432–1437, 2003.

Nava S, Grassi M, Fanfulla F, et al: Non-invasive ventilation in elderly patients with acute hypercapnic respiratory failure: a randomised controlled trial, *Age Ageing* 40:444–450, 2011.

Nava S, Gregoretti C, Fanfulla F, et al: Noninvasive ventilation to prevent respiratory failure after extubation in high risk patients, *Crit Care Med* 33:2465–2470, 2005.

Navalesi P, Fanfulla F, Frigerio P, et al: Physiologic evaluation of noninvasive mechanical ventilation delivered with three types of masks in patients with hypercapnic respiratory failure, *Crit Care Med* 28:1785–1790, 2000.

O'Brien G, Criner GJ: Mechanical ventilation as a bridge to lung transplantation, *J Heart Lung Transplant* 18:255–265, 1999.

Park M, Sangean MC, Volpe MS, 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* 32:2407–2415, 2004.

Pérez de Llano LA, Golpe R, Ortiz Piquer M, et al: Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome, *Chest* 128:587–594, 2005.

Peter JV, Moran JL, Phillips-Hughes J, et al: Effect of non-invasive positive pressure ventilation on mortality in patients with acute cardiogenic pulmonary oedema: a meta-analysis, *Lancet* 367:1155–1163, 2006.

Philip-Joet FF, Paganelli FF, Dutau HL, Saadjan AY: Hemodynamic effect of bilevel nasal positive airway pressure ventilation in patients with heart failure, *Respiration* 66:136–143, 1999.

Plant PK, Owen JL, Elliot MW: A multicentre randomised controlled trial of the early use of non-invasive ventilation in acute exacerbation of chronic obstructive pulmonary disease on general respiratory wards, *Lancet* 335:1931–1935, 2000.

Plant PK, Owen JL, Elliott MW: Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial, *Lancet* 355:1931–1935, 2000.

Principi T, Pantanetti S, Catani F, et al: Noninvasive continuous positive airway pressure delivered by helmet in hematological malignancy patients with hypoxemic acute respiratory failure, *Intensive Care Med* 30:147–150, 2004.

Roberts CM, Stone RA, Buckingham RJ, et al; National COPD Resources and Outcome Project implementation group: Acidosis, non-invasive ventilation and mortality in hospitalised COPD exacerbations, *Thorax* 66:43–48, 2011.

Rothaar RC, Epstein SK: Extubation failure: magnitude of the problem, impact on outcomes, and prevention, *Curr Opin Crit Care* 9:59–66, 2003.

Squadrone V, Coha M, Cerutti E, et al: Continuous positive airway pressure for treatment of postoperative hypoxemia, *JAMA* 293:589–595, 2005.

Thys F, Roeseler J, Reynaert M, et al: Noninvasive ventilation for acute respiratory failure: a prospective randomised placebo-controlled trial, *Eur Respir J* 20:545–555, 2002.

Trevisan CE, Vieira SR; Research Group in Mechanical Ventilation Weaning: Noninvasive mechanical ventilation may be useful in treating patients who fail weaning from invasive mechanical ventilation: a randomized clinical trial, *Crit Care* 12:R51, 2008.

Valipour A, Schneider F, Kossler W, et al: Heart rate variability and spontaneous baroflex sequences in supine healthy volunteers subjected to nasal positive airway pressure, *J Appl Physiol* 99:2137–2143, 2005.

Vianello A, Bevilacqua M, Arcaro G, et al: Non-invasive ventilatory approach to treatment of acute respiratory failure in neuromuscular disorders. A comparison with endotracheal intubation, *Intensive Care Med* 26:384–390, 2000.

Vignaux L, Vargas F, Roeseler J, et al: Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study, *Intensive Care Med* 35:840–846, 2009.

Winck JC, Azevedo LF, Costa-Pereira A, et al: Efficacy and safety of non-invasive ventilation in the treatment of acute cardiogenic pulmonary edema—a systematic review and meta-analysis, *Crit Care* 10:R69, 2006.

Wood KA, Lewis L, Von Harz B, Kollef MH: The use of non-invasive positive pressure ventilation in the emergency department: results of a randomized clinical trial, *Chest* 113:1339–1346, 1998.