Noninvasive Ventilatory Support Modes

MASSIMO ANTONELLI, GENNARO DE PASCALE, and GIUSEPPE BELLO

INTRODUCTION

Noninvasive ventilation (NIV) refers to the provision of ventilatory assistance using techniques that do not bypass the upper airway. The theoretical advantages of NIV include avoiding the complications associated with endotracheal intubation, improving patient comfort, and preserving airway defense mechanisms. NIV may be delivered through various devices including negative and positive-pressure ventilators. During the first half of the 20th century, negative-pressure ventilation was the main means of providing mechanical ventilatory assistance outside the anesthesia suite. Because of several disadvantages relative to negative-pressure ventilation, including patient discomfort, restrictions on positioning, lack of airway protection, problems with correct fitting, time-consuming application, and lack of portability, negative-pressure ventilators have seen diminishing use in favor of positive-pressure assistance modes since the early 1960s. Therefore, only positive-pressure support modes are discussed here.

The following sections deal with the history and epidemiology of NIV, as well as currently available equipment and techniques, practical applications, appropriate indications, and possible adverse effects. In this chapter, continuous positive airway pressure (CPAP) delivered noninvasively is referred to as CPAP. The use of intermittent positive-pressure ventilation (IPPV) with or without positive end-expiratory pressure (PEEP) is referred to as NIV.

BACKGROUND

The first report of noninvasive positive-pressure dates to 1912, when Bunnell (1) used a face mask to maintain lung expansion during thoracic surgery. In 1936, Poulton and Oxon (2) used a vacuum cleaner to generate gas flow and a spring-loaded valve to oppose expiration to treat a patient with cardiogenic pulmonary edema (CPE). A number of studies conducted by Barach et al. (3–5) over the 1930s showed that CPAP delivered through a face mask could be useful in the treatment of CPE and other forms of respiratory failure. Noninvasive IPPV administered through a mouthpiece was first described by Motley (6) in the 1940s and was used widely until the early 1980s, either for aerosol delivery in patients with chronic obstructive pulmonary disease (COPD) and asthma, or as a means of ventilatory assistance. The use of noninvasive IPPV declined sharply after the demonstration of lack of benefit in comparison to simple nebulizing treatments (7).

The proliferation of NIV occurred during the 1980s, after the introduction of nasal mask ventilation in the management of obstructive sleep apnea (8). Despite a lack of randomized controlled trials, NIV became the ventilatory mode of first choice for patients with neuromuscular diseases and chest wall deformities (9–12). In the early 1990s, the encouraging results obtained in the treatment of acute respiratory failure (ARF) by using NIV (13–15) stimulated investigation on various applications in the acute care setting. The desire of avoiding complications of endotracheal intubation (16–19), potentially lowering morbidity and mortality rates in selected patients with ARF (20–23), has been the major driving force of the increasing use of NIV in the acute care setting over the past decades.

In their 28-day international study on patients admitted to 361 ICUs who received mechanical ventilation for more than 12 hours, Esteban et al. (24) found that NIV through a facial mask was used in 4.9% of overall patients and in 16.9% of patients ventilated because of an exacerbation of COPD. Similarly, in a prospective 3-week survey of 70 French ICUs performed in 2002, Demoule et al. (25) showed that 23% of patients requiring ventilatory assistance received NIV as a first-line treatment; a significant increase compared to 1997 (16%) (26). Also the incidence of NIV for patients admitted to the ICU without tracheal intubation was strongly implemented.

Interestingly, NIV-implementing programs outside the ICU coordinated by a medical emergency team (MET) may also be introduced in clinical practice, with a high success rate and few complications (27). The estimated utilization rate in the clinical setting remains markedly varied, mainly due to differences in physician knowledge and adequate equipment (28).

EQUIPMENT AND TECHNIQUES

The following paragraphs will discuss various interfaces and ventilatory modes available for administration of NIV; cough-enhancing techniques will also be described.

Interfaces

Interfaces are devices that connect ventilator tubing to the face, allowing the delivery of pressurized gas into the airway during NIV. Currently available interfaces include nasal and oronasal masks, helmets, and mouthpieces. Selection of a comfortable interface that fits properly is a key issue for the success of NIV.

Nasal Masks

The standard nasal mask is a triangular or cone-shaped clear plastic device that fits over the nose and uses a soft cushion or flange to seal over the skin (Fig. 103.1). Because of the pressure exerted over the bridge of the nose, the mask may cause skin irritation and redness, and occasionally ulceration (Fig. 103.2). For the occasional patient who cannot tolerate commercially available masks, custom-molded, individualized masks that conform to facial contours of the patient can be constructed. Several types of strap systems have been used to hold the mask in place. Depending on the interface, straps...
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may be useful in patients who develop irritation or ulceration on the nasal bridge while using nasal or oronasal masks.

**Oronasal Masks**

Oronasal or face masks cover both the nose and the mouth (Fig. 103.4). The oronasal mask is largely used in patients with copious air leaking through the mouth during nasal ventilation.

Nasal pillows or seals consist of soft rubber or silicone plugs that are inserted directly into the nostrils (Fig. 103.3). As they exert no pressure over the bridge of the nose, nasal pillows may be provided with Velcro fasteners. The nasal mask is generally preferred for chronic administration of NIV. In patients with a nasogastric tube, a seal connector in the dome of the mask may be used to avoid air leakage.

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mask ventilation. Interference with speech, eating, and expectoration, and the likelihood of claustrophobic reactions, are greater with oronasal than with nasal masks. In the acute setting, however, oronasal masks are preferable to nasal masks because dyspneic patients are mouth breathers, predisposing to greater air leakage during nasal mask ventilation. The oronasal masks, like the nasal mask, may cause skin necrosis over the nasal bridge (29). When the opening pressure of the upper esophageal sphincter (25 to 30 cm H2O) is overcome, the positioning of a nasogastric tube may protect from gastric distension, even though this is not a common event.

A type of oronasal mask is the “full” face mask, which is made of clear plastic and uses a soft silicone flange that seals around the perimeter of the face avoiding direct pressure on facial structures. Over last years, new face mask models have been diffused with the aim at improving patient comfort and interface performance. Characteristics of recent models of full face mask include a lightweight design, a seal connector specifically dedicated to the passage of the feeding tube, a soft and thin membrane of the mask contour, and a mask holder that incorporates more than four points of attachment to secure the head straps.

**Helmet**

The standard helmet (Fig. 103.5) is made of transparent latex-free polyvinyl chloride, and is secured by two armpit braces at the plastic ring that joins the helmet with a seal connection soft collar adherent to the neck (30,31). The pressure increase during ventilation makes the soft collar sealing comfortable to the neck and shoulders, avoiding air leakage (30). The whole apparatus is connected to an ICU ventilator by a standard respiratory circuit. The two ports of the helmet act as inlet and outlet for inspiratory and expiratory gas flows. The inspiratory and expiratory valves are those of the mechanical ventilator. A specific connector placed in the plastic ring can be used to allow the passage of a nasogastric tube, thus reducing air leaks. A security valve is used to reduce the risk of asphyxia. The patient is allowed to drink through a straw or to be fed a liquid diet. Two inner inflatable cushions may be used to increase comfort and reduce the internal volume. The main advantages of the helmet include a good tolerability in both adult and pediatric populations (32), with a satisfactory interaction of the patients with the environment; a lower risk of dermal lesions; and, compared with the mask, easier applicability to any patient regardless of the face contour. In a recent model of helmet, a zip opening ensures patient accessibility without the need to remove the interface, and alternative fastening systems on the top of the helmet cab avoid skin damage along the braces of the armpits.

**Mouthpieces**

Mouthpieces are simple and inexpensive devices used to provide NIV for as long as 24 hours a day to patients with chronic respiratory failure (Fig. 103.6). If nasal air leaking reduces efficacy, ventilator tidal volume may be increased or cotton plugs or nose clips may be used for occluding the nostrils. NIV via mouthpieces has proved to be a valid alternative to tracheostomy in some patients with chronic respiratory muscle insufficiency (33).

**CPAP and Ventilatory Modes**

**Continuous Positive Airway Pressure**

CPAP delivers a constant pressure throughout spontaneous inspiration and exhalation without assisting inspiration. Because spontaneous breathing is not assisted, this technique requires an intact respiratory drive and adequate alveolar ventilation. CPAP increases functional residual capacity and opens
underventilated alveoli, thus decreasing right-to-left intrapulmonary shunt and improving oxygenation and lung mechanics (34). Moreover, CPAP may reduce the work of breathing and dyspnea in COPD patients by counterbalancing the inspiratory threshold load imposed by intrinsic PEEP (35). Effects on hemodynamics during CPAP have been widely described. By lowering left ventricular transmural pressure in patients with left congestive heart failure, CPAP may reduce left ventricular afterload without compromising cardiac index (36,37). For several years, it was hypothesized that positive airway pressure, by increasing right atrial pressure (38), reduced venous return by decreasing the pressure gradient between mean systemic filling pressure and right atrial pressure (39). However, as demonstrated in experimental (40,41) and human (42) studies, positive airway pressure does not affect the gradient for venous return, because pleural pressure is transmitted to the same extent to both the mean systemic and right atrial pressures. CPAP can be applied by various devices including low-flow generators with an inspiratory reservoir, high-flow jet venturi circuits (Fig. 103.7)—both of them with an expiratory mechanical or water valve—and bilevel and critical care ventilators. Continuous positive pressure may be administered using the demand flow (DF) or the gold standard continuous flow (CF) system. With DF CPAP, the patient has to trigger a preset pressure to open the demand valve, whereas with CF CPAP, no valves are present. The work of breathing is significantly greater with the DF system than with the CF system (43–45). It is crucial to provide an adequate airflow rate for maintaining a continuous positive pressure, especially in dyspneic patients who breathe at high-flow rates. A low CPAP level may be obtained by delivering oxygenation through high-flow nasal cannula (HFNC). During HFNC at a flow rate of 35 L/min in patients with the mouth closed, a mean nasopharyngeal airway pressure of 2.7 cm H$_2$O has been measured (46).

**Pressure Support Ventilation**

Pressure support ventilation (PSV) is a pressure-triggered, pressure-targeted, flow-cycled mode of ventilation. It delivers a preset inspiratory pressure to assist spontaneous breathing, augmenting spontaneous breaths and offsetting the work imposed by the breathing apparatus. A sensitive patient-initiated trigger causes the delivery of inspiratory pressure support that is maintained throughout inspiration, and a reduction in inspiratory flow drives the ventilator to cycle into expiration. Therefore, the patient can control either inspiratory duration or breathing rate.

**Bilevel Positive Airway Ventilation**

In bilevel positive airway pressure (BiPAP), a valve sets two pressure levels, the expiratory positive airway pressure (EPAP) level, and the inspiratory positive airway pressure (IPAP) level, even in the presence of rapidly changing flows. With this technique, ventilation is produced by the cyclic delta pressure between the IPAP and EPAP. EPAP also recruits underventilated lung and offsets eventual intrinsic PEEP.

**Controlled Mechanical Ventilation**

In the mandatory controlled mechanical ventilation (CMV) mode, no patient effort is required, as full ventilatory support is provided. In this mode, ventilator settings include inflation pressure or tidal volume, frequency, and the timing of each breath. Pressure control ventilation (PCV) delivers time-cycled preset inspiratory and expiratory pressures with adjustable inspiratory-to-expiratory ratios at a controlled rate. The resulting tidal volume is determined by the compliance of the lungs and chest wall, and the resistance to flow of ventilator tubing. In volume control ventilation (VCV), tidal volume is set and the resulting pressure depends on the thoracic and circuit compliance.

**Assist/Control Ventilation**

In assist/control (A/C) ventilation, the ventilator delivers a breath either when triggered by the patient’s inspiratory effort (assist) or independently, if such an effort does not occur within a preselected time period (control). When triggering occurs, the ventilator delivers an identical breath to mandatory breaths; volume-cycled and pressure-limited or pressure-targeted modes are available.

**Proportional Assist Ventilation**

Proportional assist ventilation (PAV) is an alternative technique in which both flow and volume are independently adjusted. In this technique, the ventilator generates volume and pressure in proportion to the patient’s effort, increasing comfort and so improving success and compliance with NIV (47). Despite the promising concept, there is a substantial lack of large clinical studies (48).
Techniques to Assist Cough

The cough mechanism may be severely impaired in neuromuscular diseases when weak expiratory muscles are combined with a markedly reduced vital capacity. An effective cough depends on the ability to generate adequate expiratory airflow, estimated at more than 160 L/min (49), which is determined by lung and chest wall elasticity, airway conductance, and expiratory muscle force. Additionally, intact glottic function is needed for yielding high peak expiratory cough flows. Manually assisted coughing consists of quick thrusts applied to the abdomen using the palms of the hands, timed to coincide with the patient’s cough effort. The maneuver should be applied cautiously after meals and with the patient positioned semi-upright to reduce the risk of aspiration of gastric contents.

Manually assisted coughing may enhance expiratory force, but it does not increase inspired volume, so that patients with severely restricted volumes may still achieve insufficient cough flows. Such a limitation may be overcome by using the mechanical insufflator-exsufflator (MI-E) (Fig. 103.8), which delivers a positive inspiratory pressure of 30 to 40 cm H₂O via a face mask and then rapidly switches to an equal negative pressure (50). The positive pressure produces an adequate tidal volume, whereas the negative pressure stimulates the high peak expiratory cough flows. An MI-E may be combined with manually assisted coughing to further augment cough effectiveness. In a randomized trial, patients who were extubated and allocated to three daily sessions of MI-E experienced a lower rate of reintubations and postextubation ICU length of stay (51).

PRACTICAL APPLICATION

NIV should be considered early when patients first develop signs of incipient respiratory failure needing ventilatory assistance. It is crucial that caregivers can identify patients who are likely to benefit from NIV and exclude those for whom NIV would be unsafe. Once the decision to institute NIV has been taken, an interface and ventilatory mode must be chosen, and a close monitoring in an appropriate hospital location must be provided. The initial approach should consist in fitting the interface and familiarizing the patient with the apparatus, explaining the purpose of each piece of equipment. Patients should be motivated and reassured by the clinician, instructed to coordinate their breathing with the ventilator, and encouraged to communicate any discomfort or fears. Collaboration among medical practitioners including physicians, respiratory therapists, and nurses is critical to the success of NIV. Aggressive physiotherapy is crucial during the periods of NIV discontinuation. Endotracheal intubation must be rapidly accessible, when indicated (Table 103.1).

Patient Selection

The criteria for selecting appropriate patients to receive NIV for ARF include clinical indicators of acute respiratory distress, such as moderate-to-severe dyspnea, tachypnea, accessory muscle use and paradoxical abdominal breathing, and gas exchange deterioration. Blood gas parameters aid in identifying patients with acute or acute superimposed on chronic CO₂ retention. A conscious and cooperative patient is crucial for initiating NIV (Table 103.2), although hypercapnic patients with narcosis who are otherwise good candidates for NIV may be an exception (52,53).

TABLE 103.1 Criteria for Noninvasive Ventilation Discontinuation and Endotracheal Intubation

- Technique intolerance (pain, discomfort, or claustrophobia)
- Inability to improve gas exchanges and/or dyspnea
- Hemodynamic instability or evidence of shock, cardiac ischemia, or ventricular dysrhythmia
- Inability to improve mental status within 30 min after the application of NIV in hypercapnic, lethargic COPD patients or agitated hypoxemic patients

TABLE 103.2 Contraindications to Noninvasive Ventilation

- Coma, seizures, or severe central neurologic disturbances
- Inability to protect the airway or clear respiratory secretions
- Unstable hemodynamic conditions (blood pressure or rhythm instability)
- Upper airway obstruction
- Severe upper gastrointestinal bleeding
- Recent facial surgery, trauma, burns, deformity, or inability to fit the interface (unless a helmet is used)
During NIV, patients can achieve a level of control and independence totally different from when intubated, and sedation is infrequently required. If benzodiazepines or opiates are administered, caution is advised to prevent undue hyperventilation. NIV should be avoided in patients with hemodynamic instability and in those who are unable to protect the airways (i.e., coma, impaired swallowing) (see Table 103.2). Patients with severe hypoxemia (PaO$_2$/FiO$_2$ <100) or morbid obesity (>200% of ideal body weight) should be closely managed only by experienced personnel and with a low threshold for endotracheal intubation (20,21,54). In the presence of a pneumothorax, NIV can be initiated provided an intercostal drain is inserted. Criteria for NIV discontinuation and endotracheal intubation must be thoroughly considered to avoid dangerous delays (see Table 103.1).

Identification of predictors of success or failure may help in recognizing patients who are appropriate candidates for NIV and those in whom NIV is not likely to be effective, thereby avoiding its application and unnecessary delays before invasive ventilation is given.

Predictors of NIV failure observed in COPD patients with ARF are the following:
- Lower arterial pH at baseline (55,56)
- Greater severity of illness, as indicated by Acute Physiology and Chronic Health Evaluation (APACHE) II score (57)
- Inability to coordinate with the ventilator (57)
- Inability to minimize the amount of mouth leak with nasal mask ventilation (57)
- Less efficient or less rapid correction of hypercapnia, pH, or tachypnea in the early hours (57)
- Functional limitations caused by COPD before ICU admission, evaluated using a score correlated to home activities of daily living (ADL) (56)

Predictors of NIV failure observed in hypoxemic patients with ARF are the following:
- Higher severity score (Simplified Acute Physiology Score [SAPS] II ≥35 (58), SAPS II ≥34 (59), higher SAPS II (60))
- Older age (>40 years) (58)
- Presence of acute respiratory distress syndrome (ARDS) or community-acquired pneumonia (58,60,61)
- Failure to improve oxygenation after 1 hour of treatment (PaO$_2$/FiO$_2$ ≥146 (58), PaO$_2$/FiO$_2$ ≥175 (59))
- Higher respiratory rate under NIV (61)
- Need for vasopressors (61)
- Need for renal replacement therapy (61)

### Ventilation Mode Selection

The choice of the correct ventilatory mode is crucial for achieving physiologic and clinical benefit during NIV. However, each ventilation mode has theoretical advantages and limitations.

Work of breathing during ARF may be significantly reduced if the selection is made properly. In a physiologic study (62) performed in hypoxemic patients with ARF, noninvasive PSV combined with PEEP improved dyspnea and gas exchange, and lowered neuromuscular drive and inspiratory muscle effort; in these patients, CPAP used alone improved oxygenation but failed to unload the respiratory muscles.

The application of external PEEP is a valid strategy to counterbalance the effects of dynamic hyperinflation in patients with acute hypercapnic exacerbations of COPD. In this setting, NIV delivered through different ventilator modes can provide respiratory muscle rest and improve respiratory physiologic parameters. No difference in clinical outcome or arterial blood gases between patients ventilated in ACV and PSV modes has been found, even though PSV is in general better accepted by the patients and associated with fewer side effects in comparison with ACV mode (63). However, in patients with severe chest wall deformity or obesity, who typically need higher inflation pressures, VCV may be preferred.

Triggering systems are critical to the success of NIV in both assist and control modes. During assisted ventilation, flow triggering reduces breathing effort more effectively as compared with pressure triggering, obtaining a better patient–ventilator interaction (64). Similarly, in COPD patients, the increase of expiratory trigger (10% to 70% of peak expiratory flow) may reduce the magnitude of delayed cycling, intrinsic PEEP and nontriggering breaths (65).

There are no clear recommendations or specific requirements from bench studies on the performance of NIV ventilators and interfaces (66). Personal experience, clinical setting, etiology, and severity of the pathologic process responsible for ARF should lead physicians’ decisions; however assisted modes, particularly PSV, are more often used. As regards pressure-targeted ventilation, it is thought that starting at low pressures to facilitate patient tolerance (appropriate initial pressures are a CPAP of 3 to 5 cm H$_2$O and an inspiratory pressure of 8 to 12 cm H$_2$O above CPAP) is appropriate and then, if necessary, to gradually increase pressures, as tolerated, to obtain alleviation of dyspnea, decreased respiratory rate, adequate exhaled tidal volume, and good patient–ventilator interaction (Table 103.3). Pressures commonly used to administer CPAP in patients with ARF range from 5 to 12 cm H$_2$O. In patients with hypoxic ARF and bilateral pulmonary infiltrates, undergoing 10 cm H$_2$O CPAP delivered via a helmet, adding a 25 cm H$_2$O sigh for 8 seconds, once a minute, improved oxygenation (67). Oxygen supplementation should be targeted to achieve an oxygen saturation above 92% or between 85% and 90% in patients at risk of worsening hypercapnia. A modality that provides a backup rate is necessary for patients with inadequate ventilatory drive.

#### Patient–Ventilator interaction and Carbon Dioxide Rebreathing

NIV tolerance is strictly correlated with an optimal synchrony between the patient’s breathing activity and ventilator parameters. When an optimal patient–ventilator interaction is
lacking, increase in the work of breathing and patient discomfort may be remarkable (68). Patient–ventilator asynchrony may be determined by a number of events including ineffective triggering, double-triggering, auto-triggering, premature cycling, and delayed cycling.

During NIV in PS modality, several forms of patient–ventilator asynchrony may occur, causing breathing discomfort. In a multicenter French study, the level of pressure support and the magnitude of leaks were identified as independent predictors of increased patient–ventilator asynchrony (number of ineffective breaths and delayed cycling) (69). In addition, ineffective triggering due to excessive levels of PS (17.5 cm H2O vs. 15 cm H2O) and less sensitive inspiratory triggers has been shown contributing to longer duration of mechanical ventilation (17.5 vs. 7.5 days) (70). Eventual air leaks during noninvasive PSV may impede the inspiratory flow decay required to open the expiratory valve, thereby prolonging inspiratory flow. In these circumstances, air leaks should be minimized by optimizing the fitting or size of the interface, or even switching to another type of interface. To reduce leaks, it may also be helpful to decrease ventilator pressure settings as much as allowed by clinical parameters. In older machines, when an air leak occurs, an option to obtain a better patient–ventilator interaction is to select pressure-limited, time-cycled ventilation modes, or even PSV mode with a maximal inspiratory time. With ventilators that allow changing the cycling off criteria (expiratory trigger), raising the cycling off airflow threshold (i.e., the percentage of peak inspiratory flow at which transition from inspiration to expiration occurs) can activate an earlier switchover to expiration, thus avoiding prolonged insufflations and patient–ventilator asynchrony.

Pressurization rate is another parameter that can be modified during PS NIV in order to reduce patient–ventilator asynchrony. In COPD patients, faster values are able to reduce the diaphragmatic metabolic consumption (expressed as pressure time product) but may determine significant air leaks and poor tolerance (71). Similarly, in hypoxic subjects, a “fast” pressure ramp significantly decreased the work of breathing even though either the lowest or the highest pressurization rates were associated with patient discomfort (72). In the presence of significant air leaks, pressure-targeted modes are preferred to deliver NIV as they can maintain delivered tidal volume better than volume-targeted modes (73). In new ventilators, an NIV algorithm, usually referred to as “NIV mode,” measures and compensates leaks in order to minimize their detrimental impact on patient–machine synchrony (74,75). Neurally adjusted ventilatory assist (NAVA) seems to be a very promising mode to help improve adaptation during NIV (76–78).

An optimal ventilator setting should also take into account the type of interface used to deliver NIV. It has been advised that the highest PEEP and PS levels clinically indicated and tolerated by the patient should be applied when NIV is administered with the helmet, in order to increase the elactance of the system, enhancing the trigger sensitivity (79). Vargas et al. (80) suggested that increasing both PEEP and PS levels and using the highest pressurization rate may be suitable when providing NIV through this interface. In their study, the helmet with the same settings as the face mask was associated with less inspiratory-muscle unloading and with worse patient–ventilator asynchrony. In contrast, specific settings with a fast ramp and higher pressures provided results similar to the mask, ameliorating the inspiratory trigger delay, without discomfort. In addition, as observed in a helmet NIV bench study, a double tube circuit (with one inspiratory and one expiratory line) seems to improve patient–ventilator interaction and reduce the rate of wasted efforts, compared with a standard circuit (a Y-piece connected only to one port of the helmet) (81).

**Humidification**

Prolonged exposure of tracheobronchial epithelium to cool and dry gases may be a critical issue during NIV. So, both humidification and warming may be required to prevent upper airways irritation. Two humidifying devices are commonly used with ICU ventilators: heated humidifiers (HHs), and heat and moisture exchangers (HMEs). The latter are the most commonly used due to their simplicity and cost-effectiveness. However, because the HMEs are placed between the Y-piece and the patient, they add a substantial amount of dead space, compared to an HH, which is placed in the inspiratory circuit. In addition, compared to HHs, HMEs may increase resistance to flow (82).

Heated humidification during NIV in patients with ARF can minimize work of breathing and improve CO2 clearance. In a physiologic study on nine COPD patients with hypercapnic ARF requiring NIV, Lellouche et al. (83) showed that the use of HMEs, compared with HHs, greatly increased work of breathing. Nonetheless, despite significantly higher minute ventilation during the HME study phase, arterial partial pressure of CO2 (PaCO2) was not different. By way of contrast, in another study on 24 patients with ARF undergoing face mask NIV with HME or HH, Jaber et al. (84) found that HME was associated with a significantly higher PaCO2.

Given the above-mentioned physiologic implications, in a recent randomized clinical trial, a multicenter French study group tested the hypothesis that HH use during NIV, compared with HME, could reduce the rate of intubation in patients with ARF (both hypoxemic and hypercapnic). Surprisingly, no differences in terms of intubation rate, ICU or hospital length of stay and ICU mortality were observed between the two groups, even in the subgroup of hypercapnic patients (85). In addition, no difference in the patients’ mucosal dryness was reported with HH in comparison with HME. The authors concluded that HHs during NIV cannot be recommended as a first-line treatment in all patients with ARF but they may be considered in the presence of persistent high PaCO2 levels associated with threatening encephalopathy. Additionally, in COPD patients under long-term NIV, no firm conclusion can be drawn on the type of humidification system to be used. A randomized crossover 1-year study on 16 COPD patients receiving long-term NIV with either HH or HME, showed that compliance with treatment and incidence of infections were similar with HH and HME, albeit patients with HH showed less dryness of the throat (86). Of note, at the end of this study, a higher number of patients decided to continue NIV with HH.

**Monitoring**

In the acute setting, patients can initiate NIV anywhere, at the onset of the acute respiratory distress, but after initiation, they should be transferred to an ICU or a step-down unit for continuous monitoring until they are sufficiently stable to be moved to a medical ward. During transfers, NIV and monitoring should not be discontinued. The early use of NIV for less acutely ill patients with COPD on a medical ward seems to be effective,
levels of dynamic hyperinflation, and substantial shortening of the diaphragm and the inspiratory intercostals and accessory muscles, thereby reducing their mechanical efficiency and endurance. The need to overcome the inspiratory threshold load due to auto-PEEP and to drive the tidal volume against airway resistances increases the respiratory muscle fatigue. During NIV, the combination of external PEEP and PSV offsets the auto-PEEP level and reduces the work of breathing that the inspiratory muscles must generate to produce the tidal volume (96).

In an early study on the use of face mask NIV in patients with ARF, Meduri et al. (13) obtained improvements of gas exchanges and avoided endotracheal intubation in a group of COPD patients. Soon thereafter, Brochard et al. (14) described the short-term (45 minutes) physiologic effects of inspiratory assistance with a face mask on gas exchange and respiratory-muscle work in 11 patients with COPD and evaluated the therapeutic use of the technique in 13 patients with COPD-E, comparing the results in the latter group with the results of conventional treatment in 13 matched historical-control patients. In the physiologic study, arterial pH rose from 7.31 to 7.38 (< 0.01), PaCO₂ fell from 68 to 55 mmHg (< 0.01), PaO₂ rose from 52 to 69 mmHg (p < 0.05), and respiratory rate reduced from 31 to 21 breaths per minute (p < 0.01) (14). Only 1 of 13 patients treated with NIV needed intubation, as compared with 11 of the 13 historical controls (p < 0.001). In addition, the NIV-treated patients were weaned from the ventilator faster and spent less time in the ICU than did the control subjects (14). Subsequently, numerous randomized controlled trials using NIV in ARF caused by COPD have been published (Table 103.5).

In the first randomized, prospective study on 60 COPD patients, Bott et al. (89) compared NIV delivered through nasal mask with conventional therapy as a treatment of ARF. Patients receiving NIV had a significant reduction of PaCO₂, dyspnea score, and 30-day mortality (10% vs. 30%). A multicenter European trial (88) on the efficacy of NIV in acute COPD-E randomized 85 COPD patients to receive face mask PSV or conventional treatment (oxygen therapy plus drugs). After 1 hour of NIV, respiratory rate, but not PaCO₂, showed a significant decrease. The group of patients treated with NIV had a significantly lower intubation rate, a lower complication rate (14% vs. 45%), length of hospital stay, and mortality rate. In another randomized study on 23 COPD patients that compared NIV with conventional treatment, the investigators reported a reduction of intubation rate, with a significant improvement in PaO₂, heart rate, and respiratory rate in the NIV group, even though PaCO₂ did not significantly decrease (90). A randomized study on 30 COPD patients with ARF (91) confirmed that early application of NIV facilitates gas exchange improvement, reduces the need for invasive mechanical ventilation, and decreases the duration of hospitalization. In a randomized trial on 50 acute COPD-E patients, NIV reduced weaning time, shortened the length of stay in the ICU, decreased the incidence of nosocomial pneumonia, and improved 60-day survival rates (99).

Other and more recent prospective randomized controlled studies on patients with ARF due to COPD-E (103,104) have confirmed the benefit of applying NIV in improving clinical status and blood gases.

A randomized prospective study by Conti et al. (102) compared the short- and long-term response to face mask NIV

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**INDICATIONS**

**Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD-E)**

In patients with ARF resulting from acute COPD-E, the use of NIV has been proven to be effective in ameliorating dyspnea, improving vital signs and gas exchange (87–91), preventing endotracheal intubation (88–91), and improving hospital survival (87,88,90). Consequently, there is a general agreement concerning the early use of NIV in such patients (92,93). In a 10 years (from 1998 to 2008) prevalence study on more than 7 million patients with acute COPD-E, a 462% increase in NIV use and a 42% decline in invasive mechanical ventilation use were observed. Surprisingly, the study documented a rising mortality rate in the subgroup of patients who needed endotracheal intubation after failing NIV (94). Such findings were explained by patients’ severity, the time before NIV failure and possible difficulties with the interface tolerance (95).

In COPD patients with acute respiratory decompensations, the increased flow resistance and the impossibility to complete the expiration before inspiration determine high but if pH is lower than 7.30, admission to an environment with intensive care monitoring is highly recommended (87).

Monitoring of patients undergoing NIV is aimed at determining whether the initial goals are being achieved, including relief of symptoms, reduced work of breathing, improved or stable gas exchange, good patient–ventilator synchrony, and patient comfort (Table 103.4). Gas exchange is monitored by continuous oximetry and arterial blood gases at baseline, after 30 to 60 minutes, and as clinically indicated; physiologic responses are evaluated by continuous electrocardiography, respiratory rate, blood pressure, and heart rates. Finally, dyspnea, as well as tolerance of the technique, symptoms of impaired sleep, patient–ventilator asynchrony, and air leak can be easily assessed through patient queries, bedside observation, and flow, volume, and pressure waveform analysis. If a poor response to NIV occurs and the specific measures used to correct the situation fail to address an adequate improvement, NIV should be considered a failure, and invasive ventilation should be promptly considered.

**TABLE 103.4 Monitoring of Patients Receiving Noninvasive Ventilation in the Acute Care Setting**

<table>
<thead>
<tr>
<th>Monitoring Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Level of consciousness</td>
</tr>
<tr>
<td>• Comfort</td>
</tr>
<tr>
<td>• Chest wall motion</td>
</tr>
<tr>
<td>• Accessory muscle recruitment</td>
</tr>
<tr>
<td>• Patient–ventilator synchrony</td>
</tr>
<tr>
<td>• Respiratory rate</td>
</tr>
<tr>
<td>• Exhaled tidal volume</td>
</tr>
<tr>
<td>• Flow and pressure waveforms</td>
</tr>
<tr>
<td>• Heart rate</td>
</tr>
<tr>
<td>• Blood pressure</td>
</tr>
<tr>
<td>• Continuous electrocardiography</td>
</tr>
<tr>
<td>• Continuous oximetry</td>
</tr>
<tr>
<td>• Arterial blood gas at baseline, after 1–2 hr, and as clinically indicated</td>
</tr>
<tr>
<td>• Level of consciousness</td>
</tr>
</tbody>
</table>

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In patients with ARF resulting from acute COPD-E, the use of NIV has been proven to be effective in ameliorating dyspnea, improving vital signs and gas exchange (87–91), preventing endotracheal intubation (88–91), and improving hospital survival (87,88,90). Consequently, there is a general agreement concerning the early use of NIV in such patients (92,93). In a 10 years (from 1998 to 2008) prevalence study on more than 7 million patients with acute COPD-E, a 462% increase in NIV use and a 42% decline in invasive mechanical ventilation use were observed. Surprisingly, the study documented a rising mortality rate in the subgroup of patients who needed endotracheal intubation after failing NIV (94). Such findings were explained by patients’ severity, the time before NIV failure and possible difficulties with the interface tolerance (95).

In COPD patients with acute respiratory decompensations, the increased flow resistance and the impossibility to complete the expiration before inspiration determine high but if pH is lower than 7.30, admission to an environment with intensive care monitoring is highly recommended (87).

Monitoring of patients undergoing NIV is aimed at determining whether the initial goals are being achieved, including relief of symptoms, reduced work of breathing, improved or stable gas exchange, good patient–ventilator synchrony, and patient comfort (Table 103.4). Gas exchange is monitored by continuous oximetry and arterial blood gases at baseline, after 30 to 60 minutes, and as clinically indicated; physiologic responses are evaluated by continuous electrocardiography, respiratory rate, blood pressure, and heart rates. Finally, dyspnea, as well as tolerance of the technique, symptoms of impaired sleep, patient–ventilator asynchrony, and air leak can be easily assessed through patient queries, bedside observation, and flow, volume, and pressure waveform analysis. If a poor response to NIV occurs and the specific measures used to correct the situation fail to address an adequate improvement, NIV should be considered a failure, and invasive ventilation should be promptly considered.
### Table 103.5: Main Randomized Controlled Studies Using Noninvasive Ventilation in Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Site</th>
<th>Intervention (NIV/control)</th>
<th>Sample Size (NIV/control)</th>
<th>Need for Eti (NIV/control, %)</th>
<th>ICU LOS (NIV/control, days)</th>
<th>Hospital LOS (NIV/control, days)</th>
<th>Survival (NIV/control, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bott et al., 1993</td>
<td>COPD</td>
<td>Ward</td>
<td>ACV/UMC</td>
<td>30/30</td>
<td>0.0/6.6</td>
<td>NA/NA</td>
<td>9.9</td>
<td>90°/70</td>
</tr>
<tr>
<td>Brochard et al., 1995</td>
<td>COPD</td>
<td>ICU</td>
<td>PSV/UMC</td>
<td>43/42</td>
<td>25.6/73.8</td>
<td>7 ± 3°/19 ± 13</td>
<td>23 ± 17°/35 ± 33</td>
<td>90.7°/71.4</td>
</tr>
<tr>
<td>Kramer et al., 1995</td>
<td>Varied</td>
<td>ICU</td>
<td>BiPaP/UMC</td>
<td>11/8°</td>
<td>9.1°, 66.6°</td>
<td>NA/NA</td>
<td>14.9 ± 3.3/17.3 ± 3.0°</td>
<td>NA/NA</td>
</tr>
<tr>
<td>Barbé et al., 1996</td>
<td>COPD</td>
<td>Ward</td>
<td>BiPaP/UMC</td>
<td>10/10</td>
<td>0/0</td>
<td>NA/NA</td>
<td>10.6 ± 0.9/11.3 ± 1.3</td>
<td>100/100</td>
</tr>
<tr>
<td>Angus et al., 1996</td>
<td>COPD</td>
<td>ICU</td>
<td>PSV/UMC</td>
<td>9/8</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>10/NA</td>
<td>100/62.5</td>
</tr>
<tr>
<td>Celli et al., 1998</td>
<td>COPD</td>
<td>ICU</td>
<td>PSV/UMC</td>
<td>15/15</td>
<td>6.7°, 40.0</td>
<td>NA/NA</td>
<td>11.7 ± 3.5°/14.6 ± 4.7</td>
<td>100/93.3</td>
</tr>
<tr>
<td>Nova et al., 1998</td>
<td>Weaning</td>
<td>ICU</td>
<td>PSV/PSV (invasive)</td>
<td>25/25</td>
<td>NA/NA</td>
<td>15.1 ± 5.4°, 04 ± 13.7</td>
<td>NA/NA</td>
<td>NA/92°</td>
</tr>
<tr>
<td>Confalonieri et al., 1999</td>
<td>CAP</td>
<td>IRCU</td>
<td>PSV/UMC</td>
<td>12/11°</td>
<td>0.0°, 54.6°</td>
<td>0.25 ± 2.1°, 7.6 ± 2.2°</td>
<td>14.9 ± 3.4/22.5 ± 3.5°</td>
<td>91.7/81.8°</td>
</tr>
<tr>
<td>Plant et al., 2000</td>
<td>COPD</td>
<td>Ward</td>
<td>BiPaP/UMC</td>
<td>118/118</td>
<td>15°, 27</td>
<td>NA/NA</td>
<td>90°/40</td>
<td>92°/91°</td>
</tr>
<tr>
<td>Martin et al., 2000</td>
<td>Varied</td>
<td>ICU</td>
<td>BiPaP/UMC</td>
<td>12/11°</td>
<td>25/45°</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>92/91°</td>
</tr>
<tr>
<td>Conti et al., 2002</td>
<td>COPD</td>
<td>ED</td>
<td>PSV/ACV, PSV (invasive)</td>
<td>23/26</td>
<td>52/NA</td>
<td>22 ± 1/21 ± 20</td>
<td>NA/NA</td>
<td>74/54</td>
</tr>
</tbody>
</table>

NIV: noninvasive ventilation; Eti: endotracheal intubation; ICU: intensive care unit; LOS: length of stay; COPD: chronic obstructive pulmonary disease; ACV: assist control ventilation; UMC: usual medical care; NA: not applicable; BiPaP: bilevel positive airway pressure; IRCU: intermediate respiratory care unit; PSV: pressure support ventilation; Weaning: patients in whom NIV was used to facilitate weaning from mechanical ventilation; CAP: community-acquired pneumonia.

*Significant difference.

*Subset analysis.
and found an improvement in lung function and decreased compared 15 patients with acute asthma who received NIV and only three patients eventually required endotracheal intubation and vital signs improved rapidly in the NIV group, NIV patients were less hypercapnic than the other group, gas.

Invasive mechanical ventilation (107) found that, although the analysis of 33 asthmatic patients treated with NIV or invasive, NIV was associated with a rapid correction of gas exchange abnormalities and improvement in dyspnea. A retrospective analysis of 33 asthmatic patients treated with NIV or invasive mechanical ventilation (107) found that, although the NIV patients were less hypercapnic than the other group, gas exchange and vital signs improved rapidly in the NIV group, and only three patients eventually required endotracheal intubation. A prospective, randomized, placebo-controlled study compared 15 patients with acute asthma who received NIV plus conventional therapy versus conventional therapy alone, and found an improvement in lung function and decreased hospital admission rate in the NIV group (108). In contrast, another randomized trial found no significant advantages of NIV in patients with acute asthma (109), and medical therapy alone can be highly effective in the management of asthmatic patients (110). Therefore, in the absence of clear evidence, no conclusions can be drawn regarding the relative effectiveness of NIV versus conventional therapy in acute exacerbations of asthma.

Hypoxemic Respiratory Failure

Trials of NIV in patients with hypoxic respiratory failure, defined as those with ARF not related to COPD, have yielded conflicting results. In hypoxic ARF patients, NIV has been adopted to decrease the amount of work of breathing, correct the rapid shallow breathing, and prevent respiratory muscle fatigue and endotracheal intubation. The studies reviewed in these sections have been conducted on heterogeneous groups of patients with hypoxic respiratory failure, whereas the analyses of homogeneous patient populations are discussed under each specific topic. Randomized controlled trials using NIV in hypoxic ARF patients are shown in Table 103.6.

Meduri et al. (13) in 1989 reported one of the first clinical applications of NIV in patients with hypoxic respiratory failure. Subsequently, Pennock et al. (116) reported a 50% success in a large group of patients with ARF of different causes, and similar good results were achieved using NIV with nasal mask in a second study (117). Wysocki et al. (111) randomized 41 non-COPD patients with ARF to NIV delivered by face mask versus conventional medical therapy. NIV reduced the need of endotracheal intubation, the duration of ICU stay, and mortality rate only in those patients with hypercapnia (PaCO$_2$ >45 mmHg), while having no significant advantages in the hypoxic group without concomitant hypercarbia. On the basis of these results, the investigators concluded that NIV may not be beneficial in all forms of ARF not related to COPD. In a study conducted by Meduri et al. (118) on the use of NIV to treat respiratory failure of varied origins, 41 of 158 patients were hypoxic. These patients required endotracheal intubation in only 34% of cases and showed a mortality rate of 22% compared with a predicted mortality (using the APACHE II score) of 40%. In a pilot study on patients with hematologic malignancies complicated by ARF (119), 15 of 16 individuals showed a significant improvement in blood gases and respiratory rate within the first 24 hours of nasal mask NIV treatment.

Antonelli et al. (20) conducted a prospective, randomized study comparing NIV via a face mask to endotracheal intubation with conventional mechanical ventilation in 64 patients with hypoxic ARF who required ventilatory assistance after failure to improve with aggressive medical therapy. After 1 hour of mechanical ventilation, both groups had a significant improvement in oxygenation. Ten (31%) patients treated with NIV required endotracheal intubation. Patients randomized to conventional ventilation developed significantly more frequent septic complications such as pneumonia or sinusitis (31% vs. 3%). Among survivors, NIV patients had a lower duration of mechanical ventilation (p = 0.006) and a shorter ICU stay (p = 0.002). On the basis of these results, this trial suggested that NIV may lead to more favorable outcomes than conventional ventilation in the management of patients with hypoxic respiratory failure. Conversely, Wood et al.

Asthma

NIV is considered an option in asthmatic patients at risk for endotracheal intubation. However, mechanical ventilation may be dangerous in patients with asthma, first, by worsening lung hyperinflation with the risk of causing barotrauma, and second, by inducing hemodynamic deterioration by increased intrathoracic pressure. To date, guidelines for NIV in severe asthma are not supported by strong data. In one study (106), only 2 of 17 severe asthmatic patients (average initial pH of 7.25 and PaCO$_2$ of 65 mmHg) required intubation after starting therapy with face mask PSV, and the use of NIV was associated with a rapid correction of gas exchange abnormalities and improvement in dyspnea. A retrospective study of 33 asthmatic patients treated with NIV or invasive mechanical ventilation (107) found that, although the NIV patients were less hypercapnic than the other group, gas exchange and vital signs improved rapidly in the NIV group, and only three patients eventually required endotracheal intubation. A prospective, randomized, placebo-controlled study compared 15 patients with acute asthma who received NIV plus conventional therapy versus conventional therapy alone, and found an improvement in lung function and decreased hospital admission rate in the NIV group (108). In contrast, another randomized trial found no significant advantages of NIV in patients with acute asthma (109), and medical therapy alone can be highly effective in the management of asthmatic patients (110). Therefore, in the absence of clear evidence, no conclusions can be drawn regarding the relative effectiveness of NIV versus conventional therapy in acute exacerbations of asthma.
### TABLE 103.6 Main Randomized Controlled Studies Using Noninvasive Ventilation in Nonchronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Site</th>
<th>Intervention (NIV/control)</th>
<th>Sample size (NIV/control)</th>
<th>Need for ETI (NIV/control, %)</th>
<th>ICU LOS (NIV/control, days)</th>
<th>Hospital LOS (NIV/control, days)</th>
<th>Survival (NIV/control, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wysocki et al., 1993 (111)</td>
<td>Varied</td>
<td>ICU</td>
<td>PSV + PEEP/UMC</td>
<td>21/20</td>
<td>17 ± 19/25 ± 23</td>
<td>NA/NA</td>
<td>62/70</td>
<td>65/70</td>
</tr>
<tr>
<td>Antonelli et al., 1998 (20)</td>
<td>ICU</td>
<td>ICU</td>
<td>PSV + PEEP/ACV, SMV</td>
<td>32/32</td>
<td>9 ± 7%/16 ± 17</td>
<td>NA/NA</td>
<td>31.3/NA</td>
<td>68.8/50.0</td>
</tr>
<tr>
<td>Antonelli et al., 1998 (20)</td>
<td>ICU</td>
<td>ICU</td>
<td>PSV + PEEP/ACV, SMV</td>
<td>32/32</td>
<td>9 ± 7%/16 ± 17</td>
<td>NA/NA</td>
<td>31.3/NA</td>
<td>68.8/50.0</td>
</tr>
<tr>
<td>Wood et al., 1998 (112)</td>
<td>Varied</td>
<td>ED</td>
<td>BiPAP/UMC</td>
<td>16/11</td>
<td>45.5/43.8</td>
<td>17.4 ± 34.3/9.1 ± 5.7</td>
<td>75/100</td>
<td>77.0/61</td>
</tr>
<tr>
<td>Girault et al., 1999 (113)</td>
<td>Weaning</td>
<td>ICU</td>
<td>PSV, ACV/PSV</td>
<td>17/16</td>
<td>12.4 ± 6.8/14.1 ± 7.5</td>
<td>27.7 ± 13.1/27.1 ± 14.3</td>
<td>100/87.5</td>
<td>62.5%/76.5</td>
</tr>
<tr>
<td>Conti et al., 1999 (100)</td>
<td>ICU</td>
<td>ICU</td>
<td>PSV/UMC</td>
<td>16/17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.9 ± 1.8/4.8 ± 1.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17.9 ± 2.9/15.1 ± 2.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>76.5%/76.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>62.5%/76.5</td>
</tr>
<tr>
<td>Antonelli et al., 2000 (21)</td>
<td>ICU</td>
<td>ICU</td>
<td>PSV + PEEP/UMC</td>
<td>20/20</td>
<td>5.5 ± 3.9/4 ± 4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA/NA</td>
<td>77%/NA</td>
<td>65/45</td>
</tr>
<tr>
<td>Martin et al., 2000 (101)</td>
<td>Varied</td>
<td>ICU</td>
<td>BiPAP/UMC</td>
<td>16/13&lt;sup&gt;a&lt;/sup&gt;</td>
<td>37.5%/77.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA/NA</td>
<td>75/46&lt;sup&gt;b&lt;/sup&gt;</td>
<td>75/46&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hilbert et al., 2001 (114)</td>
<td>ICU</td>
<td>ICU</td>
<td>PSV + PEEP/UMC</td>
<td>26/26</td>
<td>7 ± 3/10 ± 4</td>
<td>NA/NA</td>
<td>50/81&lt;sup&gt;c&lt;/sup&gt;</td>
<td>62.5%/76.5</td>
</tr>
<tr>
<td>Feurer et al., 2003 (118)</td>
<td>AHRF</td>
<td>ICU</td>
<td>BiPAP/UMC</td>
<td>51/54</td>
<td>20 ± 16.6/26.8 ± 19.8</td>
<td>NA/NA</td>
<td>82/61</td>
<td>62.5%/76.5</td>
</tr>
</tbody>
</table>

NIV, noninvasive ventilation; ETI, endotracheal intubation; ICU, intensive care unit; LOS, length of stay; PSV, pressure support ventilation; PEEP, positive end-expiratory pressure; UMC, usual medical care; NA, not applicable; AHRF, acute hypoxic respiratory failure; ACV, assist control ventilation; SMV, synchronous mandatory ventilation; ED, emergency department; BiPAP, bilevel positive airway pressure. Weaning, patients in whom NIV was used to facilitate weaning from mechanical ventilation. CAP, community-acquired pneumonia; ICU, intermediate respiratory care unit; IC, immunocompromised.

<sup>a</sup>Significant difference.

<sup>b</sup>Subset analysis.

<sup>c</sup>Hospital survival (no difference noted in 2-month mortality).
(112) had a substantially negative evaluation of the use of NIV when applied to patients with hypoxic ARF. These investigators randomized 27 patients in the emergency department to receive conventional medical therapy or NIV for the treatment of hypoxic respiratory failure. The 16 patients who were randomized to the NIV group had an intubation rate and duration of ICU stay similar to the 11 patients who received medical treatment alone, but there was a trend toward a greater rate of hospital mortality among the patients in the NIV group compared to patients in the conventional medical therapy group. Several factors may have influenced these negative results of this study. Among patients requiring endotracheal intubation, those of the NIV group had a longer delay to intubation (26 vs. 4.8 hours, \( p = 0.055 \)). In addition, it cannot be excluded that a sicker patient population was randomized to NIV. Indeed, the NIV population had a lower \( \text{PaO}_2 \) (60 vs. 71), fewer patients with COPD (12% vs. 36%), and more patients with pneumonia (44% vs. 18%), ARDS, and interstitial lung disease (1% vs. 0). Furthermore, the NIV group had a higher APACHE II score (18 vs. 16), and more required admission to an ICU (81% vs. 64%).

In a study on 10 hemodynamically stable patients with severe acute lung injury or ARDS (120), NIV had a high success rate (66%) and high hospital survival (70%). Three of the six patients who received NIV as initial mode of ventilatory assistance were discharged from the ICU within 48 hours. Survival for the 10 patients was 70%, and duration of successful NIV ranged from 23 to 80 hours. Ferrer et al. (121) have prospectively randomized 105 patients with severe hypoxic ARF to receive NIV or high-concentration oxygen. Compared with oxygen therapy, NIV decreased the need for intubation (13 [25%] vs. 28 [52%]), the incidence of septic shock (6 [12%] vs. 17 [31%]), and ICU mortality (9 [18%] vs. 21 [39%]), and increased the cumulative 90-day survival (all, \( p < 0.05 \)). Additionally, the improvement of tachypnea and arterial hypoxemia was higher in the NIV group. In a physiologic study performed by L’Her et al. (122) in patients with acute lung injury, noninvasive PSV combined with PEEP improved dyspnea and gas exchange and lowered neuromuscular drive and inspiratory muscle effort.

In ARDS, transient loss of positive pressure during mechanical ventilation may seriously compromise lung recruitment and gas exchange. For this reason, most NIV studies have excluded patients with ARDS, and limited data are currently available in the literature. The first application of NIV (via face mask CPAP) in patients with increased permeability pulmonary edema ARDS was reported by Barach et al. in 1938 (4). In 1982, Covelli et al. (123) applied face mask CPAP in 35 patients with ARDS of varied causes, with all patients improving their oxygenation within the first hour of therapy. Only five patients were ultimately intubated, two from mask discomfort and three from a change in mental status and lack of cooperation. In two randomized studies, Antonelli et al. (20,21) reported that among patients with ARDS \( (n = 31) \), NIV avoided intubation in 60%, whereas in their trial including a small number of ARDS patients \( (n = 7) \), Ferrer et al. (121) reported an 86% intubation rate. Two NIV observational studies involving 98 ARDS patients reported an intubation rate of 50% (58,120), which was similar in patients with ARDS of pulmonary or extrapulmonary origin (58). Antonelli et al. (59) prospectively investigated, under close ICU observation, the application of NIV as first-line intervention in 147 patients with early ARDS. NIV improved gas exchange and avoided intubation in 54% of treated patients. Avoidance of intubation was associated with less ventilator-associated pneumonia (2% vs. 20%, \( p < 0.001 \)) and a lower ICU mortality rate (6% vs. 53%, \( p < 0.001 \)). SAPS II more than 34 and a \( \text{PaO}_2/\text{FiO}_2 \) less than 175 after 1 hour of NIV were independently associated with NIV failure and need for endotracheal intubation. Caution is, however, required when NIV is used in hypoxic patients. In a large prospective French survey (524 patients), NIV failure was found to be independently associated with ICU mortality in patients with “de novo” ARF rather than in those ones affected by CPE or COPD-E (124). In 2012, a new ARDS definition was promulgated (125). Therefore, further studies in such setting could be useful in order to better identify patients who can benefit from early NIV application. A decisional flow chart may be adopted in applying NIV to patients with ARDS (Fig. 103.9).

The above findings are, for the most part, supportive of the use of NIV to treat hypoxic patients without hypercapnia. However, an extremely prudent approach is needed, limiting the application of NIV to hemodynamically stable patients who can be closely monitored in the ICU where endotracheal intubation is promptly available.

**Cardiogenic Pulmonary Edema**

Applying positive air pressure has been shown to decrease the work of breathing (34) and left ventricular afterload while maintaining cardiac index (37), thereby benefiting patients with cardiac dysfunction and ARF. The use of mask CPAP in patients with CPE was first described in the 1930s by Poulton and Oxon (2) and Barach et al. (3,4). More recently, several studies have examined responses to NIV of patients with CPE (126–137). In a large randomized controlled trial (138), the use of both NIV and CPAP in patients with acute CPE resulted in faster improvement of respiratory distress and metabolic disturbance, compared with standard oxygen therapy; early mortality, within first 7 days, did not significantly differ.

A systematic review and meta-analysis performed by Collins et al. (139) suggested that early application of NIV in the emergency department can decrease the relative risk of mortality by 39% and the necessity of endotracheal intubation by 57% when compared with standard medical therapy alone. However, in patients with CPE, NIV should not be viewed as the exclusive therapy, but should be accompanied by the aggressive conventional medical treatment.

In the comparison of NIV modalities, BiPAP has the potential advantage over CPAP of assisting the respiratory muscles during inspiration, which would result in faster alleviation of dyspnea and exhaustion (140). Nevertheless, according to all available data, there is no evidence to suggest superiority of either CPAP or BiPAP in terms of intubation or mortality, even in patients with CPE and hypercapnia (139,141,142). A recent meta-analysis on randomized trials comparing CPAP and BiPAP with standard therapy has showed that CPAP is able to reduce mortality and the need for intubation (especially in the presence of CPE of ischemic origin) but does not reduce the incidence of new myocardial infarction episodes compared with standard therapy (143). Differently, the BiPAP modality seems to reduce the need for intubation without improving the rate of mortality.
or new myocardial infarction. In the management of suspected acute CPE in the prehospital setting, helmet CPAP has been used as first-line treatment, allowing prompt improvement in respiratory and hemodynamic parameters. This new approach was shown to be feasible, safe, and clinically effective (144).

In conclusion, NIV should be strongly considered as a first-line treatment in patients with CPE.

**Immunocompromised Patients**

Immunocompromised patients in whom respiratory failure develops often require mechanical ventilatory assistance. Endotracheal intubation is associated with numerous complications (16–19) and, in immunosuppressed patients, invasive mechanical ventilation is associated with a significant risk of death (145–147). The benefit of NIV in immunocompromised patients with ARF has been evaluated in two interventional trials (21,114), as well as in a substantial number of observational studies (61,119,148–155); a large part of the research has been conducted in oncohematologic patients. Antonelli et al. (21) included 40 recipients of solid-organ transplantation with hypoxemic ARF who were randomized to receive NIV versus standard oxygen therapy; patients treated with NIV more often achieved a better oxygenation with lower ETI and ICU mortality rates. Similarly, Hilbert et al. (114) randomized 52 hypoxemic ARF patients with pneumonia and immunosuppression to therapy with NIV or supportive oxygen only, showing a reduction in the need for ETI and hospital mortality rate in NIV-treated patients compared with conventionally treated controls. Unlike these interventional trials, observational studies of NIV in cancer patients with ARF have yielded conflicting results. Indeed, although most of these observational studies reported improved outcomes for these patients after NIV treatment as compared with invasive mechanical ventilation, some studies failed to show any beneficial effect of NIV (152,155).

In a retrospective analysis of 137 hematologic patients admitted to the ICU with severe hypoxic ARF, Depuydt et al. (155) found that the use of NIV within 24 hours after ICU admission was not associated with better outcome as compared with invasive ventilation or supplemental oxygen only; in multivariate regression analysis, higher cancer-specific severity of illness score upon admission and more organ failure after 24 hours of ICU admission were significantly associated with increased ICU or in-hospital mortality, but the initial type of respiratory support was not. The disagreement between these findings and those of most other studies may be explained by differences in study design or patient selection, as not all forms of ARF are appropriate to be treated with NIV. As pointed out by the authors, the patients of their study might have been too ill to benefit from a trial of NIV, because as many as 74% of them met the criteria for ARDS, which has been shown to be significantly associated with NIV failure in hematologic patients (61).

A large observational multicenter Italian survey investigated the clinical impact of NIV use in 1,302 hematologic patients admitted to ICU with ARF (60). The authors, after a propensity score analysis, confirmed the role of NIV treatment ab initio (from the beginning) as an independent predictor of survival. On the other hand, CPAP has been also used to treat cancer patients with ARF in order to prevent ICU admission. Squadrone et al. (156) randomized 40 patients with hematologic malignancy, recruited in the hematologic ward during the early phases of ARF, with \( \text{PaO}_2 / \text{FiO}_2 \) levels between 200 and 300, and without
a secure diagnosis of infection, to receive CPAP delivered by the helmet or standard supplemental oxygen. Patients treated with helmet CPAP were less frequently admitted to the ICU and their ETI rate was lower than in the control group. The investigators suggested that early use of CPAP was a practical, simple, and inexpensive method to prevent deterioration of the respiratory function and complications in patients undergoing intense immunosuppression. It is reasonable to consider the NIV approach as a useful tool to avoid intubation and associated infectious complications in selected patients with immunocompromised states.

Weaning Process

In the setting of weaning and extubation, NIV use has been proposed as prophylaxis to prevent reintubation (“preventive NIV”) or as a rescue intervention in case of established postextubation respiratory failure (“rescue NIV”). These two approaches have been evaluated in large randomized trials, yielding different, but intriguing, results (157).

Early application of NIV immediately after extubation has been efficiently used as a tool to prevent postextubation ARF. Nava et al., in a multicenter randomized trial involving 97 patients with specific risk factors for postextubation ARF (i.e., congestive heart failure, excessive secretions, more than one weaning trial failure), observed that NIV application for at least 8 hours significantly decreased the rate of extubation failure (4/48 vs. 12/49; p = 0.027) and was associated with lower ICU mortality (10%; p < 0.01) (158).

Similarly, Ferrer et al. (159) randomized 162 mechanically ventilated patients who tolerated a spontaneous breathing trial but had increased risk for ARF after extubation (i.e., age more than 65 years, cardiac failure as the cause of intubation, APACHE II severity of illness score more than 12) to receive NIV for 24 hours versus conventional management with oxygen therapy. In the NIV group, ARF after extubation was less frequent (p = 0.029) and the ICU mortality was lower (p = 0.015), whereas 90-day survival did not change significantly between groups. Interestingly, in patients with hypercapnia (PaCO₂ >45 mmHg) during the spontaneous breathing trial, NIV use could significantly improve ICU mortality and 90-day survival.

The other potential application of NIV (i.e., as a rescue strategy for postextubation ARF) has been investigated in multicenter randomized controlled trials. Keenan et al. (160) studied the effectiveness of NIV compared with standard medical therapy in preventing the need for endotracheal intubation in 81 patients who developed ARF during the first 48 hours after extubation. Comparing the two groups, no significant difference was found in rates of reintubation or duration of mechanical ventilation, in hospital mortality or ICU or hospital length of stay. Similarly, in a study conducted by Esteban et al. (161), no benefits from NIV were found in avoiding reintubation in patients who had developed ARF after extubation, and NIV was even associated with higher mortality rates as compared with patients treated according to standard treatment. In this study, the time from extubation to reintubation was longer in patients who received NIV.

In a more recent clinical trial, Girault et al. compared three early weaning/extubation techniques (conventional invasive weaning group; NIV group; standard oxygen therapy group) in 208 patients with chronic hypercapnic respiratory failure (162). Although, no differences were observed in the reintubation rate within the first 7 days, NIV was able to shorten the intubation duration and the risk of postextubation ARF.

In summary, NIV approach has to be considered to reduce the risk of postextubation ARF. However, further studies are needed to better define which patient categories are most likely to benefit from its application during weaning process.

Do-Not-Intubate Orders

To date, some confusion does remain on applying NIV in do-not-intubate patients, with some warning of the potential ethical and economic cost of delaying the inevitable in patients with terminal respiratory failure (163). This has stimulated a large number of research studies on the usefulness of NIV in such a context (164). In one study of 30 patients, most elderly and suffering from COPD, in whom invasive ventilation was “contraindicated or postponed,” 18 patients (60%) were able to be successfully weaned from nasal mask NIV (165). In a trial conducted on 114 patients who declined intubation but accepted NIV to treat their ARF (166), 49 patients (43%) survived to discharge. Those patients who were awake, suffering from congestive heart failure or COPD, and those with a more efficient cough mechanism had an increased probability of survival.

In cancer patients at the end of life who have a stated desire to receive life-prolonging treatment, NIV may be of benefit as it may relieve dyspnea while preserving the ability to communicate, as well as decrease the need for sedatives, and prolong life for a period of time sufficient to accomplish personal tasks or realize possible end-of-life desires.

In those patients with the do-not-intubate order in whom the technique is unlikely to provide any survival or qualitative benefits, NIV should be avoided, whereas it might be considered when the acute process responsible for ARF is known to respond well to the technique, such as CPE or COPD exacerbation. Prior to initiation of NIV in these terminally ill patients, it is critical that the patient, family, and clinicians have a clear understanding of the possible outcomes of NIV. The caring clinician should inform the dying patients and their loved ones about the potential use of NIV, including the risks, benefits, and alternatives, and assure them that NIV can be withdrawn at any time if it fails to achieve the previously defined goals or the patient cannot tolerate the technique. In those cancer patients who cannot communicate, NIV should be discouraged as one of the theoretical advantages of palliative NIV is maintenance of the patient’s ability to communicate. Throughout the management of any terminal patient with ARF, the caregiver must remember that not guaranteeing a quality death is a serious and irretrievable error. Finally, controversy remains about which is the most appropriate setting to deliver palliative NIV in end-of-life care.

Postoperative Patients

Thoracic and upper abdominal surgery are associated with a prolonged deterioration in postoperative gas exchange, as well as reduction in functional residual capacity, PaO₂, and forced vital capacity (167,168). Mask CPAP was initially used by Bunnell (1) in 1912 to maintain lung expansion in patients undergoing thoracic surgery, and by Boothby et al. (169) in 1940 for treating postoperative hypoxemic ARF. Applying mask CPAP or NIV improves oxygenation and pulmonary
function following upper abdominal surgery (167,170–172) or coronary artery bypass graft (173–175). Squadrone et al. (171) randomized 209 patients who developed severe hypoxemia after major elective abdominal surgery to receive oxygen or oxygen plus CPAP. CPAP-treated patients had a lower intubation rate (1% vs. 10%) and a lower occurrence rate of pneumonia (2% vs. 10%), infection (3% vs. 10%), and sepsis (2% vs. 9%) (all \( p < 0.05 \)) than patients treated with oxygen alone. NIV improves gas exchange and reduces the need for intubation after lung resection (176,177) or bilateral lung transplantation (178).

A recent systematic-review summarized the results of 29 articles where the use of preventive and therapeutic NIV was investigated in postsurgical patients (179). Thoracoabdominal/bariatric surgical interventions and solid-organ transplants were included. Arterial blood gases improvement and intubation rate reduction were the main benefits associated with the use of NIV. Thus, despite the limitations of available data and the need of new randomized trials, accumulating evidence supports the use of NIV/CPAP to reduce respiratory postoperative complications in selected patients.

**Obstructive Sleep Apnea**

CPAP is recognized to be effective in correcting the respiratory and arousal abnormalities and improving sleep quality in OSA syndrome (180,181). CPAP is believed to act by pneumatically “splinting” the pharyngeal airway, thus preventing its collapse during sleep (182,183). Additionally, nasal NIV has been used in patients with ARF following obstructive sleep apnea syndrome, with improvements in clinical status and arterial blood gas values (184).

**Trauma**

ARF in trauma patients is generally associated with reduced pulmonary compliance and functional residual capacity, and subsequent restrictive defects (185). In a study of 33 trauma patients with ARF who received face mask CPAP, Hurst et al. (185) found rapid improvements in gas exchange, avoiding intubation in 94% of the cases. In a retrospective survey of 46 trauma patients with ARF who had been given mask NIV, 33 patients (72%) were successfully weaned to spontaneous breathing (186). In another study (187), NIV used as first-line treatment in 22 patients with ARF due to blunt chest trauma resulted in rapid improvement in blood gases and respiratory rate, and avoided intubation in 18 patients (82%). In a study of patients with acute hypoxic respiratory failure needing ventilatory assistance, Antonelli et al. (20) reported that 7 of the 32 patients (22%) randomized to receive NIV had trauma with pulmonary contusion or atelectasis. NIV was associated with a rapid improvement in oxygenation, and all seven patients avoided intubation and survived. Interestingly, Chiumello et al. performed a meta-analysis of ten studies addressing the use of NIV in patients with chest trauma who developed mild-to-severe respiratory failure (188). There was no difference between CPAP and PS NIV in terms of mortality, but the latter could significantly increase arterial oxygenation, leading to a reduction in the intubation rate and infectious complications incidence. However, despite the favorable results obtained, large randomized studies are still needed before definitive recommendations on the use of NIV in posttraumatic ARF can be made.

**Restrictive Diseases**

NIV has a role in the treatment of respiratory failure caused by some types of restrictive thoracic diseases. Bach et al. (189) demonstrated that NIV can prolong survival while decreasing the respiratory morbidity and hospitalization rates in patients with Duchenne muscular dystrophy. Using NIV prevented intubation in 7 of 11 episodes of ARF in a group of 9 patients with myasthenic crises (190). In ARF due to pulmonary fibrosis, prognosis is poor even when invasive mechanical ventilation is used (191). Aggressive respiratory physiotherapy is crucial in all patients with thoracic restriction.

**Bronchoscopy**

In nonintubated patients, severe hypoxemia is an accepted contraindication to fiberoptic bronchoscopy (FB). Since \( P_{aO_2} \) routinely decreases after uncomplicated FB, these patients are at high risk for developing ARF or serious cardiac arrhythmias. Performing bronchoscopy during NIV has been described either in at-risk patients who were initially breathing spontaneously and who started NIV to assist bronchoscopy, or in patients who were already receiving NIV and were scheduled to perform bronchoscopy (192–195). Antonelli et al. (192,193) proposed a technique to perform FB with bronchoalveolar lavage in hypoxic, nonintubated patients by means of facial mask NIV (Fig. 103.10). The fiberoptic bronchoscope was passed through a T adapter and then advanced transnasally. The technique was safe and effective in avoiding gas exchange worsening during FB, allowing early and accurate diagnosis of pneumonia, and preventing undesired intubation in spontaneously breathing, hypoxic patients. Alternately, if a helmet is adopted, the bronchoscope is passed through the specific seal connector placed in the plastic ring of the helmet. The internal adjustable diaphragm of the seal connection can prevent loss of the respiratory gases, maintaining ventilation throughout bronchoscopy (194).

Conscious sedation using propofol target-controlled infusion (TCI) techniques seems to be a promising approach to assist bronchoscopy in hypoxic patients under NIV (196). Similarly bronchoscopy under sedation with remifentanil TCI

**FIGURE 103.10** Fiberoptic bronchoscopy performed during noninvasive ventilation delivered through an oronasal mask. FB, fiberoptic bronchoscope; HME, heat and moisture exchanger; RC, respiratory circuit; SC, seal connection; SV, suction valve. (Photograph printed with the permission of the patient.)
has been safely and effectively used in critically ill patients undergoing spontaneous ventilation (197). During the last several years, dexmedetomidine use has been widely implementing in the clinical practice as a sedative agent, although few data are available in patients undergoing NIV (198). Due to its favorable pharmacologic profile, dexmedetomidine might be suitable as an adjuvant agent during bronchoscopy in spontaneous breathing critically ill patient with respiratory failure.

**Pediatric Population**

A growing body of evidence supports the use of NIV in children with ARF. Early case reports showed the safety and efficacy of the technique in the setting of cystic fibrosis, non-CPE and aspiration lung injury. One of the largest observational survey was reported by Essouri et al. (199) who described the application of NIV in 114 consecutive pediatric patients during a 5-year period. Even though only 22% of subjects with ARDS avoided endotracheal intubation, the authors reported an overall clinical success rate of 77%. More recently, a randomized controlled trial compared NIV treatment to standard therapy in 50 children with ARF, mainly due to bronchiolitis (200). The authors observed that patients undergoing NIV in PS modality had a sudden improvement in respiratory parameters and a significantly lower intubation rate (28% vs. 60%). Usually, facial masks have been considered the first choice to deliver CPAP/NIV. However, due to several possible disadvantages associated with its application in the pediatric population, helmet use is progressively increasing in this setting. Better tolerance of the interface may contribute to the reduction of sedatives used during spontaneous breathing (201). New assisted ventilatory modalities (e.g., NAVA) have been recently promoted in the pediatric setting in order to optimize child–ventilator interaction (202).

**ADVERSE EFFECTS AND COMPLICATIONS**

Major adverse effects of NIV seldom occur in appropriately selected patients and are minimized when the technique is applied by experienced caregivers (203). The most frequently encountered complications are related to the interface, ventilator airflow or pressure, or patient–ventilator interaction.

The pressure of the mask over the bridge of the nose may induce discomfort, erythema, or ulceration (see Fig. 103.2). There are various remedies to ameliorate this complication such as application of a hydrocolloid sheet over the nasal bridge or switching to alternative interfaces. Air leakage under the mask into the eyes may cause conjunctival irritation, and excessive pressure may be responsible for sinus or ear pain. To minimize these problems, refitting the mask or lowering inspiratory pressure may be useful. Patient–ventilator asynchrony is a common cause of NIV failure and is often related to patient agitation or inability of the ventilator to sense the onset of patient expiration because of excessive air leaking. Judicious use of sedatives may be safe and effective in the treatment of NIV failure due to low tolerance (204), and minimizing air leaks (73,205) may improve patient–ventilator synchrony.

Presumably because of the low inflation pressure used compared with invasive ventilation, NIV is well tolerated hemodynamically, but it should be avoided in patients with an unstable hemodynamic status, dysrhythmias, or uncontrolled ischemia until these problems are stabilized. Gastric insufflation occurs commonly, but is usually well tolerated. Aspiration pneumonia has been reported in as many as 5% of patients (106); the risk for aspiration is minimized by excluding patients with compromised upper airway function or problems clearing secretions and positioning a nasogastric tube in those with excessive gastric distention, an ileus, or nausea or vomiting. Although pneumothoraces occur very infrequently, inspiratory pressures should be kept at the minimum effective level in patients with bullous lung disease.

**SUMMARY**

To date, the best-established indication for NIV in the acute care setting is ARF related to COPD-E. However, evidence has been rapidly accumulating to support application of NIV to treat many other types of ARF in selected patients. Further research should better define indications and patient selection criteria, as well as establish optimal techniques of administration.

**Key Points**

- NIV has the potential of avoiding the complications associated with endotracheal intubation, improving patient comfort, and preserving speech and airway defense mechanisms.
- Advances in patient–ventilator interfaces and ventilatory modes have fostered the increasing use of NIV in the acute care setting.
- The choice of ventilatory mode should be dictated by personal experience, as well as the patient’s respiratory drive and etiologic factors and severity of the underlying disease causing respiratory failure.
- It is crucial to identify patients who are likely to benefit from NIV and exclude those for whom NIV would be unsafe.
- Several factors are critical to the success of NIV: properly timed initiation, comfortable and well-fitting interface, patient preparation, careful ventilatory mode selection, and respiratory physiotherapy.
- Patients should receive NIV in an intensive care unit or a step-down unit for continuous monitoring until sufficient stabilization.
- NIV can be used to avoid intubation, but not to replace it. Invasive ventilation remains the method of choice for patients with respiratory failure who have contraindications to NIV.
- NIV is indicated as the ventilator mode of first choice in selected patients with COPD-E.
- In acute hypoxemic respiratory failure without hypercapnia, NIV can be used as long as patients are hemodynamically stable and are closely monitored in the intensive care unit to avoid dangerous delays if intubation becomes necessary.
- NIV has a central role in the management of ARF of varied causes, improving patient outcome and efficiency of care in the acute setting.
References


