



Review Article

Tailoring non-invasive respiratory supports in acute hypoxemic respiratory failure: A practical approach for clinicians

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ABSTRACT

The use of non-invasive respiratory support (NIRS) for acute respiratory failure (ARF), particularly hypoxemic respiratory failure, has advanced in recent years, especially during the COVID-19 pandemic. NIRS modalities like high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), and non-invasive ventilation (NIV) have shown efficacy, though evidence is inconsistent, especially for “de novo” acute hypoxemic respiratory failure (AHRF). This review outlines the physiological rationale for NIRS and offers practical guidance on tailoring treatment to individual patients. Successful AHRF management with NIRS requires a personalized approach, guided by clinical expertise. Further research is needed to refine patient selection and optimize NIRS application.

Points for clinical practice

- Guidelines give strong recommendations for the use of NIRS (ie NIV) in situations such as acute respiratory acidosis in exacerbated COPD patients and AHRF due to cardiogenic pulmonary edema
- Guidelines for NIRS now include HFNC and CPAP among the options for treatment of other forms of AHRF.
- The clinical goals of NIRS are to avoid ETI and improve oxygenation while minimizing risk of contributing to lung injury and avoiding delay of a needed intubation
- It is important to stratify patients at high risk of developing or worsening lung injury and to consider that exposure to the risk of developing P-SILI may be different when using different NIRS strategies.
- It is important to identify patients who have higher inspiratory effort and determine approaches for modulating it in order to select the ideal NIRS for this purpose.

1. Introduction

In the last-years including the COVID-19 pandemic, the understanding of non-invasive respiratory support (NIRS) to treat acute respiratory failure (ARF) has evolved. Research has provided much evidence on the use of NIRS (including high flow nasal cannula (HFNC), continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) to treat ARF, but the evidence is often conflicting, especially regarding use for “de novo” acute hypoxemic respiratory failure (AHRF). This review presents up-to-date information regarding use of NIRS in ARF, mainly “de novo” hypoxemic. We first examine the physiological rationale for use of NIRS in ~~ARF~~ AHRF, and then highlight the goals and approaches to implement when selecting patients and techniques to achieve optimal benefit.

2. Hypoxemic respiratory failure and “De novo” Hypoxemic respiratory failure

Hypoxemic respiratory failure is characterized by severe hypoxemia, significant respiratory distress, tachypnea, and normal or low levels of carbon dioxide (normocapnia or hypocapnia). “De novo” Hypoxemic respiratory failure is caused by non-COPD conditions leading to acute respiratory failure, such as ARDS, acute pneumonia, trauma, or acute

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pulmonary edema, and excludes respiratory failure occurring in the immediate postoperative or postextubation period. Four primary pathophysiological mechanisms contribute to the hypoxemia 1) ventilation/perfusion mismatch, 2) increased shunt, 3) impaired diffusion, and 4) alveolar hypoventilation. The most common cause is ventilation/perfusion mismatch, where ventilation is reduced in normally perfused regions or more significantly reduced than perfusion in certain areas. In shunt conditions, deoxygenated blood bypasses ventilated alveoli, causing venous admixture. Impaired diffusion occurs when conditions lengthen the distance for oxygen to travel from alveoli to capillaries, decrease capillary surface area, or reduce transit time. While changes in ventilation (VA) affect PaCO₂, they have less impact on PaO₂, with small increases in VA causing only a modest rise in PaO₂, especially once it exceeds 7.3–8.0 kPa (55–60 mmHg) due to the oxyhemoglobin dissociation curve's sigmoidal shape [1].

3. Physiological rationale for the use of NIRS in AHRF

3.1. HFNC

The mathematical model that relates pressure, volume, and flow during ventilation is the equation of motion for the respiratory system:

$$\text{muscle pressure} + \text{ventilator pressure} = (\text{elastance} \times \text{volume}) + (\text{resistance} \times \text{flow}).$$

It has two constants (elastance and resistance) and three variables (pressure, volume, and flow), with time acting as an inferred variable. It is evident from the equation that volume is a function of flow, and pressure is a function of both volume and flow. As a result, only one single variable can be changed at a time. A CPAP system is designed to hold a constant positive Paw (control variable = pressure) throughout the entire respiratory cycle (inspiration and expiration). Conversely, with HFNC, flow is preset (control variable = flow), and Paw depends on the respiratory system's elastance and resistance. During inspiration with HFNC, Paw depends on the relative flows of HFNC and the patient's inspiration crossing through an unknown and continuously variable resistance constituted by the airways. If patient inspiratory flow is high enough, inspiratory Paw can be negative.

HFNC provides gas flows that match or even exceed the elevated inspiratory flows that patients with AHRF achieve, thus reducing entrainment of ambient air and assuring higher and more reliable FIO₂s than oxygenation techniques using lower flows [2–6]. By supplying heated and humidified gas at body conditions, it facilitates pulmonary mucociliary clearance and avoids mucus plugs, resulting in a decrease in inspiratory resistance [7–13]. HFNO also enhances CO₂ washout from anatomical dead space [14,15]. The higher the delivered flow and longer the inspiratory time, the greater the CO₂ washout. This improves efficiency of ventilation, and may have an ameliorative effect on progressive hypercapnic failure, slightly reducing PaCO₂ [16–18]. At lower respiratory rates (RR), raising HFNC flow rates does not increase washout, but at higher RRs, higher flow rates increase CO₂ clearance as well as nasopharyngeal pressure [19]. HFNC increases expiratory impedance by the effect of the high flows against exhaled air, increasing expiratory pressure and thereby end-expiratory lung volume [20]. Increasing HFNC flow also increases airway pressure (Paw) which is influenced by mouth closure. Respiration with a closed mouth substantially increases Paw compared to open-mouth respiration [20,21]. High flows of 60 L/m can induce an expiratory Paw comparable to a CPAP of 4–6 cmH₂O when breathing with the mouth closed [21]. HFNC reduces inspiratory effort compared to conventional oxygen therapy (COT), associated with an increase in the VT to esophageal pressure swing ratio (Vt/ΔPes), indicating an improvement in the mechanical properties of the respiratory system [22]. In other words, the same VT can be delivered with less inspiratory effort.

Recently, asymmetric nasal cannulas have been designed to enhance

the CO₂ washout effect and provide a mild positive distending pressure effect. An in vitro study [23] has shown that, with these cannulas, the flow from the larger prong is directed toward the contralateral cavity, creating a reverse flow. The nostril of the smaller prong creates a low-resistance path to expel the exhaled gas, thereby optimizing the washout effect. This optimization of the washout effect allows for a washout similar to that achieved at lower RRs, even at higher RRs, where clearance time is reduced. Recent studies have demonstrated that the asymmetrical HFNC interface decreases minute ventilation and reduces the work of breathing (WOB), as indicated by a reduction in the inspiratory esophageal pressure-time product, in patients with mild-to-moderate hypoxemic respiratory failure, compared to the standard interface, with no impact on PaCO₂ or oxygenation [23]. Similarly, in the hypercapnic population recovering from an acute exacerbation of COPD, asymmetrical cannulas do not significantly reduce PaCO₂ or improve PaO₂ compared to the standard cannula. Interestingly, the asymmetrical NHF cannula performed significantly better in reducing dead space ventilation and increasing ventilatory efficiency in more advanced COPD patients with severe hypercapnia and higher baseline PaCO₂ values (PaCO₂ ≥ 65 mmHg). Further research regarding asymmetrical cannulas is needed to fully explore their potential benefits [24, 25].

To recap; HFNC increases expiratory impedance, generating an increment in Paw and lengthening expiratory time (Te), decreasing RR and reducing minute volume. Moreover, longer Te, as well as the size or the type of the cannula, may allow more time for dead-space CO₂ washout [19,23]. It is also important to highlight that HFNC differs from CPAP in the way Paw is generated [21,26].

3.2. CPAP (or PEEP)

CPAP or PEEP (taken here as a synonym for CPAP) helps to maintain an adequate functional residual capacity (FRC) and reduces airway resistance, thereby enhancing oxygenation and can improve the patient's WOB. When PEEP achieves alveolar recruitment, it improves lung/respiratory system compliance, reduces intratidal alveolar opening and closing and mitigates the risk of self-inflicted lung injury [27–30]. However, actions of PEEP on gas exchange and pulmonary mechanics may be variable [31]. For example, PEEP levels that are set too high minimize the mechanical advantage of the diaphragm due to flattening, lower cardiac output, and overdistend lung parenchyma reducing lung compliance [32].

3.3. PEEP + PS (NIV)

PEEP alone, which is associated with unsupported spontaneous breathing, is unable to reduce the esophageal pressure swings in AHRF [33] (although it does in patients with COPD and auto-PEEP) (28). Adding pressure support (PS) to PEEP during NIV unloads inspiratory muscles, forestalls fatigue, improves patient comfort and alleviates subjective patient-reported dyspnea. Also, PS increases tidal volume (VT), improving alveolar ventilation, and can significantly lower PaCO₂, especially in hypercapnic patients. However, the positive attributes of PS can be negated when high leaks are present, which contribute to monitoring errors, asynchrony and intolerance [34]. In addition, the effects of NIV may differ depending on the type of interface used (helmet vs. face mask), or the underlying cause of respiratory failure.

4. NIV, CPAP or HFNC? Tailoring treatment for patients with acute hypoxemic respiratory failure

4.1. What do the guidelines say?

In 2023, the European Society of Intensive Care Medicine (ESICM) updated its guidelines for AHRF/ARDS, including the use of NIRS for managing AHRF, particularly in mild to moderate cases [35]. This

marked a shift from older guidelines [36], which recommended CPAP and NIV but excluded HFNC due to insufficient evidence. In the same line, the ERS/ATS [37] strongly supported CPAP or NIV in AHRF caused by cardiogenic pulmonary edema (CPE) to reduce intubation and mortality but offered no recommendation on the use of NIV in de novo AHRF. They did allow NIV trials for selected, cooperative patients with isolated AHRF, provided they were closely monitored in an ICU and had no contraindications like abnormal mental status, shock, or multi-organ failure.

Table 1 summarizes current guidelines recommendations for the use of NIRS in ARF as per the ERS/ATS NIV Guidelines [37], ERS HFNC Guidelines [38] and ESICM Guidelines [35]. They now include HFNC among the possible treatments for AHRF/ARDS. However, recommendations are conflicting, and they are not particularly helpful when deciding on which NIRS modality to apply to an individual patient. The uncertainty of the statements comes from addition of newer studies and the differing methodologies of randomized controlled trials (RCTs) yielding different outcomes [39–44]. For instance, some data show that

HFNC may be preferred to NIV to treat AHRF [39,43]. Other research suggests that different interfaces and settings may affect results, which makes comparing NIV, CPAP, and HFNC particularly challenging [44]. A detailed analysis of the similarities and differences between the various guidelines is beyond the scope of this treatise, but one outcome for which there is unanimous agreement is that delaying a needed endotracheal intubation (ETI) increases mortality [45–50].

The many studies performed during the pandemic have, unfortunately, not provided much clarity on the confusing and conflicting state of guidelines relating to application of various NIRS modalities in AHRF (Table 1). Performing well-designed studies with high quality data is very challenging during a pandemic. Most of the studies were low quality, and even the higher quality studies had highly disparate methods such as variations in patient populations, differing locations within hospitals (ICUs vs non-ICUs) and geographically, differing interventions, comparators, interfaces and variable techniques of application. Performing meta-analyses that can yield useful, interpretable results is well-nigh impossible. Thus, it is not surprising that guidelines

Table 1

Relevant recommendations and certainty of evidence selected from current Guidelines. (From 35, 37, 38).

Situation	Type of NIRS recommended	Recommendation	Certainty of evidence	Guidelines
Acute or acute-on-chronic respiratory acidosis in exacerbated COPD patients	Suggested NIV over HFNC, to reduce mortality or ETI	Conditional recommendation,	Low certainty of evidence	ERS HFNC in ARF, 2022 (35) ERS/ATS NIV in ARF 2017 (34) ERS/ATS NIV in ARF 2017 (34)
	Recommended NIV, as an alternative IMV (especially if pH ≤ 7.35) Recommended a trial of NIV, to prevent ETI (unless the patient is immediately deteriorating)	Strong recommendation	High certainty of evidence	
ARF due to ACPE	Recommended either NIV or CPAP, to reduce ETI and mortality (CPAP in those with hypoxemia; NIV in those with hypoxemia, hypercapnia and tachypnea, or concomitant COPD or neuromuscular disease) <u>In pre hospital setting:</u> suggested NIV or CPAP	Strong recommendation	Moderate certainty of evidence	ERS/ATS NIV in ARF 2017 (34) ERS/ATS NIV in ARF 2017 (34)
		Conditional recommendation	Low certainty of evidence	
AHRF (<u>not due</u> to ACPE)	Suggested HFNC over COT to reduce ETI, to improve oxygenation and to improve comfort	Conditional recommendation	Moderate certainty of evidence	ERS HFNC in ARF, 2022 (36) ERS HFNC in ARF, 2022 (36) ESICM ARDS and RSS 2023 (32) ESICM ARDS and RSS 2023 (32) ESICM ARDS and RSS 2023 (32) ESICM ARDS and RSS 2023 (32) ESICM ARDS and RSS 2023 (32)
	HFNC over NIV to reduce ETI and mortality	Conditional recommendation	Very low certainty of evidence	
	Recommended HFNO over COT, to reduce the risk of ETI	Strong recommendation	Moderate level	
	No recommendation for or against HFNO vs COT, to reduce mortality		High level of evidence of no effect	
	No recommendation for or against CPAP/NIV vs COT, to reduce mortality or to prevent ETI		High level of evidence for mortality	
	No recommendation for or against HFNO vs CPAP/ NIV, to reduce ETI or mortality		Moderate level of evidence for ETI	
	No recommendation for or against NIV vs CPAP		Moderate level of evidence for mortality, Low level of evidence for ETI, not in favor nor against	
No recommendation for or against the use of helmet vs face mask interface for CPAP/ NIV, to prevent intubation or reduce mortality		No evidence		
AHRF due to COVID-19	No recommendation for the use of NIV for de novo ARF		Very low level of evidence in favor	ESICM ARDS and RSS 2023 (32) ERS/ATS NIV in ARF 2017 (34)
	Suggested CPAP/NIV over HFNO, to reduce the risk of ETI	Weak recommendation	High level of evidence	ESICM ARDS and RSS 2023 (32)
	Suggested CPAP over COT, to reduce the risk of ETI	Weak recommendation	Low level of evidence in favor	ESICM ARDS and RSS 2023 (32)
	No recommendation for or against the use of CPAP/NIV vs HFNC, to reduce mortality		High level of evidence of no effect	ESICM ARDS and RSS 2023 (32)
	No recommendation for or against the use of CPAP vs COT, to reduce mortality		Moderate level of evidence of no effect	ESICM ARDS and RSS 2023 (32)

NIRS: Non-invasive respiratory supports; RSS: Respiratory Support Strategies; COPD: Chronic Obstructive Pulmonary Disease; ACPE: Acute Cardiogenic Pulmonary Edema; ARF: Acute Respiratory Failure; AHRF: Acute Hypoxic Respiratory Failure; NIV: non-invasive ventilation; IMV: invasive mechanical ventilation; HFNC: high flow nasal cannula; COT: Conventional Oxygen Therapy; CPAP: Continuous Positive Airway Pressure; ETI: Endotracheal Intubation; LOS: Length Of Stay.

such as those from the ESICM [35] cannot make any firm recommendations on which modality of NIRS is preferred under certain circumstance.

Despite the uncertainty of the current evidence, expert consensus suggests that clinicians managing AHRF patients with NIRS should have appropriate expertise including an understanding of the patient’s pathophysiology and have knowledge and experience in the application of the various modalities. It is also suggested by studies showing non-inferiority of HFNC, for example, compared to NIV in a variety of different forms of ARF [51], that clinicians could select HFNC, NIV or CPAP to achieve the same successful outcome in many patients with mild to moderate AHRF [52]. On the other hand, there are others with more severe AHRF or high inspiratory effort who might do better, on an individual basis, on particular settings of one modality versus another. It is also well to keep in mind that application of NIRS modalities is not mutually exclusive and a combination of modalities, such as NIV alternating with HFNC, may be more successful in a given patient than either used alone.

Patient tolerance of NIRS modalities is also a major determinant of selection of NIRS modality, for example, some patients become claustrophobic and intolerant of CPAP/NIV face masks and can only tolerate HFNC. In light of the above, the following paragraphs provide some strategies for providing NIRS to challenging patients with AHRF, based on physiologic principles.

4.2. Avoiding VILI and P-SILI

In the past 70 years, much knowledge and experience have accrued regarding positive pressure mechanical ventilation in general [53]. Early on, IMV, often via tracheostomy, was used to improve gas exchange and facilitate breathing. However, as time passed, the paradigm evolved and the goal now is to keep the patient alive while avoiding ventilator-induced lung injury (VILI) [54,55] and other complications. In invasively ventilated patients with AHRF, permitting spontaneous breathing (SB) helps to reduce diaphragm atrophy and improve lung aeration [56–59]. Many studies have found that SB may be beneficial for those with mild respiratory failure [60,61]. Yoshida et al [61] found that in mild lung injury, SB benefits lung recruitment; yet, in animals with severe lung injury, SB could also worsen lung injury. Nonetheless, SB could be deleterious as elucidated by the concept of patient self-inflicted

lung injury (P-SILI); it could lead to an aggravation of lung injury through changes in global or regional pressure, even without any ventilatory support [61,62].

The clinical goals of NIRS in AHRF are to avoid ETI, improve oxygenation, optimize comfort, and avoid complications such as occur with a delayed intubation. However, despite trying to achieve these goals, it is important to avoid P-SILI by stratifying patients according to their risk of developing or aggravating lung injury as a consequence of excessive respiratory drive. (Fig. 1). Increased respiratory drive derives from the complex interactions of multiple factors, including impaired gas exchange, altered lung mechanics, inflammatory stimuli, and neurological triggers [63]. Intense inspiratory effort may induce or worsen lung injury by excessive inspiratory swings that abnormally increase dynamic transpulmonary pressure (P_{Ldyn}) and lung stress [64]. This generates large VTs in a lung with a markedly reduced compliance due to aeration loss, thereby increasing both barotrauma and volutrauma. Furthermore, this large negative deflection in pleural pressure increases vascular transmural pressure and vessel permeability, contributing to alveolar flooding [65,66]. Moreover, intense inspiratory effort can potentially harm the diaphragm, leading to diaphragm myotrauma and dysfunction [66,67]. On the other hand, strong contractions of the expiratory muscles can reduce end-expiratory lung volumes, raising the risk of lung collapse and increasing the regional stress during subsequent inspiration [68,69].

"P-SILI" refers to the situation in which a patient with injured lungs and high respiratory drive inhales vigorously, leading to global/regional pressure/volume changes and exacerbation of the initial lung injury (dynamic lung stress) [70] (Fig. 2). Therefore, one purpose of NIRS would be to reduce inspiratory efforts, if possible, or at least to minimize lung stress, reducing the risk of P-SILI. Consequently, the appropriate balance between protecting the patient from P-SILI and improving oxygenation should be achieved (Fig. 3 and Fig. 4).

Therefore, the first challenge is to stratify patients according to their risk of developing or exacerbating lung injury and identify patients at high risk by virtue of their higher inspiratory effort. The second challenge is to determine approaches for modulating this risk, ideally by selecting the NIRS modality most appropriate for this purpose. The third challenge is to tailor the settings on the selected NIRS to achieve optimal outcomes (Fig. 1).

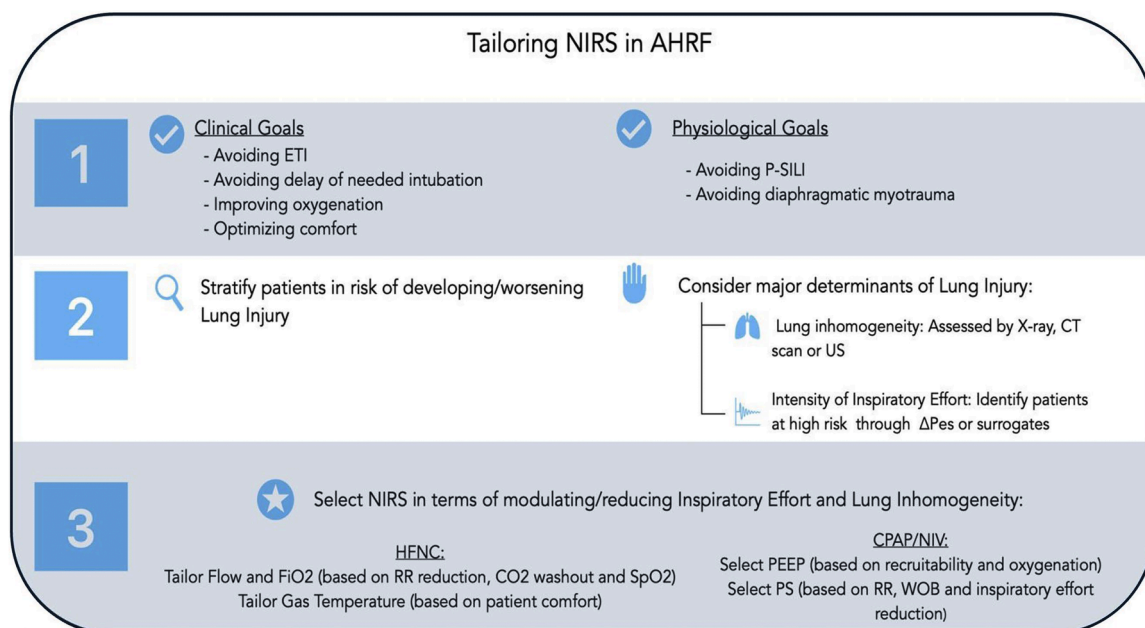


Fig. 1. Goals and suggested pathways when selecting the right non-invasive respiratory support (NIRS) in acute hypoxemic respiratory failure (AHRF).

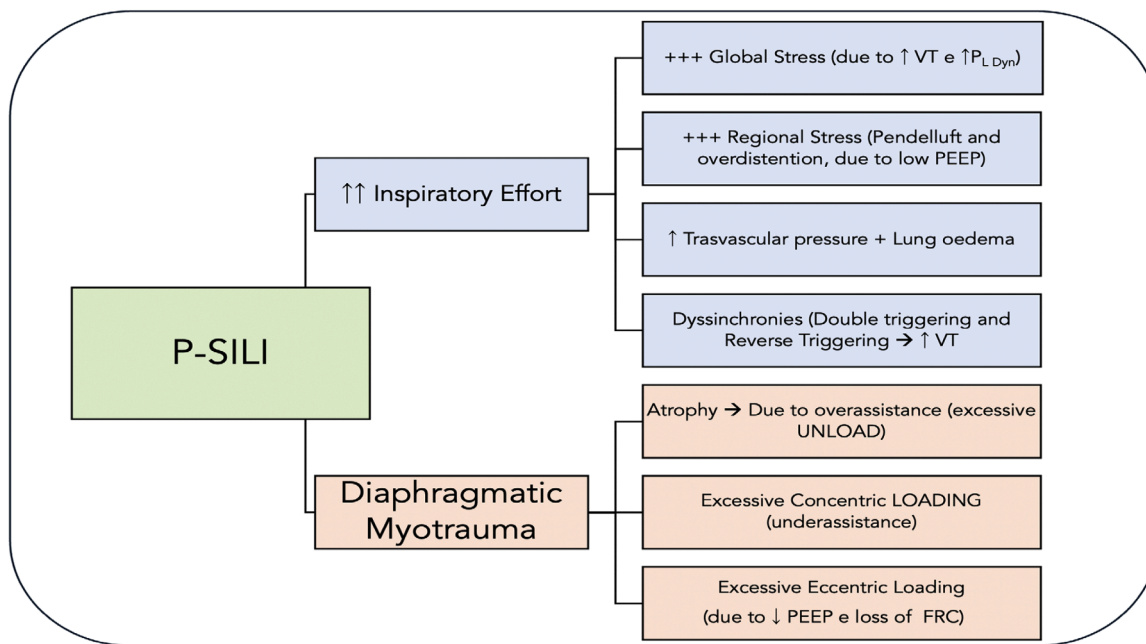


Fig. 2. Vigorous inspiratory efforts during spontaneous breathing may result in lung injury, affecting both the lung (P-SILI) and the respiratory muscles (myotrauma). Overstretching the diaphragm may worsen lung damage by increasing stress and strain applied to the lung. Strong effort with significant tidal volume (Vt) mobilization may also increase dynamic transpulmonary pressure (P_{L dyn}) and global stress. Regional stress occurs when parenchyma with different lung compliance are derecruited and overdistended (pendelluft and atelectrauma) due to insufficient PEEP application, enhancing inspiratory effort and stress. Also, increased efforts raise transvascular pressure, resulting in increased pulmonary edema. Finally, dyssynchronies during mechanical ventilation, such reverse or double triggering, can lead to increased Vt. (FRC: Functional Residual Capacity; P_{L Dyn}: dynamic transpulmonary pressure).

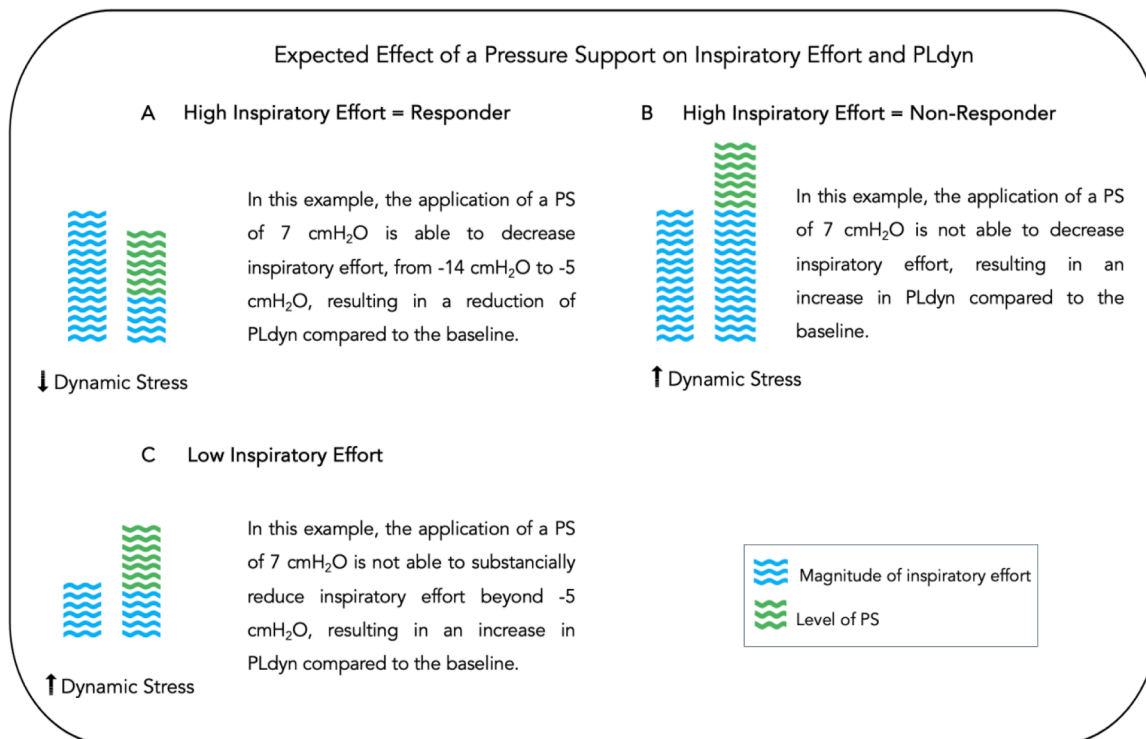


Fig. 3. Illustration of effects of intensity of inspiratory effort on PLdyn. A. When NIV succeeds in reducing patient’s high inspiratory effort, it may be superior in reducing or, at least, maintaining dynamic transpulmonary pressure (PLdyn) within a range of safety compared to other NIRS devices. B. On the contrary, some patients may not respond to PS by decreasing inspiratory effort, resulting in an increase in PLdyn. C. When patient’s inspiratory effort is not significantly high, or low, the application of PS increases PLdyn since the inspiratory effort is not significantly affected. In both cases, B and C, HFNC or CPAP may be more effective than NIV in keeping PLdyn within a safe range of values. PLdyn: dynamic transpulmonary pressure. PS: pressure support.

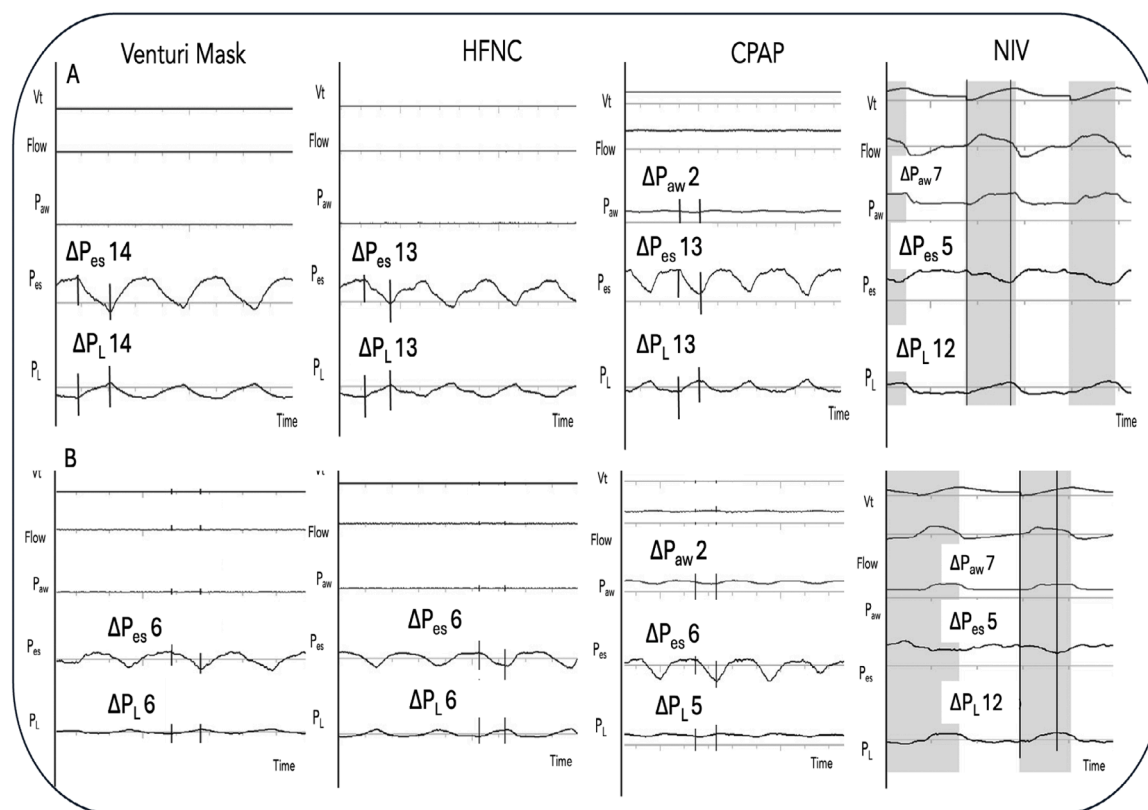


Fig. 4. Monitoring records of Vt, flow, Paw, Pes, and PL over time for two patients (A and B) under different trials: COT, HFNC (Flow 60 L/m), CPAP (10 cmH₂O), and NIV (PEEP 10 cmH₂O, PS 7 cmH₂O). FiO₂ remained unchanged in all conditions. During COT, HFNC, and CPAP trials, ΔP_{es} and ΔP_L remain unchanged in both patients. Under NIV, patients A and B respond differently: A manages to reduce P_{es} through the application of PS, thus decreasing ΔP_L . Conversely, B, with an inspiratory effort comparable to normal values (P_{es} 6 cmH₂O), increases the ΔP_L because the addition of a PS does not reduce inspiratory effort. Vt: tidal volume; Paw: airway pressure; Pes: esophageal pressure; P_L: transpulmonary pressure; $\Delta P_L = P_{L,dyn}$; COT: conventional oxygen therapy; HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure; NIV: non-invasive mechanical ventilation. P_{L,dyn}: dynamic transpulmonary pressure. PS: pressure support. (Note: Data from different patients included in the study of reference 41. During COT and HFNC, pressure, flow, and the resulting Vt were not recorded. Only inspiratory flow could be recorded during CPAP. ΔP are expressed in cmH₂O).

4.3. How to stratify patients at risk of developing or P-SILI to select the most appropriate NIRS and tailor ventilatory parameters?

To date, there is no clinical evidence confirming the existence of P-SILI, and this should be acknowledged. However, considering the possibility that it could exist, no research has demonstrated the ability to accurately identify the risk of P-SILI in the clinical setting. Nevertheless, when using NIRS, lung-protective measures should be implemented as much as possible. In non-invasively ventilated patients or in SB patients with AHRF, the major contributors to lung stress may be the magnitude of the inspiratory effort and the lung inhomogeneity. Lung inhomogeneity is determined by the etiology of hypoxemic respiratory failure (pulmonary or extrapulmonary) and can be assessed using X-rays, CT scans, or lung ultrasound [71–75].

Most randomized controlled studies stratify patients based on oxygenation indicators [76–80] such as the PaO₂/FiO₂ ratio, given the difficulty of stratifying individuals based on the chance of developing P-SILI. Deflections in esophageal pressure (ΔP_{es}) reflect the magnitude of inspiratory effort [81,82]. However, a threshold for distinguishing "high effort" from "low effort" has not yet been established. According to recent reviews, breathing efforts with a $\Delta P_{es} > 10$ –15 cmH₂O are probably too strong to be maintained for an extended period of time [83, 84]. Hypoxemic patients with sustained strong inspiratory efforts, which require a high level of pressure support, may be at a high risk of P-SILI and NIV failure. Tonelli et al. [85] observed that patients who succeeded NIV had significantly reduced respiratory effort after two hours in comparison to patients who failed.

Physiologically, esophageal manometry is useful to monitor inspiratory effort in a spontaneously breathing patient, although, it may be impractical or unacceptable to patients receiving NIRS and it is not widely used in routine practice. Thus, identifying other simpler, less invasive indicators of increased inspiratory effort, such as severity of dyspnea, RR, and the use of accessory muscles, can be used for assessing inspiratory effort and guiding clinical management [86–93]. In certain patients (ie those with severe COPD, CPE and some with AHRF, NIV + PS is the most effective type of NIRS for reducing inspiratory effort [45, 33,94,95] compared to HFNC or CPAP 4 (Fig. 3A). Therefore, the titration of pressure support should be based on the reduction in respiratory distress (Fig. 4A).

Nasal pressure swings (DPnose) can be a valuable, minimally invasive tool for real-time monitoring of inspiratory effort in AHRF patients undergoing HFNO, providing valuable insights for clinicians in their decision-making. Recent studies showed that DPnose demonstrated similar accuracy to the ROX index in predicting HFNO failure, with a high correlation to DPes. Furthermore, DPnose also showed strong accuracy in predicting escalation to mechanical ventilation (MV) [96].

Expiratory VT is proposed as one of the predictors of NIV failure when values exceed 9.8 ml/kgPBW, indirectly suggesting that ARDS patients on NIV exert a significant effort to breathe, regardless of the PS level [91,92]. It is important to emphasize that accurate monitoring of VT during NIV is a complex issue and evaluating NIV success based solely on VT is challenging. Changes in VT based on the applied PS are unpredictable and may be unreliable. Evaluating NIV success based on VT is challenging due to many factors related to the patient and the type

of ventilator used, or when unintentional leaks are present. Even with double-circuit ventilators that have an integrated expiratory pneumotachograph, monitoring VT can be inaccurate in the presence of asymmetric leaks. Additionally, most turbine driven ventilators with single-vented circuits estimate VT through software, but the accuracy of these estimates can vary due to factors such as ventilator settings, the patient's respiratory system impedance, leak type and magnitude, and the algorithm's ability to account for leaks.

So, if NIV fails to reduce inspiratory effort (Fig. 3B), clinicians should prioritize oxygenation with CPAP or HFNC and consider an alternate strategy to reduce inspiratory effort, such as mild sedation, while being cognizant of the paramount goal of avoiding delay of a needed ETI [97–99].

When patients are not hypercapnic or do not have a high WOB (fig. 3C and Fig. 4B), application of PEEP (or CPAP) alone may play a key role in enhancing lung protection during spontaneous breathing. In intubated patients or animal models, moderate to high PEEP levels have improved ventilation homogeneity and prevented pendelluft reducing lung damage and inflammatory markers [100–103]. Moreover, PEEP may also reduce inspiratory effort when the changes produced by PEEP enhance lung compliance [104,105], and it may change the force–length relationship of the diaphragm, reducing its curvature [106,107]. For this reason, titration of PEEP (during NIV) or CPAP pressures should be based on lung recruitability and improvement of oxygenation and RR. In addition, since the patient does not have an artificial airway (as in IMV), PEEP should be adjusted to maintain upper airway patency. On the other hand, titrating PEEP is a balancing act because excessive increases in PEEP may promote air leaks that contribute to asynchrony, necessitating tightening of mask straps which leads to intolerance. An increase in PEEP also necessitates an equal increase in peak airway pressure in order to maintain the same PS, predisposing to more mask intolerance.

Physiological studies have demonstrated that HFNC reduces Pes compared to COT in critical patients [22,108]. More recently, HFNC has been shown to be effective in reducing inspiratory effort in patients with AHRF with a do-not-intubate order, but only when Pes <20 cmH₂O [109]. Thus, patients with AHRF and high inspiratory effort may not respond to HFNC by lowering their WOB. Nonetheless, it could be beneficial to use HFNC during breaks off NIV [100,110]. A multicenter study assessed the role of HFNC compared to COT as a complementary therapy during breaks off NIV. Compared to COT, breaks under HFNC did not reduce the time spent on NIV, but it was more comfortable and led to a decrease in RR and dyspnea [111]. However, there are currently no recommendations regarding the dosing of alternating therapy or setting up between NIRS when using this strategy.

When implementing HFNC, clinicians should set flows (usually 40 to 60 L/min as tolerated) to achieve Paw increases, which will result in improved SpO₂ and a reduction of the patient's RR. Although this may be impossible in some patients, especially during sleep, the patient should be encouraged to breathe through the nose with the mouth closed, and the air temperature should be set according to the patient's comfort.

4.4. Thoughts on interface selection

There has long been consensus that selection of a properly sized and fit interface that is tolerable to the patient is key to the success of NIV/CPAP [112,113]. Recent meta-analyses [114–117] suggest that helmet CPAP likely reduces mortality in patients with AHRF compared to COT and that helmet NIV likely reduces ETI rates and mortality compared to face-mask NIV. However, it is important to point out that this inference was heavily influenced by results of a single center highly positive study [42] and that NIRS meta-analyses comparing interfaces are at high risk of bias since the studies included are usually unblinded, and populations studied (AHRF, etiology of AHRF, and country), NIRS employed, and trial designs included in the analysis are heterogeneous. For example, the differences between the interfaces (especially between helmet and

face mask), combined with the discrepancies in PEEP and PS settings between the studies analysed, make it very difficult to compare results [118]. In addition, many RCTs included have used NIV with face mask and only a small number of studies used helmet NIV or CPAP. Also, in most trials evaluating the face mask interface, NIV was not used continuously, compared to the more continuous use of the helmet. It is also important to note that the Network meta-analysis by Pitre et al [107] did not include a large RCT [41] in which helmet noninvasive ventilation did not significantly lower 28-day mortality compared with usual respiratory support and inclusion of this study would likely have altered the inference [114]. Thus, presently, it is premature to draw conclusions about comparative reductions in mortality, and more study is necessary to fully understand the relative effectiveness of the different NIRS or interfaces during AHRF.

4.5. Thoughts regarding sedation during NIV

Sedation has been used during non-invasive ventilation (NIV) to reduce agitation, often related to mask intolerance [119]. Moreover, sedation during NIV should lower RR and inspiratory effort while avoiding the abolition of respiratory drive and preserving upper airway patency. It may also reduce the risks associated with high-volume ventilation, thus lowering inspiratory efforts and the incidence of P-SILI. Nonetheless, sedation and analgesia are infrequently used to treat acute respiratory failure in patients undergoing NIV [120,121]. During NIV, only a hypnotic/sedative agent or analgesic agent should be used to limit the risk of oversedation, which could lead to ETI. Regular sedation assessments during NIV are crucial, as they help achieve the desired sedation level while preventing hypersedation. There are several potential beneficial effects of analgesia and sedation when using NIV. Analgesic agents, such as opioids (morphine and remifentanyl), can reduce RR without affecting respiratory drive [122–124]. Remifentanyl is considered an ideal drug for sedation due to its easy titration and metabolism independent of organ function. Low doses of remifentanyl (0.05 µg/kg/min) have been shown to provide effective analgesia and sedation in critically ill patients without impairing respiratory drive. However, there is limited evidence regarding its use during NIV, and no established guidelines for its application in this context. Remifentanyl should only be used in the ICU and must never be administered as a bolus, as this can lead to muscle stiffness, chest wall rigidity, or apnea [125].

Dexmedetomidine carries the lowest risk of depressing respiratory centers compared to other sedative drugs [126]. However, it can cause a decrease in heart rate and blood pressure due to its central sympathetic effects. Bolus administration is not recommended due to its potential adverse impact on hemodynamics. Another sedative option is propofol, which has no analgesic properties, a rapid onset (about 90 seconds), and a similarly fast offset (about 20 minutes). A recent study has shown that a remifentanyl-based sedation strategy is equally effective as dexmedetomidine in alleviating moderate to severe NIV intolerance [127]. Propofol can be used for light sedation (0.3–0.8 mg/kg/h) as the sole agent when the goal is to reduce respiratory drive and transpulmonary pressure, as it produces dose-dependent respiratory depression. However, it should be noted that unlike other agents such as benzodiazepines and opioids, there is no antagonistic drug for propofol. The most commonly used benzodiazepines for sedation in the ICU are midazolam and lorazepam. High doses of these medications are associated with sedation, muscle relaxation (including the muscles of the upper airways), anterograde amnesia, and respiratory and cardiovascular depression. However, their pharmacokinetics and pharmacodynamics can be unpredictable, and there is a risk of accumulation during continuous infusion, leading to side effects even at low doses. Additionally, these drugs may exacerbate upper airway collapse [128]. The Table 2 shows the pros and cons of sedative and analgesic agents, as well as the usage recommendations and dosing for their use in NIV [adapted from 98]. A recent systematic review and meta-analysis, which included twenty-one

Table 2

Most used analgesedation drugs during NIV. (RR: respiratory rate; Te: expiratory Time; IBW: ideal body weight; IV: intravenous; OSA: Obstructive sleep apnoea). Adapted from reference 98.

		Pro and Con:	Consider if:	Avoid if:	Dosage
Analgesic agents	Morphine	Pro – ↓ Pain – ↓RR – Hydrophilic agents (ideal in obese patients) – Rapid onset – Synergic effect with α2 agonist – Cheap Con – Requires continuous titration – Increase central and obstructive apnoea	Relief of dyspnoea Management of refractory symptoms at the end of life	Nausea Occlusion or paralytic ileus Caution in severe chronic kidney disease	Bolus of 0.03 mg/kg or as a continuous infusion at 0.01 to 0.02 mg/kg/h
	Remifentanil	Pro – Fast elimination (very short half-life time) with no accumulation – ↓ Pain – ↓ RR in a dose-dependent way (Te increases at the expense of an RR reduction) – Optimal delivery in total controlled infusion (TCI) mode – Synergic effect with α2 agonist Con – Hyperalgesia – Increase central and obstructive apnoea – IV bolus not indicated – More expensive compared to the other opioids	Need for sedation and for decreasing RR and dyspnoea Renal impairment Severe liver disease	Nausea Occlusion or paralytic ileus Bradycardia	Continuous IV infusion at 0.05–0.08 µg/kg/min (IBW)
Sedative Agents	Dexmedetomidine	Pro and Con: Pro – Selective alpha-2 receptor agonist – Short distribution T1/2α 6 min – Short elimination T1/2β 2 h – Opioid and sedative sparing effect – Could help to reduce delirium in critically ill patients Con – Bradycardia – Hypotension – IV bolus not indicated	Consider if: Need for sedation without affecting respiratory drive Delirium Severe respiratory disease (minimal respiratory depression)	Avoid if: Bradycardia Hypotension	Dosage Continuous IV infusion from 0.2 to 1.4 µg/kg/h (IBW), but higher doses (i.e. 1–1.4 µg/kg/h for 30 min) at the beginning to reach a suitable blood concentration. Reduced doses in elderly patients
	Propofol	Pro – Rapid onset time – Reduce respiratory drive – ↓Cerebral metabolic rate of oxygen (CMRO2) and anticonvulsant effect – Intra- and extra-hepatic metabolism Con – Dose-dependent cardio-circulatory effects – Plasma concentration may increase for prolonged infusion – Respiratory depression and loss of upper airway patency – Can increase plasma lipids because of the phospholipid carrier – no antagonistic drug	Need for decreasing respiratory drive Bronchospasm	Obstructive/central sleep apnoea Bradycardia Hyperlipidaemia Prolonged use and/or high doses	For light sedation (i.e. 0.3–0.8 mg/kg/h)
	Midazolam	Pro – Rapid onset time (120–300 s) – Synergic effect with alpha2 agonist Con – Paradoxical agitation – Great individual variability – half-life (2–24 h) – Active metabolite (alfa-idrossimetazolam) with risk of accumulation	Need for decreasing respiratory drive Management of refractory symptoms at the end of life	OSA, Psychosis or delirium Caution in severe chronic kidney disease Severe liver disease Acute narrow-angle glaucoma	Regimen of intermittent boluses of 0.015 to 0.03 mg/kg (IBW)

(continued on next page)

Table 2 (continued)

– Causes selective inhibition of upper airway activity

studies, showed that using sedative or analgesic medications during NIV can lower the likelihood of tracheal intubation and delirium compared to no use of these agents. Furthermore, dexmedetomidine was found to be more effective than other sedatives in improving these clinical outcomes, making it the preferred choice for patients who require close monitoring of their vital signs [129].

5. Conclusions

A personalized, bed-side approach should be chosen when selecting NIRS in ARF.

To date, the guidelines state strong recommendations for the use of NIRS (specifically NIV) in situations such as acute respiratory acidosis in patients with COPD exacerbations and ARF due to cardiogenic pulmonary edema. In contrast, given the imprecision and heterogeneity of the studies, there is inadequate data to determine which form of NIRS is most appropriate for patients with other forms of ARF, particularly those with "de novo" AHRF. The type of NIRS selected should be determined by the etiology of the hypoxemic failure, the patient's clinical condition, the time of onset of the symptoms, the degree of pulmonary and gas exchange impairment, and the patient's comfort. An experienced medical team using close monitoring in an appropriate setting are mandatory conditions when applying NIRS in the acute scenario to minimize risk of failure and ensure patient safety. More large, well-designed, randomized, multi-center trials are needed to better understand the impact of NIRS in AHRF, and determine optimal settings and monitoring techniques to optimize outcomes. Finally, finding accurate and simple surrogates for Pes could be useful to identify patients with high vs lower risk for P-SILI, rather than stratifying patients based just on PaO₂/FiO₂, could be helpful in subsequent management of NIRS.

Topics for further research

- Reliable tools for early determination of the appropriate NIRS vs intubation in patients with acute hypoxemic respiratory failure
- A threshold for defining "high effort" from "low effort" during spontaneous breathing has not yet been identified.
- Routine monitoring of inspiratory effort in a spontaneously breathing patient via esophageal pressure may be challenging and not commonly available; therefore, identifying simple surrogates would be helpful.
- Establishing lung and diaphragm protective ventilation parameters to aid in PEEP titration and proper PS selection during NIV.
- Further research is required to fully understand the role of the different interfaces during acute hypoxemic respiratory failure.

Declaration of competing interest

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