Received: 20 November 2023 | Revised: 21 January 2024 | Accepted: 26 January 2024

DOI: 10.1002/emp2.13118

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
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REVIEW ARTICLE

Pulmonary

Noninvasive respiratory support in the emergency department: Controversies and state-of-the-art recommendations

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Funding and support: By *JACEP Open* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Abstract

Acute respiratory failure is a common reason for emergency department visits and hospital admissions. Diverse underlying physiologic abnormalities lead to unique aspects about the most common causes of acute respiratory failure: acute decompensated heart failure, acute exacerbation of chronic obstructive pulmonary disease, and acute de novo hypoxemic respiratory failure. Noninvasive respiratory support strategies are increasingly used methods to support work of breathing and improve gas exchange abnormalities to improve outcomes relative to conventional oxygen therapy or invasive mechanical ventilation. Noninvasive respiratory support includes noninvasive positive pressure ventilation and nasal high flow, each with unique physiologic mechanisms. This paper will review the physiology of respiratory failure and noninvasive respiratory support modalities and offer data and guideline-driven recommendations in the context of key clinical controversies.

1 | INTRODUCTION

Acute respiratory failure occurs in 1275 persons per 100,000 adults in the United States.[1] The most common reasons for emergency department (ED) admission for acute respiratory failure are exacerbations of chronic diseases, the most common being acute decompensated heart failure (ADHF) and chronic obstructive pulmonary disease (AECOPD), followed by acute de novo hypoxemic respiratory failure (AHRF) from acute infections or lung injury. Noninvasive respiratory support (NIRS) strategies are increasingly used in the ED for patients with acute respiratory failure, increasing over 400% between 2002 and 2017.[1] Exact numbers of annual uses of NIRS are not well tracked, but best estimates suggest that hundreds of thousands of patients each year are started on NIRS in the ED,[2] a figure that has substantially increased during the COVID-19 pandemic. Given increasing physician awareness and the worsening ED boarding crisis,[3] ED NIRS use is likely to increase.

This review will describe NIRS modalities and the physiologic mechanisms by which these support acute respiratory failure, summarize controversies, existing literature and guidelines, highlight key knowledge gaps, and offer practical recommendations for NIRS use in the ED.

Supervising Editor: Robert Levine, MD

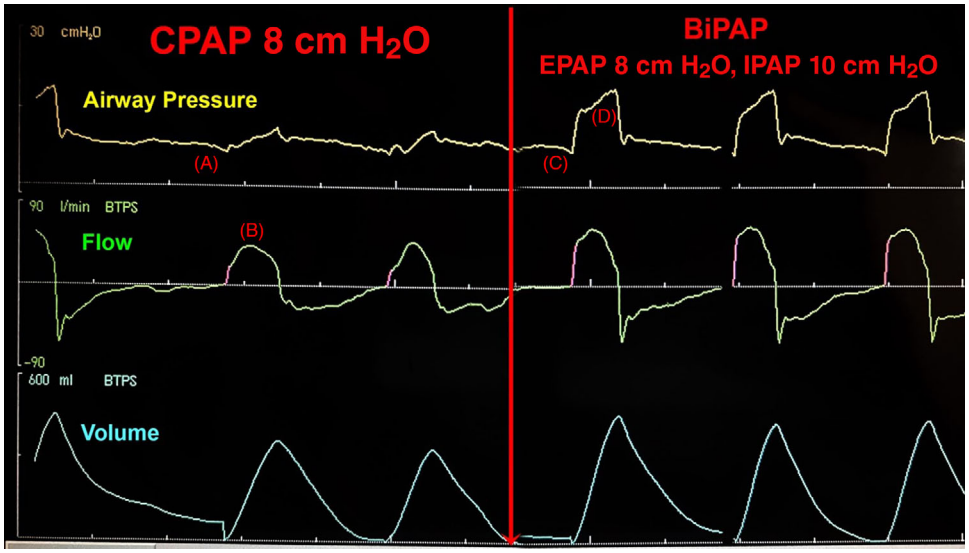

FIGURE 1 Changes in airway pressure associated with CPAP and BiPAP. This patient is on CPAP (left) at 8 cm H_2O on a ventilator with a facemask. When the ventilator senses an inspiratory effort (A), the flow increases during inspiration (B) to maintain "continuous" positive airway pressure of 8 cm H_2O. A flow-generated CPAP valve or an exhalatory PEEP valve will not provide this compensation, especially with high inspiratory effort, thus providing less support. CPAP can *indirectly* improve work of breathing, which is further *directly* improved by adding inspiratory pressure support to reduce inspiratory muscle effort (right). When using BiPAP, the ventilator will sense an inspiratory effort (C) and increase the flow until the target inspiratory pressure of 10 cm H_2O is reached (D). CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; IPAP, inspiratory positive airway pressure; PEEP, positive end-expiratory pressure.

2 | NIRS FUNDAMENTALS

2.1 | NIRS modalities

NIRS modalities include *pressure*-based support and *flow*-based support.

Pressure-based NIRS, also known as noninvasive positive pressure ventilation (NIPPV), includes continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP), and uses nasal mask, face mask, or helmet-based systems. The common feature across all of these interfaces is the intent to provide positive pressure throughout the entire respiratory cycle (ie, CPAP), and they all provide positive end-expiratory pressure (PEEP). The supporting pressure may be generated by (1) continuous flow through a specially designed valve, (2) an exhalation valve, or (3) a noninvasive ventilator. In order to generate pressure with continuous flow-generated CPAP valves, the flow is split through micropores creating a virtual PEEP valve variable to the amount of flow through it. A prominent example of a flow-based valve is the Boussignac CPAP system. With exhalation valves, such as those attached to a bag-valve mask, PEEP is generated through physical resistance to the expiratory flow, typically through tightening a spring attached to a one-way diaphragm. With noninvasive ventilators, blowers/compressors create the desired set positive pressure.

There are subtle differences between the modalities of pressure support. Boussignac and PEEP valves provide pressure throughout the expiratory phase, but the airway pressure may drop during inspiration, especially if respiratory effort is high. In contrast, the noninvasive ventilator must compensate for a decreasing airway pressure to pressurize the respiratory system at the set pressure throughout the respiratory cycle (Figure 1). BiPAP is like CPAP, but the pressure levels differ for inhalation and exhalation, referred to as inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP).

Flow-based NIRS is provided by specially designed nasal high flow (NHF) systems, which provides heated and humidified gas with a titratable FiO_2 through specially designed nasal cannula systems. Varying degrees of nares occlusion and set flow velocity provide physiological effects similar to those achieved with NIPPV (Figure 2). Heated and humidified gas improves mucociliary clearance, secretion management, and comfort. When flow rates approach or exceed inspiratory demand, inspiratory work of breathing decreases. Together, these effects result in improved gas exchange and reduced work of breathing. However, NHF physiology is not completely understood, nor how respiratory mechanics change across flow rates, nor the differences between high flow systems. Physiology studies suggest that expiratory work of breathing decreases by prolonging expiration from increased expiratory resistance with breathing against the constant flow, similar to the effect of breathing against PEEP.[4]

2.2 | Respiratory failure and work of breathing

Acute respiratory failure occurs from any condition that leads to inability to ventilate or oxygenate effectively. Ventilatory failure occurs with any imbalance in peripheral CO_2 production and pulmonary CO_2 exhalation leading to a reduced blood pH. Oxygenation failure occurs mostly through shunt and ventilation:perfusion mismatch due to myriad causes. The common final pathway for acute respiratory failure is altered respiratory mechanics, fatigue, and gas exchange

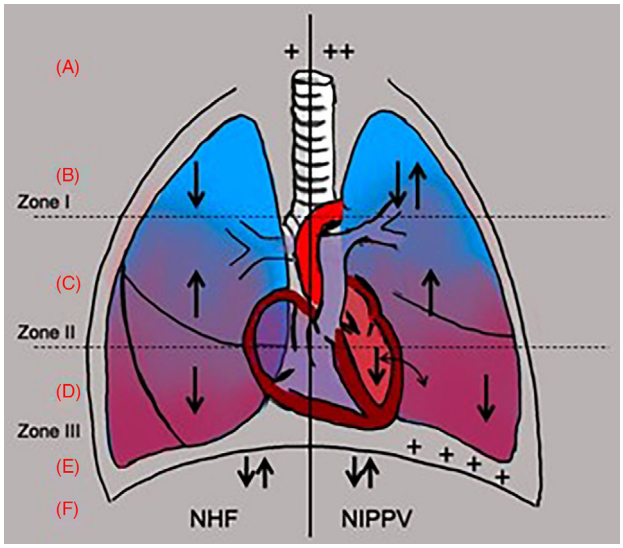

FIGURE 2 Physiology of NIRS support. In general, NIPPV (right) and NHF (left) share many physiologic properties. For NIPPV, the positive pressure generated in a closed respiratory system generates a positive pharyngeal pressure (A), that can have a distending pressure on the upper airway, but mainly translates to PEEP. NHF generates some positive pharyngeal pressure that may act as distending upper airway pressure, but is dependent on the rate of flow, degree of nares occlusion, and whether the mouth is open or closed. PEEP has several direct and indirect effects on respiratory mechanics, work of breathing, and gas exchange.[5] PEEP reduces end-expiratory airway collapse and atelectasis. The reduction in atelectasis increases the functional residual capacity and moves the lung to a more favorable portion of the pressure-volume curve, decreasing West Zone III areas (D) and increasing West Zone II areas, thus improving ventilation/perfusion (V/Q) matching and oxygenation (C). For NHF, similar effects are achieved. The constant flow throughout the respiratory cycle will increase end-expiratory lung volume (ie, PEEP like effect). If PEEP is too high with NIPPV, particularly in the poorly compliant lung, or if inspiratory pressure is too high, overdistention can occur and thus increase dead space (West Zone I) (B). In contrast, NHF likely reduces dead space (Zone I) through continuous high flow rates flushing dead space. NIPPV, by nature of the positive pressure, increases intrathoracic pressure and thus transpulmonary pressure (E). If NIRS is successful at increasing the functional residual capacity and improving oxygenation and ventilation, inspiratory force, lung strain, and drive (ie, work of breathing) will decrease (F). However, if end-expiratory lung volume is not sufficiently increased or gas exchange not significantly improved, inspiratory force, lung strain, and drive will worsen—increasing the potential for self-inflicted lung injury (*see* 3.5). NIRS, noninvasive respiratory support; NIPPV, noninvasive positive pressure ventilation; NHF, nasal high flow; PEEP, positive end-expiratory pressure.

abnormalities. However, the underlying pathophysiology that leads to the clinical syndrome of respiratory failure differs between etiologies, creating varying mechanisms for NIRS support in each disease (Table 1).

The overall goal when using NIRS is to reduce the work of breathing, which is a complex concept. In the simplest sense, a breath takes energy (work) to overcome: (1) the elastic forces of the lung (ie, lung compliance) to inflate the lung from its resting volume (functional residual capacity) to its end-inspiratory volume with a tidal volume, (2) the forces of the chest wall (chest wall compliance), and (3) the resistance to air flow. Total work of breathing is the work per breath multiplied by the number of breaths per minute. Anything that increases dead space (high ventilation/perfusion [V/Q]) leads to tachypnea and increased minute ventilation to compensate for the diminished effective alveolar ventilation. Pathologies that decrease resting lung volume or compliance (ie., ARDS, obesity) will increase the effort per breath, and the resulting increase in intrapulmonary shunt (low V/Q) will cause hypoxemia, which will lead to tachypnea. What we observe clinically is respiratory effort and rate.

2.3 | Which NIRS system and when?

Clinicians should keep these overarching points in mind when selecting pressure-based or flow-based NIRS systems for respiratory care in the ED.

1. Both NIPPV and NHF systems reduce work of breathing but need to be utilized thoughtfully in consideration of the desired effect and the patient response based on the underlying etiology (Table 3).
2. A ventilator system is necessary to achieve true CPAP. Escalation to BiPAP can further reduce work of breathing.
3. For NHF systems, it is better to wean as patients improve rather than titrate as they worsen. Start with higher flow for greatest reduction in lung strain (tidal volume in relation to resting volume) and work of breathing, even if gas exchange is improved at lower flows.

3 | CONTROVERSIES OF NIRS

3.1 | Controversy #1: Should patients with ADHF be treated with NIPPV rather than NHF?

Cardiogenic pulmonary edema from ADHF occurs from high pulmonary venous pressure, leading to interstitial congestion and alveolar edema. When pulmonary venous pressure exceeds alveolar pressure (ie, West Zone III conditions), volume loss from extravascular lung water increases areas of intrapulmonary shunt and V/Q mismatch worsens. Combined, this creates a clinical respiratory failure syndrome with hypoxemia and increased work of breathing.

NIPPV improves cardiogenic pulmonary edema mainly through the respiratory and hemodynamic effects of PEEP.[6–8] A common misconception is that PEEP "pushes" edema out of the alveoli, but this is incorrect. Although there is some minor effect of a pressure gradient from the alveoli into the peri-alveolar lymphatics,[9] pulmonary edema is mainly improved through improving myocardial performance. PEEP improves the functional residual capacity and reduces both left ventricular preload and afterload, resulting in a rapid improvement in dyspnea, respiratory rate, and hypoxemia.[7]

TABLE 1 Characteristics of acute respiratory failure phenotypes.

Characteristic	ADHF	AECOPD	AHRF
Benefit of NIRS	Improve myocardial performance	Reduce inspiratory work of breathing Offset auto PEEP and dynamic airway collapse	Reduce V/Q mismatch Improve gas exchange Reduce work of breathing
Mortality	Low	Low	High
Efficacy NIPPV versus NHF	Unclear	Noninferior	Unclear
Resting lung volume	Normal to decreased	Increased	Decreased
Failure rates	Low	Low	High
Duration of NIRS support	Hours	Hours	Days
Pathophysiology	Pulmonary edema High cardiac filling pressures Poor contractility High vascular tone	Dynamic hyperinflation, bronchospasm, parenchymal loss	Loss of functional residual capacity, alveolar atelectasis or infiltrates, endothelial permeability, inflammatory cascade

Abbreviations: ADHF, acute decompensated heart failure; AECOPD, acute exacerbation of COPD; AHRF, acute hypoxemic respiratory failure; NHF, nasal high flow; NIPPV, noninvasive positive pressure ventilation; NIRS, noninvasive respiratory support.

Clinicians generally use NIPPV for ADHF, particularly CPAP. NHF is also used to treat ADHF but to a lesser extent. However, evidence directly comparing NIPPV and NHF is limited, and studies on NIPPV generally compare it with conventional oxygen rather than NHF.[10,11] Although there are ongoing trials,[12–14] recent evidence supports NHF as a viable alternative to NIPPV for treating ADHF.[15,16] Comparisons of NHF with NIPPV are only observational. One prospective study in hypercapnic patients with cardiogenic pulmonary edema found no difference in CO_2 clearance or work of breathing,[17] whereas a retrospective study showed increased odds of failure with patients with cardiogenic pulmonary edema or hypercapnia when treated with NHF.[18] The only published trial comparing the NHF with NIPPV showed helmet CPAP had a greater improvement in respiratory failure at 1 h.[19]

Little is known about the physiologic effects of NHF on acute cardiogenic pulmonary edema. However, given that NHF increases end-expiratory lung volume without the required positive intrathoracic pressure, the benefit for ADHF patients is likely from improved lung mechanics and gas exchange rather than myocardial performance.

3.1.1 | Implications for ED practice

Although guidelines strongly recommend NIPPV for ADHF, the evidence supporting this recommendation is only moderate quality (Table 2). Therefore, clinicians should consider both NIPPV and NHF as potential initial treatments for ADHF. For NIPPV, it is reasonable to start CPAP/EPAP at a moderate level (8–10 cm H_2O) and titrate upward according to tolerance, and add IPAP to further reduce the work of breathing. For NHF, it is the opposite approach—starting at a high flow to maximize end-expiratory lung volume and weaning based on work of breathing—may be the optimal approach (Table 3).

3.2 | Controversy #2: Should patients with AECOPD or hypercapnia be treated with NIPPV rather than NHF?

For AECOPD, dynamic airway collapse leads to air trapping, auto-PEEP, hyperinflation, and increased work of breathing from overstretched inspiratory muscles and resulting tachypnea. NIPPV can support each of these effects. If the EPAP is set *below* the auto-PEEP then the EPAP will attenuate dynamic airway collapse, reducing auto-PEEP and expiratory work of breathing without contributing to total PEEP. IPAP reduces the inspiratory effort (reducing inspiratory work of breathing) on already overstretched and fatigued inspiratory muscles.

NHF likely supports AECOPD through different mechanisms, primarily by flushing dead space, which clears CO_2 more efficiently and provides fresh gas at the beginning of inspiration.[20] Dead space clearance, and the increased end-expiratory lung volume support with NHF (which potentially could offset auto-PEEP), decreases inspiratory effort and reduces work of breathing,[21,22] and has shown to be relatively effective in AECOPD.[23–31]

NIPPV is currently considered standard of care for AECOPD,[32,33] yet data suggest there is utility for NHF. One observational study and a recent systematic review and meta-analysis found no difference in treatment failure or mortality between NHF and NIPPV in AECOPD.[34,35] NHF was statistically noninferior to NIPPV in a multicenter trial based on similar reductions in $PaCO_2$ at 2 h.[36] Despite a high crossover rate from NHF to NIPPV, a planned subgroup analysis showed the effect on PCO_2 and pH, intubation rates, and treatment failure rates were similar in hypercapnic patients.[37] NHF effectively reduced $PaCO_2$ in hypercapnic patients with primarily pneumonia and COPD.[25] These data suggest NHF is reasonable in AECOPD and patients with mixed etiology respiratory failure and hypercapnia, but more clinical trials are needed in this population.

TABLE 2 Pertinent clinical practice guidelines.

Guideline	Patient population	Statement	Strength of recommendation	Certainty of evidence
European Society of Intensive Care Medicine Pleural Pressure Working Group[95]	AHRF	"We recommend using HFNC compared to COT for patients with hypoxemic respiratory failure"	Strong	Moderate
European Respiratory Society/American Thoracic Society[96]	AeCOPD	"We suggest NIV not be used in patients with hypercapnia who are not acidotic in the setting of a COPD exacerbation."	Conditional	Low
	AeCOPD	"We recommend bilevel NIV for patients with ARF leading to acute or acute-on-chronic respiratory acidosis (pH ⩽7.35) due to COPD exacerbation."	Strong	High
		"We recommend a trial of bilevel NIV in patients considered to require endotracheal intubation and mechanical ventilation, unless the patient is immediately deteriorating."	Strong	Moderate
	ADHF	"We recommend either bilevel NIV or CPAP for patients with ARF due to cardiogenic pulmonary oedema."	Strong	Moderate
	ADHF	"We suggest that CPAP or bilevel NIV be used for patients with ARF due to cardiogenic pulmonary oedema in the pre-hospital setting."	Conditional	Low
	Asthma	"Given the uncertainty of evidence we are unable to offer a recommendation on the use of NIV for ARF due to asthma."		
	Immuno-compromised	"We suggest early NIV for immunocompromised patients with ARF."	Conditional	Moderate
	AHRF	"Given the uncertainty of evidence we are unable to offer a recommendation on the use of NIV for de novo ARF."		
	Trauma	"We suggest NIV for chest trauma patients with ARF."	Conditional	Moderate
European Society of Intensive Care Medicine[88]	AHRF	"We recommend that non-mechanically ventilated patients with AHRF not due to cardiogenic pulmonary edema or acute exacerbation of COPD receive HFNO as compared to conventional oxygen therapy to reduce the risk of intubation."	Strong	Moderate
		"We are unable to make a recommendation for or against the use of HFNO over conventional oxygen therapy to reduce mortality."	None[a]	
		"We are unable to make a recommendation for or against the use of HFNO compared to continuous positive airway pressure (CPAP)/ NIV to reduce intubation or mortality in the treatment of unselected patients with acute hypoxemic respiratory failure not due to cardio- genic pulmonary edema or acute exacerbation of COPD."	None[b]	
		"We suggest that CPAP/NIV can be considered instead of HFNO for the treatment of AHRF due to COVID-19 to reduce the risk of intubation (weak recommendation, high level of evidence), but no recommendation can be made for whether CPAP/NIV can decrease mortality compared to HFNO in COVID-19."	None	High
		"We are unable to make a recommendation for or against the use of CPAP/NIV compared to conventional oxygen therapy for the treatment of AHRF (not related to cardiogenic pulmonary edema or acute exacerbation of COPD) to reduce mortality or to prevent intubation."	None[c]	
		"We suggest the use of CPAP over conventional oxygen therapy to reduce the risk of intubation in patients with acute hypoxemic respiratory failure due to COVID-19."	Weak	low
		"In this population, we are unable to make a recommendation for or against the use of CPAP over conventional oxygen therapy to reduce mortality."	None[d]	
		"We are unable to make a recommendation for or against the use of helmet interface for CPAP/NIV as compared to face mask to prevent intubation or reduce mortality in patients with acute hypoxemic respiratory failure."	None[e]	Very low
		"We are unable to make a recommendation for or against the use of NIV compared to CPAP for the treatment of AHRF."	None	No evidence

[a]High level of evidence of no effect.
[b]Moderate level of evidence for mortality, low level of evidence for intubation, not in favor nor against.
[c]High level of evidence for mortality, moderate level of evidence for intubation.
[d]Moderate level of evidence of no effect.
[e]Very low level evidence in favor.

TABLE 3 Starting settings and what to monitor for NIRS in the ED.

	NHF	CPAP	NIPPV	Desired effect	When to intubate
Acute decompensated heart failure	FiO_2 = 100% Flow = based on comfort/dyspnea and SpO_2	FiO_2 = 100% CPAP = 8–10 cm H_2O, based on comfort/dyspnea and tolerance	FiO_2 = 100% EPAP = 8–10 cm H_2O based on tolerance IPAP[a] = 5+ adjust based on comfort/dyspnea	Positive end-expiratory pressure is needed to improve myocardial performance. PEEP, as well as the EELV with NHF will improve respiratory mechanics.	At 1–2 h if: Cardiogenic shock Depressed mental status Respiratory fatigue despite optimal NIRS support Consider in patients needing coronary angiography
Acute exacerbation of COPD	FiO_2 = 50% increase to keep SpO_2 88–90% Flow = maximum available for the system used.	FiO_2 = 50% increase to keep SpO_2 88–90% CPAP = 5–8 cm H_2O, based on work of breathing	FiO_2 = 100% EPAP[b] = 5–8 cm H_2O IPAP = 10–12 cm H_2O adjust based on work of breathing	Offset autoPEEP, reduce work of breathing, and improve ventilation.	At 1–2 h if: Respiratory fatigue despite optimal NIRS Depressed mental status Severe respiratory acidosis (pH < 7.2)
Acute hypoxemic respiratory failure	FiO_2 = 100% Flow = maximum available for the system used.	FiO_2 = 100% CPAP = 10 cm H_2O	FiO_2 = 100% EPAP[c] = 10 cm H_2O IPAP[d] = 5 cm H_2O, adjust based on tidal volume	Improve FRC and V/Q mismatch, reduce respiratory effort and overall work of breathing	Within 3–4 h if: High respiratory effort despite maximal flow with NHF or PEEP 10+ with NIPPV Unfavorable ROX index[e] (low SF ratio to a high respiratory rate) Tachypnea (RR > 30) despite maximal support Hypoxemia (SpO_2 < 90%)

[a]IPAP in ADHF is only for comfort and support of inspiratory work of breathing if needed.
[b]EPAP in AECOPD offsets dynamic airway collapse and autoPEEP, but IPAP is needed for inspiratory work of breathing to help offload the overstretched inspiratory muscles.
[c]EPAP in AHRF is needed to recruit any recruitable lung parenchyma to reduce overall inhomogeneity, improve functional residual capacity, and reduce V/Q mismatch.
[d]IPAP in AHRF reduces inspiratory work of breathing, but at the risk of injurious tidal volumes. The difference between IPAP and EPAP is the airway driving pressure to support ventilation. However, it is a complex relationship with respiratory effort. If tidal volumes are low, the EPAP may need to be increased to get above the critical opening pressure of dependent lung units, especially in patients with obesity or poor chest wall compliance.
[e]ROX index is the (SpO_2:FiO_2)/respiratory rate and is an assessment of the relationship between the degree of hypoxemia (SpO_2:FiO_2) to the work of breathing (respiratory rate).

3.2.1 | Implications for ED practice

Guidelines strongly recommend NIPPV for patients with AECOPD, hypercapnia *and* acidosis (Table 2). However, the best approach for AECOPD, hypercapnia *without* acidosis, is unclear. Since the cause of acute respiratory failure in most ED patients is likely undetermined when NIRS is started, NHF is a reasonable initial approach to AECOPD. If the patient exhibits acidemia with a high work of breathing on maximal NHF, clinicians may consider switching to NIPPV. Unlike ADHF where PEEP/CPAP is the pressure that most improves respiratory failure, in AECOPD it is the IPAP that most reduces work of breathing. So when using NIPPV, keep EPAP below auto-PEEP (5–8 cm H_2O) and increase inspiratory pressure support until work of breathing and minute ventilation improve (Table 3).

3.3 | Controversy #3: Should patients with AHRF should be treated with NHF rather than NIPPV?

In patients with AHRF, pneumonia, infection, or inflammation lead to volume loss from parenchymal airspace disease that reduces functional residual capacity and worsens V/Q mismatch. These changes lead to tachypnea and hypoxemia. As opposed to patients with AECOPD that have reduced inspiratory force from hyperexpanded lungs, patients with AHRF have increased inspiratory force via the Starling mechanism if respiratory effort is preserved. Also unlike patients with AECOPD or ADHF where NIRS is generally only required for a short duration, AHRF often requires respiratory support for longer durations and often worsens in the process while the underlying etiology is being treated.

NIPPV presents a double-edged sword in patients with AHRF. Spontaneous breathing on positive pressure can improve regional ventilation to dependent lung zones (improved V/Q mismatch),[38–40] which improves cardiopulmonary function[39,41] and prevents diaphragm atrophy.[42,43] These benefits are associated with fewer mechanical ventilation days[41,42,44] and potentially reduced inflammatory mediators in bronchoalveolar lavage analysis.[45,46] On the other hand, increased inspiratory force in the presence of inhomogeneous airspace disease leads to regional amplification of transpulmonary pressures (the difference between alveolar pressure and surrounding pleural pressure), which results in regional redistribution of intratidal volume (ie, *pendelluft* flow)—risking focal areas of barotrauma and

overall injurious tidal volumes (i.e., patient-self-induced lung injury [P-SILI]).[47–51]

NHF has several beneficial effects on respiratory mechanics in patients with AHRF that provide ventilation and oxygenation support beyond simply flushing anatomic dead space with fresh oxygen.[52] NHF provides flow-dependent effects on lung mechanics similar to NIPPV but without the pressure.[22,53–55] These benefits include lower esophageal pressure swings (reduced inspiratory effort), improved dynamic lung compliance (tidal volume/esophageal pressure change), a lower pressure-time product, and an overall reduction in lung strain (i.e., tidal volume/functional residual capacity).[54] There is a common misattribution of small amounts of PEEP generated by NHF. Although NHF does generate some positive pharyngeal pressure, there is a flow-dependent increase in end-expiratory lung volume (EELV, ie, functional residual capacity), that is relatively preserved despite almost complete loss of positive nasopharyngeal pressure (ie, "PEEP") when the mouth is opened on end-expiration.[4] This EELV increase, or PEEP-like effect, reduces atelectasis and increases oxygenation.[21,22,56] These findings suggest that the effect on oxygenation is unlikely through any positive pharyngeal pressure. Additionally, NHF may reduce respiratory drive and work of breathing without potentiating injurious tidal volumes.[54] Beneficial effects on work of breathing (respiratory rate) and oxygenation (oxygen saturation) can be seen as soon as 15 min after initiating NHF, with improvements in PaO_2 and PaO_2/FiO_2 ratio occurring within 1 h.[57] If flow rates with NHF sufficiently support the patient's inspiratory flow demand, the patient will be breathing an FiO_2 set by the system and undiluted by ambient air.

Clinical data for AHRF are complex to interpret. NIRS strategies are increasingly used as first-line treatment for AHRF, including for ARDS.[58–62] NIPPV and NHF are both associated with better outcomes (reduced intubation rates, pneumonia, ICU stay and mortality) than conventional oxygen therapy, but there are few direct comparisons of NHF versus NIPPV,[10,11,32,33,60,63–66] at least until the COVID-19 pandemic. Observational studies report high NIPPV failure rates in patients with AHRF, which are associated with an increased mortality and longer ICU stay.[62,67–70] NIPPV was the first-line treatment modality in 15% of patients in a large observational study, with an overall failure rate of 32%,[62,71] which linearly increased with the severity of ARDS (22% in mild ARDS, 42% in moderate, 47% in severe), and carried a 30% increase in mortality (45 vs. 16%).[62]

The landmark FLORALI trial showed a reduced 90-day mortality with NHF in differentiated ICU patients with AHRF due to pneumonia, a secondary outcome, but no difference in intubation rates.[72] However, the patients selected for FLORALI came from the ICU setting and had well-defined diagnoses. These results are difficult to extrapolate to the ED, where the cause of the patient's ARF is often initially undifferentiated and a NIRS strategy must be selected prior to a clear diagnosis. Doshi et al[73] showed that NHF was noninferior to NIPPV for intubation rates in a broad, in a small trial of undifferentiated ED patients.

NIRS studies in AHRF due to COVID-19 show wildly disparate results. Some show improved outcomes with NHF compared with conventional oxygen[74–76] or NIPPV.[77] Some show improved outcomes with NIPPV compared with conventional oxygen[78] or NHF.[79] Some show no difference when compared with conventional oxygen[76,78,80–82] or each other.[79,80,83–85] However, the increased use of NIRS during the COVID-19 pandemic advanced our knowledge of NIRS-related physiology in AHRF and led to a rethinking of the definition of ARDS.[86–90]

Recent systematic reviews and meta-analyses show that NIRS is associated with reduced intubation and mortality, but the benefits are skewed by helmet NIPPV. One meta-analysis showed that both NIPPV and NHF reduced intubation and mortality compared with conventional oxygen, but no difference between facemask NIPPV and NHF.[91–93] Three studies showed no difference in intubation and mortality between NIPPV and NHF.[91–93] However, a subgroup analysis showed that NHF was associated with a lower intubation rate than NIPPV in patients with a low PaO_2:FiO_2 ratio < 150), but not [relatively] high PaO_2:FiO_2 ratios.[94] Several clinical practice guidelines have attempted to synthesize the evidence into guidelines in recent years, and pertinent recommendations are summarized in Table 2.[89,95,96] Overall, more high quality trials are needed for patients with AHRF, as highlighted by the most recent guidelines from the European Society of Intensive Care Medicine.

3.3.1 | Implications for ED practice

The guidelines are relatively uninformative for ED patients given the complexity in interpreting the disparate data (Table 2). The data overall suggest there is equipoise among NHF and NIPPV in patients with AHRF. Since the goal with either NIRS modality in AHRF is to reduce the work of breathing, start with maximal flow when using NHF and higher PEEP (10 cm H_2O) when using NIPPV to maximize end-expiratory lung volume, functional residual capacity, and reduce VQ mismatch and inspiratory force (Table 3). We recommend using a noninvasive ventilator for NIPPV, rather than alternative options such as PEEP valves or flow generated CPAP valves unless in prehospital or resource limited settings.

3.4 | Controversy #4: Does NIRS failure increase the risk of death?

NIRS failure, particularly NIPPV, is associated with excess mortality,[62,97,98] raising the question whether there is confounding (ie, "sicker patients failed and their mortality is higher.") or if one or all NIRS modalities may be iatrogenically injurious. Recent evidence suggests there are potential risks to spontaneous breathing on positive pressure in some patients with AHRF and high respiratory drive that may worsen lung injury.[48–51] There is a complex relationship between neural and peripheral contributions to respiratory drive and effort.[99] High respiratory effort while spontaneously breathing on positive pressure perpetuates injurious tidal volumes.[47,97,100,101] In addition, the inhomogeneous amplification of transpulmonary pressures generated from high respiratory effort breaths are thought to contribute to P-SILI, which is a, if not the, suspected mechanism for the observed high failure rates and excess mortality with NIRS

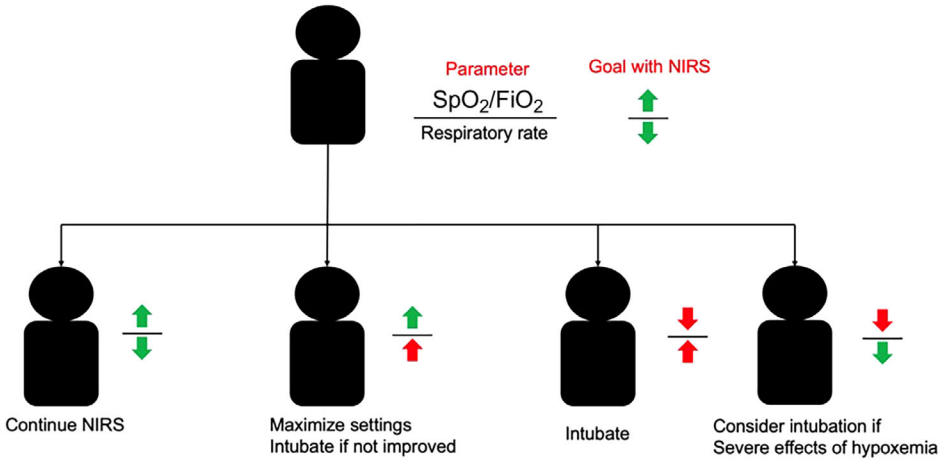

FIGURE 3 Conceptually monitoring for failure. The goal with NIRS is to improve oxygenation and reduce work of breathing. Although the ROX index was developed for monitoring NHF, conceptually it provides an excellent framework for clinically monitoring patients for failure. This framework is not comprehensive and has some limitations, but oxygenation is determined by the SpO_2/FiO_2 ratio (an indicator of severity of intrapulmonary shunt), and work of breathing by the respiratory rate. If the patient requires a low FiO_2 to maintain a good oxygen saturation (high SpO_2/FiO_2 ratio) and the respiratory rate is decreased, continue NIRS and monitor. However, if the respiratory rate remains high (typically >30) on optimized NIRS (maximal flow on NHF and optimized pressures on NIPPV), the patient should be intubated. If neither parameter is improved, the patient should be intubated early as NIRS is not meeting its goal. The tougher situation is the patient that has an improved respiratory rate but still requires a high FiO_2 to maintain an acceptable or marginal oxygen at saturation (low SpO_2/FiO_2 ratio). In this case, as long as the work of breathing is down, the options are to add an inhaled pulmonary vasodilator, tolerate the hypoxemia if no signs of organ dysfunction, or intubate. NIRS, noninvasive respiratory support; NHF, nasal high flow; NIPPV, noninvasive positive pressure ventilation.

failure.[60,62,64,67,70,71,102,103] This high drive can potentially be reduced with higher levels of PEEP,[104] but this generally requires a helmet. This likely, at least partially, explains the improved outcomes with helmet NIPPV compared with facemask NIPPV.[63] Thus, there remains a double-edged sword with NIRS. Successful use of NIRS improves outcomes (reduced mortality, ventilator days, etc), whereas an unsuccessful trial of NIRS may increase mortality. As a result, identifying the mechanisms underlying failure and reliable methods of predicting failure are arguably the most important knowledge gap for the future of NIRS.

Predicting failure using widely available clinical data is challenging. Several studies have identified factors either associated with or predictive of failure for both NIPPV and NHF that all generally involve indices of work of breathing or severity of hypoxemia in some form or another.[57,68–70,97,105–110] The ROX index [(SpO_2/FiO_2)/respiratory rate], was derived and validated to determine whether a patient is likely to succeed or fail NHF.[111] Values > 4.88 have fairly good predictive value for not requiring intubation, whereas values < 2.85 at 2 h, < 3.47 at 6 h, and < 3.85 at 12 h were predictors of NHF failure,[111] leaving a large uninformative middle range of values. Additionally, the ROX index is only validated for one specific type of high flow system and is largely flow dependent, with increases in ROX index when going from 30 to 60 L per minute of flow potentially reflecting higher severity of lung disease rather than effort.[112] More recent work has used deep learning models to develop predictive algorithms to identify patients at risk of requiring mechanical ventilation in hospitalized COVID-19 patients,[113] and predicting NIRS failure in patients with acute respiratory failure, with very promising results.[114]

3.4.1 | Implications for ED practice

Identifying failure early is critical. Although patients may have adequate oxygenation or ventilation, if respiratory effort is not reduced, those patients are at high risk of eventual failure, intubation, and a higher mortality. Special attention should be paid toward assessing respiratory effort despite oxygenation. Conceptually, the ROX index can assess the degree of hypoxemia and shunt (SpO_2/FiO_2) to the work of breathing (respiratory rate) regardless of NIRS modality (Figure 3). If there is adequate oxygenation and low work of breathing, risk of failure is low. If there is adequate oxygenation and high work of breathing, or high shunt and high work of breathing, then intubation should not be delayed. With rare exceptions in patients with AHRF, failure of one NIRS modality to reduce work of breathing should be considered an indication for intubation, not crossover to the other NIRS modality.

3.5 | Controversy #5: Are patients managed with NIPPV at greater risk of P-SILI than with NHF?

To date, P-SILI is largely a theoretical risk without clear evidence, however two recent studies have shown direct evidence in support of the P-SILI hypothesis. Grieco et al[98] compared inspiratory effort ($\Delta P_{esophageal}$) between NHF and helmet NIPPV in patients with AHRF in a crossover trial. The transpulmonary pressure swing (ΔP_L) was overall higher with NIPPV, especially when inspiratory effort was low in patients on NHF. However, those with high inspiratory effort while on NHF had the largest reduction in effort when crossed over to helmet NIPPV, indicating that NIPPV was protective for some patients

and injurious for others. High inspiratory effort and transpulmonary pressure swings were associated with requiring intubation later at 12 hours in those treated with NIPPV, but that association was not significant for NHF.[98] These findings were further supported in the second study, where Tonelli et al[105] enrolled patients with AHRF to NIPPV by facemask with PEEP set at 4–8 cm H_2O and pressure support titrated to keep tidal volume < 9.5 mL/kg. Patients that failed NIPPV by 24 hours had significantly increased inspiratory effort ($\Delta P_{esophageal}$) and transpulmonary pressure (ΔP_L) at 2 hours than patients that were successfully treated with NIPPV.[105] These patients also had worsened chest imaging at 24 hours, whereas patients with reduced inspiratory effort at 2 hours had improved imaging at 24 hours. $\Delta P_{esophageal}$ changes <10 cm H_2O at 2 hours of NIPPV most accurately predicted NIPPV failure at 24 hours.[105]

Essentially, the negative correlation between inspiratory effort ($\Delta P_{esophageal}$) and lung compliance ($VT/\Delta P_L$) means that when vigorous spontaneous effort is present, the baseline reduced lung volumes proportionally increase the strength of spontaneous effort because of greater diaphragmatic contractile force via the Starling mechanism. Additionally, a higher spontaneous effort is associated with more failure, despite similar distending pressures.[105] The increased spontaneous effort results in *pendelluft* and local overdistention of dorsal lung regions, which causes P-SILI.

Pressure-based support with NIPPV also likely increases the risk of P-SILI through high transpulmonary pressure swings, which are inhomogenously distributed and exaggerated if inspiratory effort is preserved. Flow-based support with NHF increases resting lung volume without an increase in tidal volume or pressure as is the case with NIPPV, theoretically reducing the risk for P-SILI. However, NHF has several physiological effects that may either increase or decrease the risk of failure and/or P-SILI in patients with AHRF depending on which predominates[4]—another knowledge gap. Higher flows, particularly with the mouth closed, increase inspiratory resistance that requires increases in inspiratory muscular contraction to generate an equivalent tidal volume. This increases the overall work per breath and the regional amplification of the increased work per breath would increase regional strain resulting in more *pendelluft* flow. However, the increase in end-expiratory lung volume and unchanged tidal volume would reduce both global and regional strain and work per breath, resulting in reduced *pendelluft* flow, assuming effort is decreased. The increased expiratory resistance may decrease the pressure-time product by prolonging the exhalation phase to reduce the respiratory rate and overall work of breathing. In both the Grieco et al[98] and Tonelli et al[105] studies, inspiratory effort was not significantly correlated with the severity of hypoxemia (PaO_2:FiO_2), limiting the ability of PaO_2:FiO_2 to identify patients with harmful respiratory effort—another key knowledge gap to find reliable clinical methods of measuring and monitoring respiratory effort.

3.5.1 | Implications for ED practice

There are limited data on the risk of P-SILI for each modality, although the risk is theoretically lower with NHF given the proposed mechanisms. Until future studies can inform these risks and illuminate the underlying physiology, vigilance on monitoring for failure is critically important. Pitfalls based on current evidence include delaying intubation in a patient with high work-of-breathing because of falsely reassuring gas exchange and crossover from one NIRS modality to the other.

4 | CONCLUSION

NIRS use in the ED will continue to increase, especially as visits and ED length of stay continue to climb postpandemic.[3] ED management of respiratory failure carries momentum affecting the subsequent hospital course and outcomes for patients with acute respiratory failure.[115–118] Consequently, it is important for the emergency physician to understand how each NIRS modality works, the goals in each form of respiratory failure, and even more critically how to monitor for, and act on failure.

AUTHOR CONTRIBUTIONS

J. M., H. E. W., and M. T. conceptualized the paper. J. M. wrote the initial draft. All authors critically reviewed, edited, and approved for publication.

CONFLICT OF INTEREST STATEMENT

J. M. and H. E. W. have received travel support from Fisher & Paykel.

DATA AVAILABILITY STATEMENT

Not applicable.

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How to cite this article: Mosier JM, Tidswell M, Wang HE. Noninvasive respiratory support in the emergency department: Controversies and state-of-the-art recommendations. *JACEP Open*. 2024;5:e13118. https://doi.org/10.1002/emp2.13118