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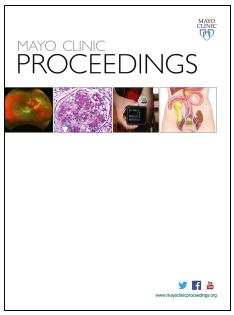

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Non-Invasive Positive Pressure Ventilation in Patients With COVID-19

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Abbreviations

AHRF = acute hypoxemic respiratory failure

ARDS = acute respiratory distress syndrome

BiPAP = bilevel positive airway pressure

COVID-19 = Coronavirus disease 2019

CPAP = continuous positive airway pressure

HFNC = High flow nasal cannula

NIPPV = non-invasive positive pressure ventilation

OR = odds ratio

SARS = severe acute respiratory syndrome

Introduction

Much of the debate around the Coronavirus disease 2019 (COVID-19) pandemic in the popular press has focused on invasive (via endotracheal tube or tracheostomy) ventilation of severely sick patients and potential ventilator shortages. Amid increasing concerns of medical professionals about the harms associated with invasive ventilation, there is interest to explore the role of non-invasive positive pressure ventilation (NIPPV) in the treatment of acute hypoxemic respiratory failure (AHRF) and acute respiratory distress syndrome (ARDS) due to COVID-19. In this commentary we aim to summarize what is known about the role of NIPPV in patients with AHRF and ARDS due to COVID-19 and other viral infections, point out evidence gaps and make a case for consideration of NIPVV as a possible alternative to early intubation in patients with COVID-19.

Aims to limit intubations are mainly based on concerns about ventilator-induced lung injury and the recognition that the pathophysiological and anatomical features of COVID-19 related lung infection are different from classic ARDS, for which invasive mechanical ventilation is considered the standard of care. COVID-19 is primarily causing injury to the capillary endothelium instead of essential injury to the alveolar epithelium.[1] Lungs affected by COVID-19 show marked ventilation-perfusion mismatch but preserved compliance,[2] making the recruitment maneuver and the use of high positive end-expiratory pressure potentially deleterious. The risk of ventilator-induced lung injury in patients with COVID-19 is further increased by the lack of specialized personnel (e.g. shortage in respiratory therapists and intensivists) and the lack of appropriate equipment (e. g. use of devices used for chronic mechanical ventilation, use of a single device for several patients).

NIPPV includes treatment with continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP).[3] CPAP is useful in AHRF, as it recruits collapsed alveoli, improves ventilation-perfusion matching, and therefore oxygenation. BiPAP is useful for the treatment of hypercapnic respiratory failure, as it supports ventilation by using a different level of in-and expiratory continuous airway pressure, thus increasing tidal volume and minute ventilation. Patients with COVID-19 pneumonia and ARDS typically have severe hypoxemia and relatively well preserved lung mechanics.[2] It is therefore reasonable to assume that patients with COVID-19 will benefit from CPAP therapy. However, as many patients with COVID-19 and severe respiratory failure are obese and may therefore have risk factors for hypercapnia including obstructive sleep apnea and obesity hypoventilation syndrome, BiPAP therapy should be considered on a case-by-case basis.

Guideline recommendations

Guideline recommendations on the use of NIPPV in COVID-19 vary widely (Table 1).[4-11] COVID-19 guidelines of the American Thoracic Society[9] and the Infectious Diseases Society of America[10] focus primarily on pharmacologic interventions and make no mention of NIPPV. The majority of organizations including the National Institutes of Health,[7] the Society of Critical Care Medicine/ European Society of Intensive Care Medicine Surviving Sepsis Campaign,[4] the English National Health Service,[5] the Italian Thoracic Society and the Italian Respiratory Society,[6] as well as the World Health Organization[8] support the use of NIPPV in patients with COVID-19 and AHRF, at least in certain circumstances. For the World Health Organization, this constitutes a change in policy compared with earlier during the pandemic. In contrast, the Australian and New Zealand Intensive Care Society recommend against the use of NIPPV in patients with COVID-19 in favor of early intubation.[11] Conflicting recommendations reflect the uncertainty about the benefits and

harms of NIPPV in patients with COVID-19 and concerns that the aerosol produced by the use of NIPPV poses an increased infection risk for health care professionals.[12]

Prone positioning

Prone positioning has been shown to reduce mortality in severe ARDS.[13] There is emerging evidence that prone positioning is beneficial in patients with ARDS due to COVID-19, and that NIPPV can be provided to these patients in the prone position in a general ward.[14]

What are the benefits and harms of NIPPV compared with early intubation in COVID-19?

NIPPV has been widely used in China and some European countries during the current pandemic, but to date there is insufficient evidence to support this use.

An Italian retrospective chart review study of patients with COVID-19 found that of 71 patients on helmet CPAP, 26 (37%) were intubated and 54 (76%) died (before or after intubation). The availability of ventilators was limited in the study setting, thus not allowing for a comparison between CPAP use and early intubation.

NIPPV was commonly used during the severe acute respiratory syndrome (SARS) epidemic in China that emerged in 2002, but only four small observational studies that mention NIPPV are available,[17] one of which focused on the nosocomial infection risk and included only two patients on BiPAP.[18] Another study did not specify the ventilation type that was used and did not evaluate outcomes in patients on NIPPV.[19] In the two remaining studies, both from Hong Kong, BiPAP treatment was used in all patients on NIPPV.[20,21] Intubation was avoided in 14 out of 20 (70%) patients on BiPAP and was associated with a shorter ICU stay (3.1 days vs 21.3 days, $p < 0.001$) compared with intubated patients in one study.[20] It was, however,

unclear if early intubation as opposed to BiPAP use would have resulted in better outcomes, especially for the patients who required intubation despite treatment with BiPAP. The other study assessed the outcomes in patients with SARS in one hospital that used BiPAP as initial ventilatory support compared with outcomes in 13 hospitals in which only invasive mechanical ventilation was used.[21] Patients in the hospital using BiPAP did not significantly differ from the patients in the hospitals not using any NIPPV in terms of demographic characteristics, co-morbidities and disease severity on admission apart from significantly higher Lactate dehydrogenase levels in the patients admitted to the NIPPV hospital. Patients in the NIPPV hospital had lower adjusted odds ratios (ORs) for intubation (OR 0. 36; 95% CI 0.16 - 0.79) and death (OR 0. 24; 95% CI 0.08 -0.72) compared with patients in the hospitals only using mechanical ventilation.

A systematic review identified 22 studies conducted on the use of NIPPV during the 2009 influenza A pandemic caused by the swine influenza (H1N1) virus, of which the majority were case series and none were randomized trials.[17] In a Spanish registry study of 685 patients with H1N1 pneumonia 177 patients were treated with NIPPV (specific type of ventilation not specified), which was successful in 72 patients (41%); the remainder of patients required intubation. When NIPPV treatment failed, the delay in intubation was not associated with increased mortality compared with patients who were intubated without a trial of NIPPV (26.5% versus 24.2%, $p < 0.001$).[22] The lack of randomization introduces selection bias. Patients who were directly intubated were likely sicker than those treated with NIPPV initially, and it is therefore unclear whether in comparable patients failure of NIPPV would not increase mortality compared with early intubation.

In summary, there is insufficient evidence about the effectiveness of NIPPV in AHRF due to viral pneumonia. Observational studies suggest that the use of NIPPV has the potential to reduce the need for intubation. It is unclear whether patients in whom NIPPV treatment fails would have had better outcomes if they would have been intubated earlier without a trial of NIPPV. Patients who can overcome severe COVID-19 without requiring intubation will benefit from avoiding sedation, inability to communicate, potential delirium and post-traumatic stress disorder. Table 2 gives an overview of potential benefits and disadvantages of different breathing support strategies in acute respiratory failure.

What are the benefits and harms of CPAP compared with oxygen administration and high flow nasal cannula in patients with AHRF due to COVID-19?

High flow nasal cannula (HFNC) is an emerging therapy for AHRF that can warm and humidify gas, which can decrease airway inflammation, improve mucus clearance and enhance patient comfort. HFNC can deliver a 21% to 100% fraction of inhaled oxygen at flow rates of up to 60 liters/min and generates a positive end-expiratory pressure which prevents alveolar collapse.

Similar to NIPPV, recommendations about the use of HFNC in COVID-19 vary widely, and there is currently no available evidence to assess the effectiveness of HFNC compared with standard oxygen or CPAP.

A European multicenter trial of 310 patients with AHRF (caused by pneumonia in 84% of the patients) found that treatment with HFNC, standard oxygen, or NIPPV did not result in significantly different intubation rates. HFNC was associated with lower 90-day mortality

than either standard oxygen or NIPPV.[23] This could potentially suggest a role for HFNC in patients with AHRF due to COVID-19.

What is the risk of viral transmission to healthcare professionals caring for COVID patients on NIPPV?

Recommendations against the use of NIPPV and/or HFNC in patients with AHRF due to COVID are at least partially based on concerns about virus spread in aerosols produced by these procedures. However, very little is known about the risk of viral transmission associated with different aerosol generating procedures. A systematic review found that tracheal intubation had a significantly higher risk of transmission of acute respiratory infections to healthcare professionals (OR 6.6, 95% confidence interval [CI] 2.3 to 18.9, 4 cohort studies) than NIPPV (pooled OR 3.1, 95% CI 1.4 to 6.8, 2 cohort studies).[24] A study that used laser smoke visualisation to assess dispersion distances during aerosol producing procedures using a human patient simulator found that the maximum exhaled air dispersion distance was greatest (100 cm) using a nasal cannula at an oxygen flow rate of 5litres/min while there was only negligible air dispersion with the use of CPAP via oronasal mask at a pressure of 20 cmH_2O.[25]

The risk of viral transmission with NIPPV can be significantly reduced with the use of a filter on the expiratory circuit and the automatic measurement and quantification of a leak at the interface (which allows prompt leak correction and reduction of virus dispersion). Although intubation is associated with a high risk of viral transmission, the risk can be reduced by techniques of apneic oxygenation and rapid sequence intubation with paralysis.
Invasive mechanical ventilation has a reduced risk of viral transmission compared with NIPPV once a closed ventilation circuit is established.

In summary, there is insufficient evidence to determine whether CPAP and HFNC are associated with a higher viral transmission risk than standard oxygen delivered via nasal cannula or different mask types, especially when relatively high oxygen flow rates are used. The use of filters on the expiratory circuit of NIPPV may indeed result in lower viral transmission rates with NIPPV than with the use of standard oxygen or HFNC. Precautions to minimize transmission from aerosol-generating procedures in COVID-19 patients are warranted, including the use of negative-pressure rooms, personal protective equipment including a respirator that ensures a level of protection equal or greater than N95/FFP2 and the use of viral/bacterial filters with any devices.

Ongoing and future research

On July 1, 2020, only 12 studies (including five randomized trials) that investigate NIPPV in COVID-19 were registered on ClinicalTrials.gov. This compares to a total of 2447 registered studies using the term “COVID”. The table in the supplement provides an overview of all identified studies and their characteristics. A US randomized trial assesses the effectiveness of CPAP treatment at home compared with no intervention in patients with presumed or confirmed COVID-19 who are sent home from the emergency room with mild pneumonia or respiratory illness. One randomized trial from the US and Sweden respectively compares helmet CPAP with HFNC; whereas an Italian trial compares helmet CPAP with no intervention. A French trial compares the effectiveness of standard oxygen, CPAP, HFNC, and invasive ventilation while also assessing the effectiveness of dexamethasone versus placebo using a factorial design.

Conclusions

In the absence of sufficient evidence and pending trial results, NIPPV should be considered as an alternative to early intubation, and the type of NIPPV should be based on case-by-case decision making that takes into account a patient's characteristics (e.g. the ability to independently move into a prone position) and co-morbidities (e.g. obstructive sleep apnea or chronic obstructive pulmonary disease). There is currently insufficient evidence to assess the effectiveness of HFNC compared with NIPPV in COVID-19. Safety concerns around aerosol spread of SARS-CoV-2 during NIPPV treatment make such trials difficult to conduct. Nevertheless, evidence from large well-conducted randomized trials is urgently needed because future pandemics with other viral pneumonias are likely. These trials should address the effectiveness of NIPVV compared with early intubation and HFNC, and the risk of viral transmission to health care workers when patients are using different breathing support strategies.

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Table 1. Guidance statements regarding the use of NIPPV in COVID-19

Recommendation	Organization	Guidance Statement
NIPPV[i] is recommended (at least in certain circumstances)	Society of Critical Care Medicine/ European Society of Intensive Care Medicine, Surviving Sepsis Campaign, June 2020[4]	For adults with COVID-19[f] and acute hypoxemic respiratory failure despite conventional oxygen therapy, we suggest using over conventional oxygen therapy (weak recommendation, low quality evidence). In adults with COVID-19[f] and acute hypoxemic respiratory failure, we suggest using HFNC[g] over NIPPV[i] (weak recommendation, low quality evidence). In adults with COVID-19[f] and acute hypoxemic respiratory failure, if HFNC[g] is not available and there is no urgent indication for endotracheal intubation, we suggest a trial of NIPPV[i] with close monitoring and short-interval assessment for worsening of respiratory failure (weak recommendation, very low-quality evidence)."
	National Health Service (NHS) United Kingdom, April 6, 2020, Version 3[5]	"CPAP[d] is the preferred form of non-invasive ventilatory support in the management of the hypoxaemic COVID-19[f] patient. Its use does not replace invasive mechanical ventilation (IMV[h]), but early application may provide a bridge to IMV[h]." "The use of NIV[j] (BiPAP[c]) should be reserved for those with hypercapnic acute on chronic ventilatory failure. "
	Italian Thoracic Society (AIPO/ITS) and Italian Respiratory Society (SIP/IRS) March 8, 2020[6]	"NIV[j] can be used during isolation for confirmed cases. Patients with previous respiratory diseases can benefit mainly from NIV[j]. NIV[j] can prevent worsening in hypercapnic COPD[e] patients not at risk of pulmonary edema, who are without pneumonia, multiple organ failure or refractory hypoxemia. Do not use NIV[j] in the Emergency Department in confirmed positive patients. NIV[j]/CPAP[d] can be used in the post extubation phase of ARDS[b]. NIV[j]/CPAP[d] can be used in less severe patients only if the patient is in a protected environment."
	National Institutes of Health (NIH)[7] updated June 11, 2020	"For adults with COVID-19[f] who are receiving supplemental oxygen, the COVID-19[f] Treatment Guidelines Panel (the Panel) recommends close monitoring for worsening respiratory status and recommends early intubation by an experienced practitioner in a controlled setting (AII). For adults with COVID-19[f] and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC[g]) oxygen over noninvasive positive pressure ventilation (NIPPV[i]) (BI). In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV[i] for adults with COVID-19[f] and acute hypoxemic respiratory failure for whom HFNC[g] is not available (BIII)."
	World Health Organization May 27, 2020, Interim	"In selected patients with COVID-19[f] and mild ARDS[b], a trial of HFNO [high-flow nasal oxygen], non-invasive ventilation – continuous positive airway pressure (CPAP[d]), bilevel positive airway pressure

	Guidance[8]	(BiPAP[c]) may be used."
NIPPV[i] is not mentioned/has no role in COVID-19[f] management	American Thoracic Society April 3, 2020[9]	NIPPV[i] is not mentioned in the guidelines "For patients with refractory hypoxemia due to progressive COVID-19[f] pneumonia (i.e., ARDS[b]), we suggest prone ventilation. For patients with refractory hypoxemia due to progressive COVID-19[f] pneumonia (i.e., ARDS[b]), we suggest that extracorporeal membrane oxygenation (ECMO) be considered if prone ventilation fails."
	Infectious Diseases Society of America Updated June25, 2020[10]	NIPPV[i] is not mentioned in the guidelines. There are no comments on any breathing support strategies in the guidelines.
NIPPV[i] is not recommended	Australian and New Zealand Intensive Care Society Australia, April15, 2020, Version 2[11]	"Routine use of non-invasive ventilation (NIV[j]) is not recommended. Current experience suggests that NIV[j] for COVID-19[f] hypoxic respiratory failure is associated with a high failure rate, delayed intubation, and possibly increased risk of aerosolization with poor mask fit. Deteriorating patients should be considered for early endotracheal intubation and invasive mechanical ventilation. If NIV[j] is appropriate for an alternate clinical presentation of COVID-19[f] (e.g. concomitant COPD[e], APO[a]), this should be provided using similar precautions as for HFNO."

[a]APO = acute pulmonary edema; [b]ARDS = acute respiratory distress syndrome; [c]BiPAP = bilevel positive airway pressure; [d]CPAP = continuous positive airway pressure; [e]COPD: chronic obstructive pulmonary disease; [f]COVID-19 = Coronavirus disease 2019; [g]HFNC = high flow nasal cannula; [h]IMV = invasive mechanical ventilation; [i]NIPPV = noninvasive positive pressure ventilation; [j]NIV = noninvasive ventilation

Table 2: Potential benefits and disadvantages of different breathing support strategies in acute respiratory failure

Type of breathing support	Benefits	Disadvantages
NIPPV[d] (CPAP[b] or BiPAP[a])	• Less invasive than intubation (A proportion of patients will survive without requiring intubation) • Avoids sedation, inability to communicate, potential delirium and post-traumatic stress disorder associated with intubation, if intubation can be avoided • May better alleviate dyspnea, work of breathing, hypoxia or hypercapnia compared to HFNC[c] and standard oxygen • May be used outside of the intensive care unit (for example, in a dedicated respiratory ward) • Provides a treatment option in patients with Do-Not-Intubate orders	• Compared with intubation (and sedation), patients on NIPPV[d] may take larger tidal volumes and have an increased risk of subsequent lung injury • If NIPPV[d] fails, and intubation is required, the "delayed" intubation may be associated with a higher risk of complications due to a rushed procedure • Requires specialist nursing care, compared with HFNC[c] and standard oxygen • NIPPV[d] might be more aerosol producing (compared to HFNC[c], standard oxygen, and invasive mechanical ventilation, apart from the high risk during intubation), though this risk can be reduced with viral filters, etc. • A tight fitting mask may be uncomfortable for patients, especially when used continuously for extended length of time; some patients cannot tolerate NIPPV[d] • May not allow for adequate mucociliary clearance
Early intubation	• Enables increased control of hypoxia, hypercapnia, and work of breathing compared with NIPPV[d], HFNC[c], and standard oxygen • Potentially avoids rushed intubation associated with risk of complications later compared with a failed trial of NIPPV[d] • Once intubated with a closed respiratory circuit, the aerosol generating risk may be lower compared to NIPPV[d] • Treatment of choice when patient has significant inability to protect airway (e.g. due to severe encephalopathy) • Compared to NIPPV[d] or HFNC[c], intubation with sedation may better facilitate patient undergoing certain procedures or transporting to a different medical facility (e.g. patient cannot lie flat for a computed tomography scan)	• Requires specialist care in the intensive care unit (physician, nurses, respiratory therapists) • Often requires sedation, inability for patient to communicate and may have increased association with delirium and post-traumatic stress disorder • May be associated with longer hospitalization and higher mortality compared to patients who have avoided intubation on NIPPV[d] • Risk of vocal cord damage, procedural hypotension, and other adverse effects directly associated with placement of an endotracheal tube • Potential for lung injury associated with positive end-expiratory pressure • High risk of viral transmission during intubation (can be limited by techniques of apneic oxygenation and rapid sequence intubation with paralysis) and also during

		procedures which require opening the circuit such as bronchoscopy or suctioning. • Compared with NIPPV[d], it is unclear if early intubation is associated with improved patient outcomes.
HFNC[c]	• Compared to standard oxygen, HFNC[c] may be associated with improved hypoxia, improved hypercapnia (minor positive end-expiratory pressure support), and dyspnea • Compared to NIPPV[d] (and intubation), HFNC[c] is generally better tolerated and more comfortable, especially for extended continuous use. • Enables patient to speak, eat, and drink. • May even be more comfortable than high flow standard oxygen (HFNC[c] has heated humidifier) • Compared to NIPPV[d], HFNC[c] may allow for improved mucociliary clearance • Provides a treatment option in patients with Do-Not-Intubate orders • May be used outside of the intensive care unit (for example, in a dedicated respiratory ward)	• May require special nursing competency • Provides only minimal positive end-expiratory pressure compared to NIPPV[d] and invasive ventilation • Aerosol producing procedure and risk of viral transmission, especially on high flow rates
Standard oxygen via nasal prongs	• Does not require specialist nursing competency • Does not require a bed in the intensive care unit • More widely available than ventilators or BiPAP[a] machines • Provides a treatment option in patients with Do-Not-Intubate orders • Compared to NIPPV[d], may be less aerosol producing	• Is often less efficacious in improving hypoxia, hypercapnia, dyspnea, and work of breathing compared with HFNC[c], NIPPV[d], and intubation • May cause iatrogenic hypercapnic respiratory failure if the oxygen is not titrated and the patient is at risk of hypercapnia • High flow rates are aerosol producing

[a]BiPAP = bilevel positive airway pressure; [b]CPAP = continuous positive airway pressure; [c]HFNC = high flow nasal cannula; [d]NIPPV = noninvasive positive pressure ventilation