REVIEW ARTICLE

C. Corey Hardin, M.D., Ph.D., *Editor*

Noninvasive Respiratory Support for Adults with Acute Respiratory Failure

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N Engl J Med 2022;387:1688-98.
DOI: 10.1056/NEJMra2204556

Acute respiratory failure is a common indication for admission to an intensive care unit. Invasive mechanical ventilation, particularly positive-pressure ventilation, has been the cornerstone of the management of severe forms of acute respiratory failure since the 1950s.[1] However, despite major advancements in critical care management, the complications and mortality associated with intubation and positive-pressure ventilation are not insignificant.[2] Efforts to circumvent invasive mechanical ventilation through the use of noninvasive devices have therefore garnered much attention. For some conditions, such as cardiogenic pulmonary edema and chronic obstructive pulmonary disease (COPD) exacerbations, noninvasive respiratory support is highly beneficial,[3] whereas for hypoxemic respiratory failure, the presence of associated conditions such as sepsis and shock[4] may make the use of noninvasive respiratory support risky and its benefits more difficult to delineate.

Three main methods of noninvasive support are used in the acute care setting: a high flow of gas delivered through a large-bore nonocclusive nasal cannula (i.e., high-flow nasal cannula), continuous positive airway pressure (CPAP), and noninvasive ventilation (i.e., pressure-support ventilation with positive end-expiratory pressure [PEEP]). In this review, we provide an overview of the physiological effects, different configurations, clinical indications, and evidence for the use of noninvasive respiratory support in adults with acute respiratory failure.

Physiological Effects

Respiratory failure has two main components: ventilatory dysfunction and hypoxemia. Ventilatory dysfunction leads to dyspnea, increased work of breathing, use of accessory muscles, and hypercapnia: this situation is best managed with the use of a method that offers frank ventilatory support. Hypoxemia reflects inadequate gas exchange and warrants different forms of oxygen therapy and specific device settings (mostly positive pressure) to improve gas exchange. Clinical respiratory distress and severe hypoxemia often go together in various combinations because injuries that cause abnormal gas exchange often result in abnormal mechanics and high work of breathing, but they can also be dissociated.[5] The different noninvasive respiratory support interfaces and methods are shown in Figure S1 in the Supplementary Appendix,[6] available with the full text of this article at NEJM.org, and Table S1 describes each of the physiological effects.

High-Flow Nasal Cannula

High gas flow rates (≥30 liters per minute and up to 60 to 80 liters per minute) with a set fraction of inspired oxygen (FIO_2) of 0.21 to 1.0 can be administered through a nasal cannula.[7] Heating (to 34° to 37°C) and humidification make gas delivery comfortable,[8] and the high flow, usually higher than the patient's own

inspiratory peak flow, allows for the effective delivery of the intended F_{IO_2}. In addition, high flows generate a small level of nonadjustable PEEP — slightly higher when the mouth is kept closed — and reduce ventilation requirements and inspiratory muscle effort through a washout of the dead space in the upper airway during expiration.[9] This allows fresh gas with a controlled F_{IO_2} to be available at the beginning of each inspiration, thereby slightly reducing the quantity of ventilation that needs to be generated by the patient to clear carbon dioxide. The use of a high-flow nasal cannula is often associated with a prolonged expiration through a resistive effect that reduces the respiratory rate.[10,11] This method may also assist in mucociliary clearance of secretions through humidified gas,[12-15] is easy to apply, and generally causes minimal discomfort.[16]

CPAP and PEEP

With CPAP, the patient breathes with a constant level of positive pressure that is maintained during both inspiration and expiration.[17] CPAP may be deployed with intensive care mechanical ventilators or with continuous-flow open circuits. The latter have a high-gas-flow generator that allows the F_{IO_2} to be adjusted up to 1.0 and a PEEP valve with minimal resistance. CPAP can also be delivered through open-to-atmosphere valves that have internal microchannels through which a jet of oxygen is delivered.[17] These systems can also be humidified.[18]

Although PEEP does not have a direct effect on ventilation, it can indirectly act as assistance to ventilation through various mechanisms: counterbalancing the mechanical load imposed by residual end-expiratory alveolar pressure (dynamic hyperinflation at the end of expiration) in COPD exacerbations, combating atelectasis (e.g., postoperative hypoxemia after abdominal or thoracic surgery), providing a mechanical stent of the upper airways (e.g., in patients with obstructive sleep apnea), or acting as a threshold external pressure to overcome the critical opening pressure of the airway (e.g., in patients with obesity).[19] In patients with hypoxemia, when impairment of oxygenation is secondary to a loss of aerated alveoli (e.g., in the context of severe infectious pneumonia or acute respiratory distress syndrome) leading to intrapulmonary shunt, PEEP may facilitate alveolar recruitment, thus improving arterial oxygenation.[20-22] When PEEP is applied to improve oxygenation, it is important to clinically estimate its effect on the work of breathing. Excessive PEEP can induce hyperinflation and reduce the efficiency of diaphragmatic contraction.

In cases of left ventricular dysfunction,[19,23] PEEP may have beneficial effects by increasing the intrathoracic pressure and thus decreasing preload, as well as by reducing the work of breathing. By decreasing the negative intrathoracic pressure swings generated by the activity of the respiratory muscles, PEEP decreases the afterload on the left ventricle. These effects are negligible in the context of normal cardiac function, but PEEP in the form of CPAP or noninvasive ventilation can be very effective in relieving respiratory distress in patients with cardiogenic pulmonary edema by improving both cardiac and respiratory function.

Noninvasive Ventilation

Noninvasive ventilation is a patient-triggered, pressure-targeted mode of ventilation in which positive inspiratory pressure is delivered above a PEEP level at each patient-triggered breath. Inspiratory pressure and PEEP are set by the health care team. The inspiratory pressure directly increases the tidal volume by raising the pressure gradient between the mouth and the alveoli, allowing the patient to reduce the required breathing effort. Situations involving hypoventilation and respiratory acidosis are best treated with noninvasive ventilation, which results in a substantial reduction in work of breathing.[24] Decreasing work of breathing can also decrease oxygen consumption and further improve gas exchange.[25,26] In patients with hypoxemic respiratory failure, the effect of positive inspiratory pressure needs to be monitored to ensure that it does not lead to excessive tidal volumes, a situation that is predictive of subsequent failure.[27,28]

This mode can be applied with the use of intensive care ventilators that compensate for leaks or by dedicated "bilevel" positive-airway-pressure machines.[29-31] Dedicated bilevel machines have sophisticated algorithms to compensate for leaks, but they also have fewer monitoring capabilities than conventional ventilators. Leaks during noninvasive ventilation are dependent on the preset pressures and can make the delivery of ventilation uncomfortable for the patient.[17]

CPAP AND NONINVASIVE VENTILATION INTERFACES

Implementation of noninvasive support involves selecting the appropriate interface. The most commonly used patient interface for CPAP and noninvasive ventilation is the oronasal face mask, which covers the nose and the mouth and is secured firmly with head straps. Gas leaks around the mask limit the efficacy of the device and may induce failure of this method, given the inability to effectively deliver desired pressures[30]; gas leaks also make monitoring of the tidal volume less precise. Oronasal face masks that are tightly fitted to minimize leaks may result in facial ulcerations and cause discomfort, making this method substantially less acceptable to patients — particularly with prolonged use. Total face masks, which exert no direct pressure on the nose, can be used with less skin breakdown, and their efficacy is similar to that of masks with lower internal volumes.[32] Despite their larger internal volume, they rarely increase functional dead space.[32,33] Nasal mask interfaces are not commonly used in the acute care setting, given the limited pressures that can be delivered. Comfort of the interface is critical for the use of CPAP or noninvasive ventilation. Clinicians should ideally have a variety of interfaces and sizes available so that individual patients' needs can be properly met.

The helmet is a larger interface for the delivery of CPAP or noninvasive ventilation. It is a cylinder-shaped hood made of transparent plastic that is fitted around the neck with a metal or plastic ring and a soft collar. The helmet is fixed in place with two under-arm straps attached to the neck ring.[34,35] Although some patients may experience claustrophobia or report excessive amounts of noise, discomfort from the helmet is generally minimal, and it does not exert direct regional pressure on the skin. The helmet allows for more prolonged use of CPAP or noninvasive ventilation than does the oronasal face mask. Recent designs have improved the patient–ventilator interaction, allowing for higher levels of PEEP (10 to 12 cm of water) than with traditional interfaces.[14,36] Higher levels of PEEP are necessary to avoid collapse of the hood in patients with large tidal volumes. Furthermore, high gas flows may be necessary to avoid carbon dioxide rebreathing. Accurate measurement of expired tidal volume is, however, not usually feasible with standard helmet noninvasive ventilation.[37]

INDICATIONS AND CLINICAL EVIDENCE

The indications and evidence from clinical studies for the use of different methods of noninvasive respiratory support are discussed below. Figure 1 also summarizes the various clinical conditions and associated evidence.

ACUTE HYPOXEMIC RESPIRATORY FAILURE

Acute hypoxemic respiratory failure is often characterized by a combination of lung inflammation or infection, permeability pulmonary edema, and atelectasis resulting in impaired oxygenation, ventilation, and respiratory mechanics.[38] Invasive mechanical ventilation, delivered with targeted pressures and volumes to prevent ventilator-induced lung injury, is used in the context of worsening gas exchange[39] and high effort to breathe. This invasive approach, however, often involves heavy sedation. Noninvasive respiratory support may facilitate gas exchange while maintaining wakefulness and spontaneous breathing.[40] Moreover, the spontaneous generation of negative intrathoracic pressures can have beneficial effects on gas exchange and the distribution of ventilation. However, at least experimentally, prolonged exposure to vigorous spontaneous breathing under conditions of worsening severity can also be associated with harms.[41] In addition, the presence of nonpulmonary organ dysfunction (most commonly brain or cardiovascular dysfunction) may necessitate intubation to protect the airway and reduce oxygen consumption. Despite uncertainty surrounding its effectiveness, noninvasive respiratory support is used frequently with the hope of reducing the need for intubation.[4] Indeed, during the coronavirus disease 2019 (Covid-19) pandemic, noninvasive ventilatory support has been delivered in up to 41% of patients with acute hypoxemic respiratory failure caused by severe Covid-19; the types of support included a high-flow nasal cannula, CPAP, and noninvasive ventilation.[42-44]

A large number of clinical trials have been performed, and a series of meta-analyses have shown that the risk of endotracheal intubation is

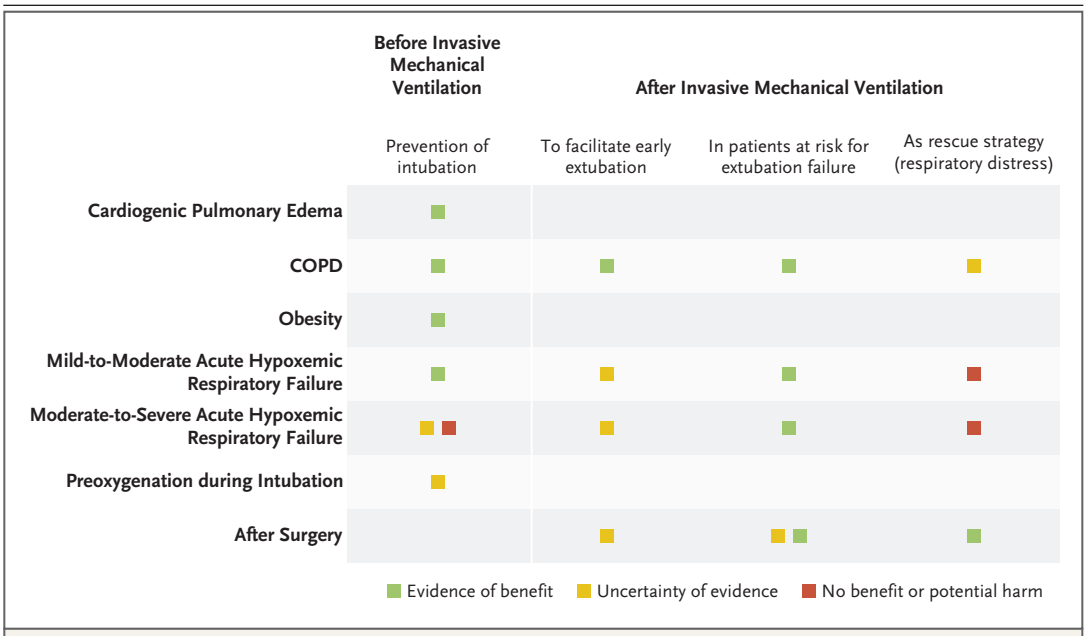

Figure 1. Summary of Evidence for Noninvasive Ventilation across Acute Care Conditions.

The greatest benefit of preemptive use of noninvasive ventilation in the context of acute hypoxemic respiratory failure is seen in selected high-risk patients (e.g., those with obesity or cardiac conditions). Helmet noninvasive ventilation and therapy with a high-flow nasal cannula are under investigation for moderate-to-severe acute hypoxemic respiratory failure; the risk of failure is increased in patients who have a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of less than 150 while receiving face-mask noninvasive ventilation. In the context of extubation after surgery, no benefit has been found for preemptive use of continuous positive airway pressure after abdominal surgery; however, a potential benefit of preemptive use of a high-flow nasal cannula has been found in this context in higher-risk patients and patients with hypoxemia. A potential benefit of rescue noninvasive ventilation after abdominal surgery has also been found. COPD denotes chronic obstructive pulmonary disease.

lower among patients with hypoxemic respiratory failure treated with either a high-flow nasal cannula or noninvasive ventilation than among those treated with conventional oxygen therapy. However, no effect on mortality has been shown consistently for patients with this indication.[3,45]

A landmark trial compared three methods — high-flow nasal cannula, conventional oxygen therapy, and face-mask noninvasive ventilation with a high-flow nasal cannula used in between sessions — in patients with a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2:FIO_2) of less than 300 and showed that the 90-day risk of death was higher with conventional oxygen and noninvasive ventilation than it was with the use of high-flow nasal cannula alone.[46] High tidal volumes and low Pao_2:FIO_2 ratios (<200) were associated with an increased risk of intubation (Fig. 2). High tidal volumes 1 hour after the initiation of noninvasive ventilation were associated with in-

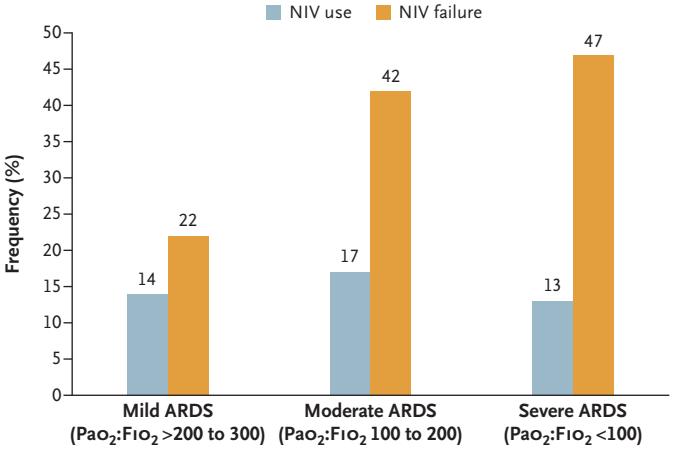

Figure 2. Frequency of Use and Failure of Face-Mask Noninvasive Ventilation (NIV) for ARDS.

Failure was defined as endotracheal intubation. The figure is based on data from Bellani et al.[4] ARDS denotes acute respiratory distress syndrome, FIO_2 fraction of inspired oxygen, and Pao_2 partial pressure of arterial oxygen.

creased mortality, which aroused concerns about whether pressures delivered under noninvasive ventilation potentially precipitated ventilation-induced lung injury. A network meta-analysis comparing all methods of noninvasive respiratory support across 25 trials showed that all the methods were associated with a lower risk of intubation than conventional oxygen therapy.[47]

A small, single-center, randomized, controlled trial evaluated different interfaces for noninvasive ventilation.[36] A lower risk of intubation and lower 90-day mortality was found with the use of a helmet than with the use of a face mask for noninvasive ventilation. Although the trial was stopped early, the results were intriguing, since randomized clinical trials evaluating these interfaces head-to-head had previously been lacking. Patients in the helmet group appeared to have less discomfort from noninvasive ventilation at higher PEEP values (median, 8 cm of water) than patients in the face-mask group (median PEEP, 5 cm of water).[36] A trial evaluating a helmet for noninvasive ventilation as compared with high-flow nasal cannula was conducted during the Covid-19 pandemic.[14] The patients who had been randomly assigned to receive noninvasive ventilation with a helmet received therapy with a high-flow nasal cannula in between sessions of noninvasive ventilation. Lower rates of intubation (secondary outcome) were found in the group assigned to receive noninvasive ventilation through a helmet than in the group assigned to a high-flow nasal cannula. Other trials involving patients with Covid-19 have shown CPAP and therapy with a high-flow nasal cannula to be more effective in decreasing the risk of intubation than conventional oxygen therapy.[48,49]

Immunocompromised patients have historically been deemed to be good candidates for noninvasive respiratory support and in particular for noninvasive ventilation. This idea was driven by early trials that were conducted when invasive ventilation was associated with extremely high mortality in this cohort.[50,51] However, mortality among immunocompromised patients with respiratory failure has decreased substantially over time.[52] Given this change, the contemporary data currently do not support avoiding invasive ventilation at all costs and do not support adopting a strategy that differs from that used for nonimmunocompromised patients.[47]

In synthesizing the literature on acute hypoxemic respiratory failure, we found that all noninvasive respiratory support devices have been shown to potentially decrease the risk of endotracheal intubation more effectively than conventional oxygen therapy, at least among patients with mild-to-moderate respiratory failure and in the absence of associated conditions (e.g., severe organ failure or shock). However, the current evidence for a benefit of noninvasive respiratory support for more severe forms of respiratory failure (Pao_2:FIO_2 ratio <150) is less clear, with some data suggesting potential risks associated with face-mask noninvasive ventilation.[4] Important uncertainties surround questions regarding whether to use noninvasive respiratory support, which device to use, the risk factors associated with failure, and how to monitor for failure in patients with higher severities of hypoxemia. Table 1 outlines considerations in the selection of a noninvasive device for acute hypoxemic respiratory failure and the factors associated with failure.

CARDIOGENIC PULMONARY EDEMA

In patients with cardiogenic pulmonary edema, noninvasive respiratory support strategies are used as bridging therapy during hypoxemia and respiratory distress while urgent medical therapies (e.g., diuretics and vasodilators) are administered; in this clinical context, noninvasive respiratory support serves to decrease the work of breathing, increase functional residual capacity, and enhance cardiac function. CPAP and noninvasive ventilation with a face mask have been evaluated extensively in patients with cardiogenic pulmonary edema.[55,56] A series of systematic reviews has shown a reduced risk of endotracheal intubation and reduced in-hospital mortality associated with these methods.[3] In the absence of shock or an indication for urgent revascularization, clinical practice guidelines recommend the use of CPAP or noninvasive ventilation in this context. From a clinical standpoint, when these patients present with both hypoxemia and hypercapnia, it seems advisable to use noninvasive ventilation as a first choice.

COPD EXACERBATION AND HYPERCAPNIC RESPIRATORY FAILURE

Noninvasive ventilation with a face mask has been very effective in the context of COPD exacer-

Table 1. Practical Considerations in the Management of Acute Respiratory Failure with Noninvasive Respiratory Support to Prevent Intubation.*

Consideration	Recommendations and Common Practices	Areas of Uncertainty
Where to monitor patient	Patients should be treated in a monitored setting (e.g., step-down unit or ICU) by an experienced health care team with expertise in noninvasive respiratory support (e.g., physician, respiratory therapist, and nurse). The team should have knowledge of monitoring, adjustments of settings, identification of failure, and urgent intubation.	The Covid-19 pandemic forced many institutions to use HFNC outside the traditional setting of a step-down unit or ICU. Thresholds for safe use of HFNC therapy in the inpatient wards have not been defined.
Which method to use	Use face-mask NIV for COPD, OHS, or congestive heart failure exacerbation. Consider intubation for acute hypoxemic respiratory failure (in the absence of an underlying chronic condition) in patients with high severity of illness, shock, acute kidney injury, decreased level of consciousness, or severe hypoxemia. Consider trial of HFNC or trial of CPAP or NIV for acute hypoxemic respiratory failure (in the absence of an underlying chronic condition) in patients with mild or moderate hypoxemia.	Criteria for selecting between HFNC and CPAP or NIV are not clearly defined in the literature. Treatment should first include the method the health care team is most comfortable with, followed by an early evaluation of the presence of risk factors associated with failure.
Risk factors associated with failure	Pao_2:Fio_2 <150 with presence of ARDS indicates high risk of face-mask NIV failure and death.[4] Pao_2:Fio_2 <200 1 hr after initiation of face-mask NIV, particularly in the context of large tidal volumes (>9 to 9.5 ml/kg),[27,28] indicates high risk of face-mask NIV failure. If above features are present, consider time-limited trial of HFNC or helmet NIV (if there is institutional familiarity) with frequent reevaluation (e.g., every 1 or 2 hr).	Promising evidence has suggested benefit (reduced risk of intubation) with helmet NIV as compared with face-mask NIV and HFNC in patients with moderate hypoxemic respiratory failure. Ongoing clinical trials are under way. Institutions with familiarity with helmet NIV may consider its use in patients with moderate hypoxemia, particularly in the presence of high work of breathing.
Measures to monitor for failure	Monitor the respiratory rate, Pao_2:Fio_2 trajectory, level of consciousness, and ROX index[53] (HFNC) or HACOR score[54] (NIV).†	

* ARDS denotes acute respiratory distress syndrome, COPD chronic obstructive pulmonary disease, CPAP continuous positive airway pressure, Covid-19 coronavirus disease 2019, HFNC high-flow nasal cannula, ICU intensive care unit, NIV noninvasive ventilation, OHS obesity hypoventilation syndrome, Pao_2 partial pressure of arterial oxygen, and PEEP positive end-expiratory pressure.

† The ROX index is the ratio of the oxygen saturation divided by fraction of inspired oxygen (Fio_2) to the respiratory rate. The HACOR scale is based on heart rate, acidosis, consciousness, oxygenation, and respiratory rate.

bations, since it efficiently offloads respiratory muscles and counteracts dynamic hyperinflation. This method often prevents intubation as a bridge to administering effective therapies (e.g., glucocorticoids, bronchodilators, and antibiotic agents).

A series of randomized, controlled trials have evaluated the effectiveness of face-mask noninvasive ventilation as compared with conventional oxygen therapy for COPD exacerbations. Face-mask noninvasive ventilation consistently showed success in preventing intubation and decreasing hospital mortality among these patients.[3] Noninvasive ventilation is therefore strongly recommended as the first-line therapy for this population. Currently, there is insufficient evidence surrounding the role of a high-flow nasal cannula for COPD exacerbations. Much less evidence supports the routine use of noninvasive ventilation in the context of asthma exacerbations.[57] Lastly, patients with obesity hypoventilation and mixed forms of respiratory failure represent an increasingly large group of patients with hypercapnia and respiratory acidosis.[58] These patients may also benefit from both the PEEP and the driving pressure of noninvasive ventilation.[59]

AFTER EXTUBATION

Noninvasive respiratory support strategies have been evaluated to facilitate early liberation (weaning) from invasive mechanical ventilation, to prevent extubation failure in high-risk patients, and as a rescue strategy in acute respiratory failure after extubation (Fig. 1). Early libera-

tion from invasive ventilation through transitioning to face-mask noninvasive ventilation has been evaluated as a weaning strategy. This strategy has had great success among patients with COPD specifically, with a meta-analysis showing a reduced length of hospital stay and lower mortality.[60]

Despite fulfilling criteria for successful extubation, 12 to 20% of patients may be determined to need reintubation within the week after extubation. As compared with conventional oxygen therapy, the application of noninvasive ventilation or a high-flow nasal cannula immediately after extubation has been successful in preventing reintubation in certain high-risk populations, such as patients with COPD,[60] coexisting cardiac conditions, or obesity.[61] In a comparative evaluation, application of noninvasive ventilation in combination with a high-flow nasal cannula in patients who were at risk for being reintubated was associated with a lower risk of reintubation and postextubation respiratory failure at day 7 than the use of a high-flow nasal cannula alone.[62] In a post hoc analysis, heterogeneity in the treatment effect was found, with lower risks of reintubation and death in the intensive care unit (ICU) by day 7 associated with noninvasive ventilation than with a high-flow nasal cannula among patients with obesity (body-mass index [BMI, the weight in kilograms divided by the square of the height in meters], ≥30) or overweight (BMI, 25 to 30) but not among patients of normal or lower-than-normal body weight.[63]

The application of noninvasive respiratory support as a rescue maneuver in the context of postextubation acute respiratory failure has not shown great success. The use of face-mask noninvasive ventilation in this context has been associated with delayed intubation and increased mortality.[3,61,64] These findings, however, may not be generalizable to patients with COPD exacerbations or cardiogenic pulmonary edema, since the trials of rescue noninvasive ventilation have predominantly involved patients with pneumonia. Ultimately, close monitoring and frequent reevaluation is essential to monitor for failure and avoid delaying reintubation.

POSTOPERATIVE RESPIRATORY FAILURE

Given the prominent role of atelectasis or pulmonary edema in postoperative respiratory failure, noninvasive respiratory support could have a promising role. As compared with usual care, the application of preemptive CPAP was not shown to decrease a composite of pneumonia, endotracheal intubation, or death within 30 days after postoperative extubation in a recent large, randomized trial involving patients undergoing abdominal surgery.[65] However, in a meta-analysis of 11 trials, preemptive use of a high-flow nasal cannula decreased the risk of intubation more effectively than conventional oxygen therapy. This benefit, however, was driven by higher-risk populations (e.g., patients with obesity).[66] CPAP and noninvasive ventilation have been effective in decreasing the incidence of reintubation and complications in patients who have postextubation hypoxemia after abdominal surgery.[67,68]

MONITORING AND IDENTIFICATION OF FAILURE AND SELECTION OF DEVICES

Failure of noninvasive respiratory support is reported in only 15 to 20% of COPD exacerbations[69] but in up to 40 to 60% of cases of acute hypoxemic respiratory failure.[4,70] The likelihood of failure increases with the severity of respiratory failure (Fig. 2) and associated coexisting conditions. The decision to use noninvasive methods in patients with brain or circulatory dysfunction should be made very cautiously, except when the dysfunction can be reversed by noninvasive ventilatory support.

Noninvasive ventilation failure has been found to be an independent risk factor for death in the ICU in patients with hypoxemic respiratory failure.[4,71] In a secondary analysis of the trial evaluating helmet noninvasive ventilation as compared with a high-flow nasal cannula,[14] patients with a low partial pressure of arterial carbon dioxide ($PaCO_2$) (<35 mm Hg) derived the greatest benefit from helmet noninvasive ventilation with respect to a decreased risk of intubation. This effect was not seen among patients with a normal or higher $PaCO_2$ (≥35 mm Hg). The authors postulated that the low $PaCO_2$ may represent high inspiratory effort and may define a subgroup of patients who are at greatest risk for patient self-inflicted lung injury during spontaneous breathing.[72] Although moderate-to-high levels of PEEP can reduce the high inspiratory

Table 2. Monitoring for Failure of Noninvasive Respiratory Support in Patients with Acute Hypoxemic Respiratory Failure.*

Variable	Device Evaluated	Description
Pao_2:FIO_2[4,27,28]	Face-mask NIV	Pao_2:FIO_2 <200 at 1 hr after NIV associated with increased risk of intubation; Pao_2:FIO_2 <150 associated with increased risk of death (as compared with up-front strategy of invasive mechanical ventilation)
Tidal volume[4,27,28]	Face-mask NIV	Tidal volume >9 to 9.5 ml per kilogram of predicted body weight 1 hour after NIV associated with increased risk of intubation and death
Respiratory rate[53,54,75]	Face-mask NIV	Low or decreasing respiratory rate associated with greater likelihood of NIV success; respiratory rate does not always correlate with inspiratory effort
Simplified Acute Physiology Score II[27]	Face-mask NIV	Higher scores indicate higher severity of illness, which is associated with higher likelihood of failure and receipt of invasive mechanical ventilation; no definitive threshold defined in the literature
Composite scores		
ROX index[53]	HFNC	Tool for prediction of HFNC therapy failure and receipt of invasive mechanical ventilation, validated in patients with acute hypoxemia due to pneumonia who were receiving HFNC therapy; index evaluated at 2 hr, 6 hr, and 12 hr after initiation
HACOR score[54]	Face-mask NIV	Evaluation of heart rate, acidosis, consciousness, oxygenation, and respiratory rate; threshold of >5 at 1 hr after initiation of NIV associated with subsequent receipt of invasive mechanical ventilation
Measures under evaluation		
$Paco_2$[72]	Helmet NIV	Possible surrogate for inspiratory effort; $Paco_2$ <35 mm Hg associated with a greater likelihood of success with helmet NIV than with HFNC in reducing the risk of invasive mechanical ventilation (effect not seen when value is ≥35 mm Hg)
Changes in esophageal pressure at onset of inspiration[76]	Helmet NIV	Possible surrogate for inspiratory effort in patients with Pao_2:FIO_2 <200; lack of reduction in the change in esophageal pressure to <10 cm of water with application of helmet NIV in patients with a baseline value of >10 cm of water associated with a higher risk of intubation
Point-of-care lung ultrasound score[77]	Face-mask NIV, HFNC	Lung aeration and morphologic abnormalities on ultrasonography quantified with a simplified protocol in six lung ultrasound areas and assigned score of 0 to 3 for each lung area; the total lung ultrasound score was significantly higher in patients with Covid-19 who had HFNC or NIV failure leading to invasive mechanical ventilation

* The predominant cause of acute hypoxemic respiratory failure evaluated across these studies was pneumonia. Face masks may have been an oronasal mask or a full mask. $Paco_2$ denotes partial pressure of arterial carbon dioxide.

effort through reducing atelectasis and diaphragmatic effort and create a more homogeneous delivery of pressures across the lungs,[73] some patients may continue to generate large intrathoracic pressure swings and large tidal volumes, which may ultimately lead to excessive work of breathing, oxygen consumption, cardiac overload, or patient self-inflicted lung injury.[74] Delayed intubation may result in suboptimal intubating conditions, since these patients will have little physiological reserve.

A series of physiological variables have been identified as being associated with failure of noninvasive respiratory support, as shown in Table 2.[4,27,28,76] Precise and reliable methods to measure a threshold of inspiratory effort that is harmful remain under investigation; the change in esophageal pressure during inspiration has been investigated as a measure of inspiratory effort and as an early warning signal.[76] Composite scores incorporating a combination of respiratory variables and trends over time have also shown potential for the identification of noninvasive respiratory support failure. The ROX index (the ratio of the oxygen saturation divided by FIO_2 to the respiratory rate) calculated at multiple points after initiation of the use of a high-flow nasal cannula has been associated with failure of this mode of therapy in patients who have acute respiratory failure in the absence of an underlying chronic condition.[53] The HACOR scale (heart rate, acidosis, consciousness, oxygenation, and respiratory rate) has been evaluated after 1 hour of face-mask noninvasive ven-

tilation to predict failure.[54] Physiological factors associated with failure of the methods in patients with acute respiratory failure in the absence of an underlying chronic condition are outlined in Table 2.

Given the risk of failure and the mortality associated with this risk, caution must be exercised when deciding to treat a patient with non-COPD, noncardiogenic, acute hypoxemic respiratory failure. The approach to selecting a noninvasive device, settings, adjustments, monitoring, and decisions to transition to invasive ventilation require a health care team–based approach. At many institutions, this team includes respiratory therapists who have familiarity and expertise in the range of noninvasive devices and interfaces, bedside nurses with experience in managing respiratory failure, and physicians. Specific factors regarding the patient, the physiological aspects of acute respiratory failure, the health care team, and institutional factors that may guide decision making regarding the selection of noninvasive respiratory support selection are outlined in Table S1. Table 1 provides an outline of considerations for the use of the different noninvasive devices, which measures to monitor, and factors that may be associated with failure. It is likely that patients with different phenotypes respond differently to the noninvasive respiratory supports available.

AREAS OF UNCERTAINTY

Many questions remain with respect to the use of noninvasive respiratory support. The effectiveness of noninvasive respiratory support in combination with interventions such as prone positioning, the accurate measurement of inspiratory effort, the role of sedation in reducing harms associated with spontaneous breathing, and the role of extracorporeal gas-exchange methods coupled with noninvasive respiratory support to avoid intubation are all areas in need of further investigation.

CONCLUSIONS

The different methods of noninvasive respiratory support are important tools to support oxygenation and ventilation across a variety of indications. Noninvasive respiratory support has a role in preventing intubation and decreasing mortality for patients with specific conditions. The benefit of averting intubation needs to be balanced against the harms of delaying intubation, especially in patients with acute hypoxemic respiratory failure. Early clinical identification of failure is important to circumvent delayed intubation, and therefore careful monitoring is required.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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