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REVIEW

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Monitoring patients with acute respiratory failure during non-invasive respiratory support to minimize harm and identify treatment failure

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Abstract

Non-invasive respiratory support (NRS), including high flow nasal oxygen therapy, continuous positive airway pressure and non-invasive ventilation, is a cornerstone in the management of critically ill patients who develop acute respiratory failure (ARF). Overall, NRS reduces the work of breathing and relieves dyspnea in many patients with ARF, sometimes avoiding the need for intubation and invasive mechanical ventilation with variable efficacy across diverse clinical scenarios. Nonetheless, prolonged exposure to NRS in the presence of sustained high respiratory drive and effort can result in respiratory muscle fatigue, cardiovascular collapse, and impaired oxygen delivery to vital organs, leading to poor outcomes in patients who ultimately fail NRS and require intubation. Assessment of patients' baseline characteristics before starting NRS, close physiological monitoring to evaluate patients' response to respiratory support, adjustment of device settings and interface, and, most importantly, early identification of failure or of paramount importance to avoid the negative consequences of delayed intubation. This review highlights the role of respiratory monitoring across various modalities of NRS in patients with ARF including dyspnea, general respiratory parameters, measures of drive and effort, and lung imaging. It includes technical specificities related to the target population and emphasizes the importance of clinicians' physiological understanding and tailoring clinical decisions to individual patients' needs.

Keywords Non-invasive respiratory support, Acute respiratory failure, Respiratory monitoring

Introduction

Acute respiratory failure (ARF) is one of the leading causes of intensive care unit (ICU) admission worldwide [1]. From a pathophysiological perspective, ARF is characterized by hypoxemia, which may occur alongside with hypoventilation and hypercapnia due to ventilatory pump failure, or hypo-normocapnia (isolated acute hypoxemic respiratory failure -AHRF) in the context of direct or indirect lung insults. The result is a cardio-respiratory incapacity to sustain adequate oxygen delivery to vital organs and to eliminate CO_2, contributing to acid–base imbalance [2, 3]. Despite supplemental oxygen being sometimes sufficient to overcome these abnormalities, the increased ventilatory demands may require escalation to more advanced respiratory support [1].

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Non-invasive respiratory support (NRS) strategies can elicit a physiological response sufficient to meet patients' needs during acute illness, potentially avoiding intubation and invasive mechanical ventilation (IMV). However, especially in sicker patients, delaying IMV initiation may expose the patient to excessive respiratory effort and increased oxygen consumption, further aggravating patients' condition and overall clinical outcomes. As a result, deciding whether to implement NRS, how, and for how long are key clinical decisions.

In this review, we provide an overview of the relevance and available tools for monitoring adult patients during NRS for ARF. We specifically focus on the physiological effects and main indications for NRS, importance of device/interface selection, determinants, and implications of NRS failure. Finally, we describe available tools for monitoring and how to interpret them in the clinical context to guide decisions related to adjustments of ventilator settings and timely intubation to avoid harm. NRS during awake prone positioning and post-extubation are out of the scope of this review.

Physiological effects of non-invasive respiratory support

NRS includes High-Flow Nasal Oxygen (HFNO), Continuous Positive Airway Pressure (CPAP), and Non-Invasive Ventilation (NIV). To adequately interpret monitoring parameters, it is crucial to understand the physiological effects of each strategy.

HFNO provides heated and humidified fresh gas at a high flow rate (30–80 L/min) through a special nasal cannula with a set fraction of inspired oxygen (FiO_2) from 0.21 to 1.00 [4]. The gas delivered at high flow rates reduces nasal and upper airway inspiratory resistance while increasing expiratory resistance [5, 6]. As a result, HFNO decreases room air entrainment ensuring stable FiO_2 delivery, increases end-expiratory lung volume, generating small amounts of positive end-expiratory pressure (PEEP) (1 to 7 cmH_2O varying with settings and conditions) homogenizing ventilation distribution and improving oxygenation [6, 7]. Lastly, delivery of fresh gas results in CO_2 wash-out reducing anatomical dead space and decreasing CO_2 rebreathing [8]. These effects result in a reduced inspiratory effort and respiratory rate in many patients, particularly those with high ventilatory demands [5, 7].

CPAP maintains a constant PEEP level throughout the breathing cycle. It can act as a mechanical stent for the upper airways and increase end-expiratory lung volume with or without alveolar recruitment [9]. When NIV is applied, inspiratory pressure support (PS) is added above the set PEEP. Both CPAP and NIV can reduce work of breathing, improve respiratory mechanics, and gas exchange [10]. They can be applied through different interfaces, *i.e.,* facemask and helmet. The latter can reduce leaks and discomfort, allowing for higher PEEP as compared to facemasks [11, 12]. Active humidification and heating of inhaled gas may enhance patients' tolerance and increase the chances of success [13].

Main indications for NRS

Based on these physiological principles and the available clinical evidence, HFNO is currently recommended as first-line therapy in AHRF. Helmet NIV/CPAP remains a reasonable alternative with supporting evidence available for more severe patients with AHRF (PaO_2/FiO_2 150—200 mmHg) [11, 14, 15]. Extensive data supports the use of CPAP/NIV delivered via facemask or helmet interfaces in patients with cardiogenic pulmonary edema (CPE) due to the beneficial effects of positive pressure in this context (*i.e.,* reduced pre- and afterload) [16–20]. Studies showing the benefit of HFNO were also performed for CPE and it can be used as an alternative when CPAP and NIV are not tolerated/available. [18]. Bilevel facemask NIV remains the first line respiratory support modality for hypercapnic exacerbation of chronic obstructive pulmonary disease (COPD) over helmet NIV and CPAP. [18, 21]. Some studies have shown promising results using HFNO in these patients [17, 21–23], however its use should be reserved only for patients with NIV intolerance in the acute setting. Patients with chest trauma might benefit primarily from facemask or helmet NIV/CPAP [18, 24]. Of note, in a retrospective cohort study HFNO has shown to be better tolerated and leading to equivalent success rates when compared to NIV in these patients [25]. Clinical guidelines recommend the use of CPAP/NIV in immunocompromised patients with ARF over conventional oxygen support [18]. Recent data suggest that helmet might be superior or at least equally effective to facemask CPAP/NIV [26–28]. Furthermore, HFNO can also be considered an alternative in these settings, given that some studies have reported similar results when compared to NIV [29].

Who may not be a good candidate for NRS?

Patients with more severe systemic disease at baseline (*e.g.,* vasopressor need, multiple organ failure) and/or lung injury are less likely to benefit from NRS but rather should be considered for IMV if within patients' goals of care. Older patients and those with higher SAPS II, non-respiratory sequential organ failure assessment (SOFA) score on admission, greater number of quadrants affected on chest X-ray, diagnosis of pneumonia or severe ARDS ($PaO_2/FiO_2 < 100$ mmHg), with concomitant immunosuppression, lower Glasgow Coma Scale, and need of vasoactive drugs have more chances to fail NRS [30–36].

An important caveat of NRS is that, despite unloading the respiratory muscles, there is still some energy expenditure due to respiratory muscles' contraction which might further compromise end-organ function in critically ill patients [37]. Additionally, in the context of more severe lung injury and systemic inflammation, theoretical risk of P-SILI and myotrauma increases [38]. If for any reason clinicians decide to undergo a trial of NRS in these patients, very close monitoring should be implemented and early consideration to transition to IMV should be consider if there is a lack of initial positive response.

Relevance of interface selection and settings

Interface selection during NRS is important. Patients with AHRF and a PaO_2/FiO_2 between 150 and 200 mmHg will likely benefit from HFNO as first-line therapy as shown in a randomized clinical trial (RCT) when compared to facemask NIV and conventional oxygen therapy [14]. In this context, asymmetrical cannulas, larger prong/nare diameter relationship, highest tolerable set flow (ideally 50–60 L/min) and individualized temperature selection may boost physiological benefits and comfort of HFNO [4, 7, 39–42]. Helmet NIV could be an alternative to HFNO during AHRF as it elicits a similar physiological response and was shown to be superior to facemask NIV in a different RCT [12, 15]. In addition, helmet CPAP offers the option to be implemented without the need of a mechanical ventilator [43]. In the remaining clinical scenarios, oronasal or full-face masks can be used interchangeably. Full-face interfaces offer an even distribution of pressure over the skin and are not applied over the nasal bridge but increase the chances of claustrophobia as compared to oronasal masks. Setting-up appropriate humidification is crucial. Heat-moisture exchangers have shown similar results in terms clinical outcomes than active humidification during NIV [44], but might impose higher work of breathing and lose efficacy when large leaks are present. Specific recommendations regarding other circuit set-up and NRS settings are described elsewhere [45–48].

Importantly, close monitoring of interface adequacy and comfort is crucial until patients' stability is reached. In some cases, change in the interface might be required in addition to frequent adjustments of ventilator settings.

What are the determinants and implications of NRS failure?

NRS failure is epidemiologically defined as the subsequent need for endotracheal intubation. However, the decision to intubate is inherently based on clinical judgment, influenced by factors such as healthcare teams' experience, local practices, and patient-specific considerations, all of which can vary significantly across ICUs. Therefore, clinical significance of "NRS failure" can also be greatly different across settings. In fact, observational data suggest that intubation based on pathophysiological thresholds are scarcely implemented in clinical practice when patients are receiving facemask NIV [49, 50].

Pathophysiological link between NRS failure with delayed intubation and worse clinical outcomes is not clear. At least three possible pathways warrant consideration as potential mediators in the putative causal relationship between NRS failure with delayed intubation and worse clinical outcomes: (1) direct harm to the lung and respiratory muscles from excessive breathing effort in the context of acute illness (*i.e.,* patient self-inflicted lung injury -P-SILI- and myotrauma [51–54]; (2) progression of underlying illness without sufficient unloading of the respiratory muscles and low oxygen delivery to vital organs; (3) complications related to intubation and IMV such as sedation [55], immobilization, diaphragm disuse atrophy, sleep disorders [56], ventilator-induced lung injury [57]. Importantly, the latter mechanism would only be relevant for the potential causal relationship between NRS failure, need for IMV and worse clinical outcomes and not necessarily related to the timing of intubation relative to failure, as complications of IMV are common to both early and delayed intubation. Therefore, monitoring baseline characteristics to ensure a more appropriate selection of candidates for NRS, the magnitude of breathing effort, and the trajectory of illness severity during NRS are important to minimize the risk of harm to the lung, diaphragm, and associated decrease oxygen delivery to vital organs.

How to monitor the response to NRS?

To minimize the risk of failure, a pragmatic approach to implement NRS in patients with AHRF is proposed as a guide focusing on monitoring before and during NRS (Fig. 1). This algorithm is intended to guide decisions in patients with inflammatory conditions leading to AHRF or ARDS. It does not entirely apply for CPE or postoperative patients, where different information might be incorporated into clinical judgment.

The goals of respiratory monitoring during NRS are to (1) evaluate treatment response, (2) guide adjustments in ventilator settings ensuring adequacy to patients' ventilatory demands and breathing pattern (*e.g.,* increase/decrease support and correct asynchronies), and, importantly, (3) identify early which patients may benefit from IMV. A multimodal approach should integrate patients' initial clinical characteristics and trajectory focusing on illness severity, measures of respiratory effort, gas

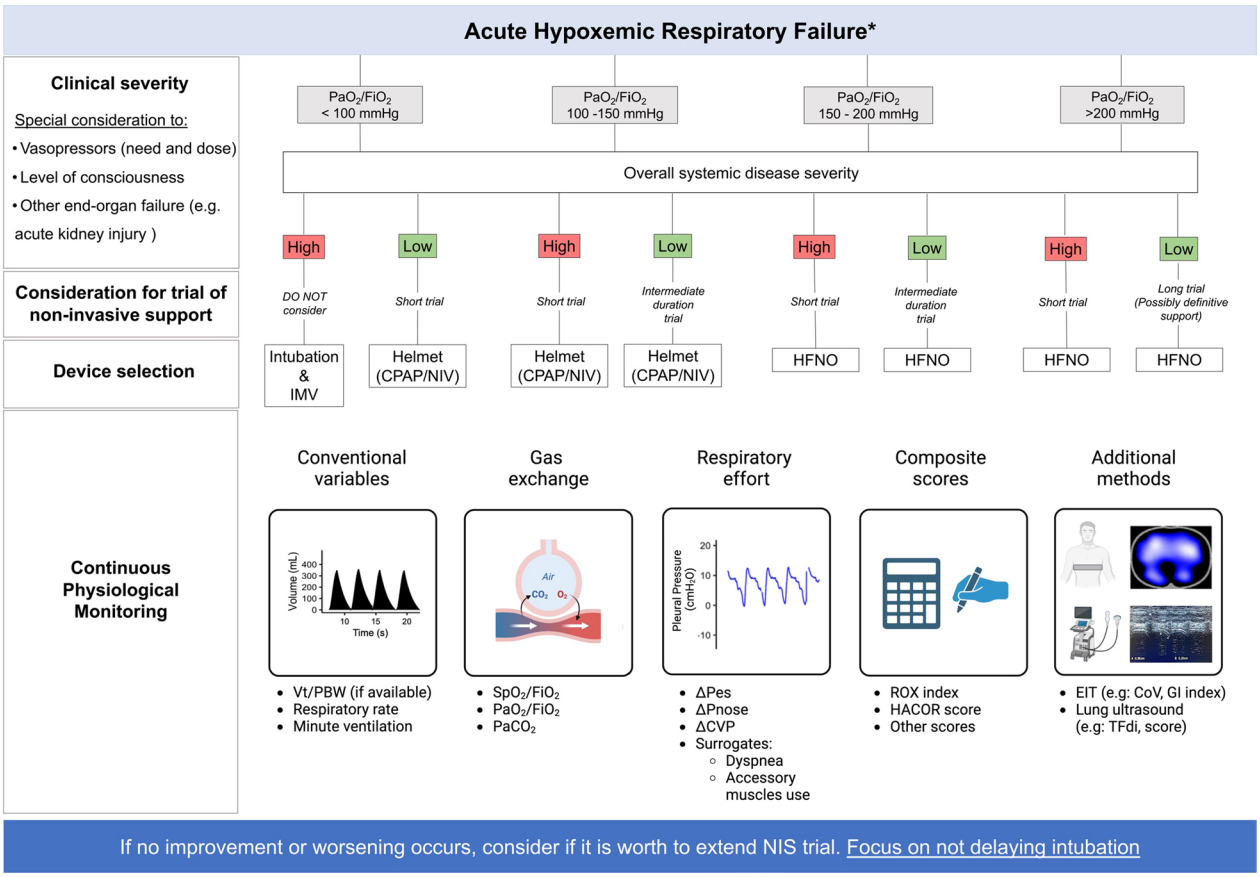

Fig. 1 Integration of baseline characteristics and monitoring tools during non-invasive respiratory support. A simple algorithm is proposed based on baseline characteristics (i.e., oxygenation and clinical severity) to decide on the appropriateness of a trial of non-invasive respiratory support. Available tools to monitor response are also summarized. Duration of short trial and trial of intermediate duration depends on patients' individual response to therapy, authors suggest considering 1–2 h for a short trial and 3–6 h for a trial of intermediate duration. * intended to guide decisions in patients with acute hypoxemic respiratory failure of infectious etiology (e.g., Community acquired pneumonia) or ARDS. PaO_2/FiO_2 ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; IMV invasive mechanical ventilation; CPAP continuous positive airway pressure; NIV non-invasive ventilation; HFNO high flow nasal oxygen; Vt/PBW ratio of tidal volume to predicted body weight; SPO_2/FiO_2 ratio of oxygen saturation to fraction of inspire oxygen; $PaCO_2$ arterial partial pressure of carbon dioxide; ΔPes esophageal pressure swing; ΔPnose swing in nasal pressure; ΔCVP swing in central venous pressure; EIT electrical impedance tomography; CoV center of ventilation; GI index inhomogeneity index; TFdi thickening fraction of the diaphragm

exchange, and other variables including lung imaging (Fig. 1—Table 1).

A summary of most important monitoring tools and variables that can be used during NRS is detailed in Tables 1 and 2, highlighting technical characteristics, clinical interpretation of findings, caveats, and suggested adjustments based on results.

Dyspnea and comfort

Dyspnea and discomfort should be regularly assessed during NRS. First, dyspnea frequently occurs in the context of and is associated with high respiratory drive [58, 59] Additionally, dyspnea intensity has been independently associated with a greater risk of intubation and mortality among spontaneously breathing patients with ARF and therefore these patients merit closer monitoring [60, 61]. Finally, intolerance and discomfort related to the NIV interface are closely associated with NIV failure highlighting the importance of appropriate interface selection and fitting [34, 35]. In general, better comfort was reported with HFNO and helmet NIV as compared to facemask NIV. Importantly, while using facemask interface, the need for adjustments is frequent as well as resting periods, requiring alternating support with a different interface/device (*e.g.,* HFNO).

The preferential method to measure dyspnea in conscious communicative patients is the self-reported visual analog scale (VAS), quantifying dyspnea as a continuous

Table 1 Monitoring variables

Category	Variable	Complexity	NRS device evaluated	Thresholds for NRS failure	Comments	Caveats
Conventional variables	Tidal Volume (Vt)	+	Facemask NIV	> 9–9.5 mL/kg PBW after 1 h	Indirect estimate of respiratory effort and stress	Influenced by leaks, mechanics and settings. Not feasible with helmet, HFNO or single-limb circuits
	Respiratory Rate (RR)	+	Facemask NIV—HFNO	> 25 bpm or lack of improvement	Widely used	Poor measure of drive. Influenced by anxiety, pain, discomfort. Sensitive to lack of HFNO response
	Minute Ventilation	+	Facemask NIV	> 11 L/min	Composite of Vt and RR	Idem Vt and RR
Respiratory effort	Esophageal Pressure Swing (ΔPes)	+ + +	NIV—HFNO	> 10 cmH_2O after 2 h	Gold standard for inspiratory effort	Expertise and time for catheter insertion. Complex validation during NRS
	Central Venous Pressure Swing (ΔCVP)	+ + +	Helmet NIV—facemask CPAP	Unknown	Alternative to ΔPes for high effort	Requires CVP catheter and lack of arrhythmia. Lacks clinical validation
	Nasal Pressure Swing (ΔPnose)	+ +	HFNO	> 5 cmH_2O after 2 h	Minimally invasive and correlated with ΔPes	Custom-made equipment connected to pressure transducer
	Dyspnea	+	NIV	≥ 4 points in VAS	Associated with effort and clinical outcomes	Communicative patients
Gas exchange	PaO_2/FiO_2	+ +	Facemask NIV	< 200 mmHg after 1 h and/or worsening	Overall marker of severity and response to treatment	Influenced by extrapulmonary factors (hemodynamics, drugs)
	SpO_2/FiO_2	+	HFNO	< 113–115 in the first 12 h or worsening	Overall marker of severity and response to treatment	SpO_2 valid if SpO_2 < 97%. Affected by skin color, perfusion and temperature
	Carbon Dioxide	+ +	Facemask NIV	< 32 mmHg prior to NIV	Hypocapnia may reflect high effort	Hypocapnia may be absent with high dead space / shunt
Composite scores	HACOR (heart rate, acidosis, consciousness, oxygenation, respiratory rate)	+ +	Facemask NIV—HFNO	> 5 points after 1 h	–	Requires arterial blood gases
	ROX (SpO_2/FiO_2 to RR ratio)	+	Facemask CPAP—HFNO	< 4.88 after 6–12 h (HFNO); < 6.64 after 24 hs (CPAP)	–	Idem SpO_2/FiO_2 and RR
	BREF (Base excess RR, PaO_2/FiO_2.)	+ +	HFNO, helmet, and facemask CPAP/NIV	Unknown	To estimate ΔPes > 10 cmH2O in non-intubated patients receiving NRS	Arterial blood gases
Other methods	Ultrasound	+ +	Facemask and Helmet NIV—HFNO	LUS score ≥ 12; LUS areas ≥ 5 points; Thickening fraction < 36.3%	Lung aeration and diaphragmatic function	Operator dependent
	Electrical Impedance Tomography	+ + +	HFNO	Unknown	Regional ventilation and perfusion	Not widely available, expensive. Expertise and additional offline analysis

variable. The patient points to a vertical line representing their dyspnea intensity on a horizontal line ranging from 0 to 100 mm (lack of dyspnea to maximum dyspnea). Alternatively, a simpler numeric-rating scale (NRS) can be used ranging from 0 to 10 using numbers or representative figures [62]. VAS and NRS can be implemented to assess also patients' comfort during NRS.

Basic variables

Expired tidal volume (Vte) can be monitored during NIV/CPAP. Because it represents the output of respiratory effort and a determinant of lung stress, it is often considered an indirect estimate of those variables. In fact, a high Vte (≥9.5 mL/Kg of predicted body weight [PBW]) has been consistently associated with failure and overall worse outcomes during facemask NIV in patients with moderate-to-severe AHRF [63–65]. However, clinical interpretation of a high Vte during NIV/CPAP should consider the physiological context. First, variables different than the respiratory effort can also influence the monitored Vte, *e.g.,* high PS associated with high respiratory system compliance can lead to high Vte [66, 67]. However, an increase in Vte without changes in ventilator settings and assuming stability of respiratory system mechanics within a relatively short time is usually indicative of an increase in respiratory effort either because of a high respiratory drive or improvement in neuromuscular coupling. Second, setting PS to target high Vte (10 to 15 mL/Kg of PBW) has recently shown to reduce the number of patients with a hypercapnic exacerbation of COPD requiring intubation [68]. This finding suggests that high PS with high Vt may be effective in relieving dyspnea and effort without added risk of VILI in a subgroup of patients; however, in all cases close monitoring is advised. Specifically, occurrence of ineffective efforts is frequent in the context of overassistance (*i.e.,* excessive support) in patients with auto-PEEP, therefore careful inspection of ventilator waveforms is recommended. Finally, leaks, associated with other asynchronies and often intolerance, are also frequent with higher support and should be avoided [69].

Some technical considerations are important when monitoring Vte during NRS. With helmet CPAP/NIV, quantifying Vte accurately is not feasible because part of the insufflated volume is used to distend the interface. Similarly, dedicated NIV ventilators with single-limb configurations and intentional leak do not measure but calculate Vte based on predefined algorithms, thus the accuracy of Vte estimation might be worse than with double-limb ICU ventilators [70–72]. In any case, when monitoring Vte, leaks should be minimized. During HFNO, Vt monitoring is not widely available for clinical use, dynamic changes in lung impedance measured with electrical impedance tomography (EIT) could theoretically be used for longitudinal follow-up, but validation is missing [73–75].

Respiratory rate (RR) remains one of the most monitored variables during NRS. Clinicians often associate a high RR with high respiratory drive and effort; however, it is often a late sign of high respiratory drive [76]. High RR is common in critically ill patients and can reflect other factors such as systemic inflammation, anxiety, pain, discomfort and abnormal respiratory mechanics [77]. Furthermore, ineffective efforts may mask the patients' true RR when auto-PEEP is present and respiratory muscles' output is insufficient to trigger the ventilator [69]. Despite these caveats, RR remains a key variable to consider, especially during HFNO as its expected physiological effect on decreasing RR is very strong [5]. A lack of decrease in baseline RR often represents a lack of clinical response, particularly during HFNO. In fact, a high RR and a lack of initial decrease during NRS were shown to predict failure during facemask and helmet CPAP/NIV, and HFNO [33, 78–81]. However, given the complex physiology underlying RR regulation, it is not recommended to make decisions based solely on RR.

As expected, higher minute ventilation, *i.e.*, the product of Vt and RR, was also found to be associated with NIV failure in patients with AHRF and mild ARDS [63, 82].

Gas exchange

Changes in oxygenation are important determinants of NRS success/failure in patients with ARF, partly because they are a marker of severity and clinical response to therapy and are frequently considered as a criterion influencing the decision to intubate. Teasing out the relative importance of each factor is, therefore, challenging.

All NRS strategies, especially those that promote higher airway pressure, can increase oxygenation by multiple mechanisms. In fact, patients with ARF usually experience a transient improvement in oxygenation during NIV/CPAP that can return to baseline after device removal [83]. Importantly, transient improvement in oxygenation during NRS without a clear trend towards clinical improvement might give false reassurance and contribute to poor outcomes in patients' ultimately failing NRS and receiving delayed intubation [30, 83].

Oxygenation can be monitored both continuously by pulse oximetry and intermittently by arterial blood gases to obtain precise PaO_2/FiO_2 ratio prior to NRS initiation and after the first 2–6 h of treatment. A lower baseline PaO_2/FiO_2 and a lack of improvement over time are independent predictors of NIV/CPAP failure [30, 31, 64, 81, 84]. In addition, lower SpO_2/FiO_2 ratio

Table 2 Physiological consideration for suggested interventions based on monitoring

Variable	Potential physiological mechanism	Consider interventions
RR increase	High drive	↑ PS, ↑ PEEP, ↑ flow rate (HFNO), ↑ FiO_2 to SpO_2 target 98%
	When combined with low Vte, loss of lung aeration	↑ PEEP, ↑ PS, ↑ flow rate (HFNO), optimize body position
	Neuromuscular uncoupling by excessive PEEP	↓ PEEP
	Anxiety, discomfort, agitation	Trial of different interface, conscious sedation*, and analgesia
RR decrease	Adequate drive, positive response to NRS	Evaluate progressive withdrawal of PS / PEEP, flow rate
	With ineffective efforts, overassistance	↓ PS, set FiO_2 to a lower SpO_2 target (90–95%)
	Excessive opioids or sedatives	Reduction in drug dose
	Together with other signs of fatigue, imminent respiratory arrest	Intubate immediately
High Vte	High effort	↑ PEEP, ↑ flow rate to maximum tolerable (ideally 60 L/min—HFNO), ↑ FiO_2 to SpO_2 target 98%, consider helmet NIV, consider IMV
	When combined with low RR, opioid intoxication	Consider opioid dose reduction
	Excessive PS	↓ PS
Low Vte	Adequate effort, positive response to NIV	Consider weaning
	Low effort, excessive sedative dose	Reduction of sedatives
	Low compliance due to lung aeration loos	↑ PEEP, optimize body position
High or increase in PaO_2/FiO_2	Lung recruitment	Progressive withdrawal of respiratory support—Consider weaning
	Low proportion of low V/Q—shunt units (↓ severity)	Consider weaning
Low or decrease in PaO_2/FiO_2	High proportion of low V/Q—shunt units (↑ severity)	↑ PEEP, optimize body position, consider helmet interface
High $PaCO_2$	High proportion of high V/Q—dead space units (↑ severity)	↑ PS, revaluate PEEP level
	Decreased muscular performance (weakness, excessive PEEP)	↑ PS, reconsider PEEP level
Low $PaCO_2$	High effort	Escalate NRS to helmet, ↑ PS, reconsider PEEP level, consider IMV
	Low proportion of high V/Q—dead space units (↓ severity)	Consider weaning

*conscious sedation: a trial of dexmedetomidine infusion (for agitation), low dose opioid (for dyspnea/pain) administration can be considered cautiously and with close monitoring

is associated with HFNO failure at various time points within the first 24 h [33, 85]. However, technical pitfalls related to SpO_2 measures should be considered, such as skin color and temperature, hemodynamics and perfusion, anemia and hyperoxia among others [86].

Interpreting levels of partial pressure of carbon dioxide ($PaCO_2$) in the context of AHRF is complex. A relatively low $PaCO_2$ can be indicative of less severe lung injury (lower dead-space/shunt fraction) and lack of respiratory muscle fatigue. However, very low $PaCO_2$ associated with high respiratory drive and effort can be secondary to an exaggerated ventilatory response caused by strong stimuli that overwhelm the patients' control of breathing [76, 87–90]. In a recent single center study, a $PaCO_2$ lower than 32 mmHg was strongly associated with NIV failure [91]. Additionally, a secondary analysis of a randomized trial showed that patients with more pronounced hypocapnia (< 35 mmHg) benefitted from helmet NIV when compared to HFNO. This effect may be attributed to the higher PEEP and PS provided by helmet, likely reducing respiratory drive and effort more effectively [91, 92].

The absence of hypocapnia does not exclude high drive and effort as high minute ventilation may not be sufficient for CO_2 clearance in patients with high dead space/shunt fraction or when respiratory muscles' exhaustion occurs [76]. An increase in $PaCO_2$ within the first days of NIV was independently associated with NIV failure in ARDS, probably indicating deterioration of lung function (*i.e.,* VILI, P-SILI) and/or respiratory muscles' performance (*i.e.,* diaphragmatic fatigue, muscle injury) [31].

Monitoring $PaCO_2$ to ensure a downtrend is key during acute hypercapnic respiratory failure. Even though blood samples are often required, transcutaneous monitoring, despite not being widely available, offers an attractive

alternative that closely correlates with $PaCO_2$ with a small bias during acute respiratory failure [93].

Respiratory effort

Direct monitoring of breathing effort with esophageal pressure (Pes) offers invaluable information. However, it is challenging to implement in the acute setting. It provides information related to baseline ventilatory demands and it is a direct measure of the physiological response to NRS in terms of respiratory muscles' unloading and risk of P-SILI. The gold standards for inspiratory effort quantification based on Pes are the muscular pressure (instantaneous effort) and pressure–time product of the respiratory muscles (effort during whole inspiration). However, both parameters require calculations that depend on the estimation of chest wall compliance. Measurement of the tidal swing in Pes (ΔPes) is a good estimate of inspiratory effort and can be easily implemented at the bedside [88]. Risk of P-SILI can be estimated by calculating driving transpulmonary pressure (*i.e.,* the difference between airway and esophageal pressure), allowing to quantify the dynamic lung distending pressures. Specifications about how to perform Pes measurements and calculations are detailed elsewhere [94, 95].

In a prospective observational study, a reduction in ΔPes > 10 cmH_2O after 2 h of facemask NIV was found to be the best predictor of NIV success in moderate-to-severe AHRF [65]. Furthermore, ΔPes reduction was positively associated with improvement in radiographic changes within 24 h and 30-day mortality. Despite these findings being exploratory, they support the hypothesis of P-SILI being mediated by the magnitude of breathing effort during NIV and demonstrate the association between worsening lung function following higher breathing effort and poor clinical outcomes. Similarly, in patients during helmet NIV a reduction in ΔPes to values < 10 cmH_2O and dynamic lung stress to < 20 cmH_2O were associated with a lower need for subsequent intubation [12].

There are technical challenges related to Pes monitoring during NRS. Inserting an esophageal catheter in non-intubated patients with respiratory distress and ensuring adequate positioning by performing an occlusion test to measure ΔPes to delta airway pressure (ΔPaw) ratio can be complex. We offer three alternatives. (1) Aim for a set depth of catheter insertion around 40 cm from the nostril. First, insert esophageal catheter up to around 60 cm and ensure proper inflation of the balloon with the manufacturers' recommended filling volume, waveform morphology should resemble that of gastric pressure, *i.e.,* positive deflection with tidal, relaxed, inspiration. Then, withdraw the catheter 20 cm and check that waveforms' morphology resembles that of esophageal pressure, *i.e.,* negative deflection during inspiration and cardiac oscillations (Fig. 2). (2) Use a mouthpiece and a pneumotachograph connected to a stand-alone device to measure simultaneous Paw, flow and Pes and perform a regular occlusion test [96]. (3) Use a tightly fitted facemask with a dual limb circuit connected to the ventilator and perform a regular occlusion test. When measuring an occlusion test, air leaks should be avoided. It is important to emphasize that a proper occlusion maneuver is essential for ensuring a valid estimation of pleural pressure via Pes monitoring.

Diaphragmatic ultrasound is a non-invasive technique to monitor inspiratory effort. Quantifying diaphragm thickening fraction (Tfdi) can be done at the zone of apposition with a linear probe positioned on the 8th–9th intercostal space, anterior axillary line [88]. A small prospective study showed that a low Tfdi (< 36%) assessed within the first 96 h of NIV identified patients who failed NIV with acceptable diagnostic accuracy, suggesting that early diaphragmatic dysfunction may play a role in NIV failure [97].

The central venous pressure swing (ΔCVP) has shown good concordance with ΔPes, being useful in identifying strong respiratory effort and titrating PS [98]. A ΔCVP > 15 cmH_2O was shown to precisely identify high inspiratory effort in hypoxemic patients during helmet NIV [99]. The main limitation is that central venous catheter insertion is uncommon in patients receiving NRS.

Another minimally invasive technique to monitor inspiratory effort is the nasal pressure swing (ΔP_{nose}) [100]. To monitor ΔP_{nose}, a custom-made catheter covered by a self-expanding foam plug is placed in the same nostril as the nasogastric tube and connected to a pressure transducer (auxiliary port on the ventilator or stand-alone device). The contralateral nostril should be kept patent. When HFNO is used, the cannula is placed only in the patent nostril during monitoring. The ΔP_{nose} has demonstrated excellent correlation with ΔPes during HFNO and facemask NIV [100]. In a cohort study of 102 patients with AHRF receiving HFNO, a ΔP_{nose} > 5.1 cmH_2O accurately identified failure and need for escalation in ventilatory support (*i.e.,* use of NIV or IMV) (Area Under the Receiver Operating Curve [AUROC] = 0.98; 95% confidence interval: 0.96–1, $P < 0.001$) [101].

Another important variable often considered by clinicians is the evidence of non-diaphragmatic inspiratory muscle activation, as it is often indicative of high respiratory drive and effort [102]. Sternocleidomastoid activates when the inspiratory effort is close to 35–40% of the maximum inspiratory pressure, which coincides with thresholds proposed to prevent diaphragmatic fatigue [103, 104]. Activation of other non-diaphragmatic

inspiratory muscles, such as intercostals, scalene, and alae nasi increases linearly with inspiratory effort [103, 105]. However, the high interobserver variability and lack of bedside quantitative measure of non-diaphragmatic inspiratory muscle activity remain a challenge. Surface electromyography may help to overcome these limitations in the future [105].

Composite scores

The HACOR score (heart rate, acidosis, consciousness, oxygenation, and RR) was developed and validated in hypoxemic patients receiving facemask NIV. A value higher than 5 after 1 h of NIV was shown to accurately predict failure of facemask NIV (AUROC = 0.89) and helmet CPAP (AUROC = 0.74) [79, 106]. The HACOR score was recently updated and validated incorporating additional baseline clinical variables directly related with a higher risk of failure (*e.g.,* immunosuppression and septic shock), further highlighting the relevance of considering initial disease severity to estimate the risk of failure [107].

The ROX index (SpO_2/FiO_2 ratio divided by RR) is a simple and widely used clinical score. Threshold values associated with NRS failure vary according to the respiratory support modality and patient population. For HFNO in AHRF, a value lower than 4.88 was associated with increased risk of failure when collected at various timepoints during the first 12–24 h [33]. A ROX index lower than 6 was shown to predict NRS failure in COVID-19 AHRF receiving CPAP, but with acceptable precision only 24 h after CPAP initiation [108]. Finally, in patients receiving facemask NIV, a higher risk of failure was consistently observed with decreasing ROX values (*i.e.,* 23%, 34.1%, 64.3%, and 100% with a ROX index higher than 10, 6–10, 2–6, and lower than 2 after 1–2 h of NIV, respectively) [109]. Moreover, an increase in ROX over time is seen in patients who succeed NRS and stability or lack of improvement in those who ultimately require intubation [33].

Other indices such as the VOX index (Volume Oxygenation—calculated as SpO_2/FiO_2 to Vt) or composite scales to estimate the inspiratory effort like the BREF score (base excess -B-, respiratory rate -RE-, and PaO_2/FiO_2 -F-) might be useful when less monitoring tools are available. However, these still require further refinement and validation in prospective larger multicenter cohort studies [85, 110].

Additional tools

Lung ultrasound (LUS) can be used to non-invasively quantify lung aeration as a baseline predictor of success/failure and to monitor response to NRS. In a prospective cohort study in patients with AHRF due to COVID-19, an aeration-based LUS score measured on admission while receiving supplemental oxygen showed acceptable performance to predict helmet NIV and HFNO failure [111]. Additionally, an independent prospective cohort study in the same population has shown that a combination of LUS score and ROX index measured during NIV can accurately predict negative outcomes in these patients [112].

Electrical impedance tomography (EIT), although not widely available, can be used to assess lung aeration and response to NRS, provide a non-invasive, indirect, measure of Vt, and monitor regional ventilation distribution [113]. Only few small single center studies have evaluated the performance of EIT-derived parameters to predict the response to HFNO or NIV in patients with ARF [74, 114, 115]. Overall, these studies show that a more asymmetrical ventilation is potentially associated with higher risk of failure, however, more data are required for bedside translation of the findings [74, 114, 115].

When to define failure based on bedside monitoring

Patients with ARF who receive NRS strategies and are never intubated have better outcomes than those who require IMV, highlighting the relevance of pursuing a trial of NRS in the appropriate patients. However, there is a risk of delaying intubation associated with higher mortality if NRS is prolonged despite a lack of clinical improvement [30]. Although evidence is still conflicting, large observational data suggest that more hypoxemic patients ($PaO_2/FiO_2 < 150$ mmHg) initially managed with NIV have worse clinical outcomes than matched patients who receive IMV initially [31]. Currently, there is no consensus regarding maximal duration of NRS trials or clear-cut thresholds for monitored variables used to decide how and when to escalate respiratory support.

Early, *i.e.,* within 1–2 h, improvement or, alternatively, clear worsening might be informative. Interestingly, upward or downward trends in most of the monitoring variables described can already predict failure or success within the first few hours (Table 1). Additionally, high secretion burden, decreased level of consciousness (*i.e.,* Glasgow Coma Scale < 10) and inability to achieve proper interface fit despite sufficient adjustments and trial of different interfaces at any time during NRS therapy should prompt consideration for escalation in respiratory support.

Clinical decision making becomes even more challenging when there is a relative early improvement after starting NRS without additional change within the following 24 h. In this context, fixed time intervals for regular monitoring (*e.g.,* every 4–6 h) are advisable. It is

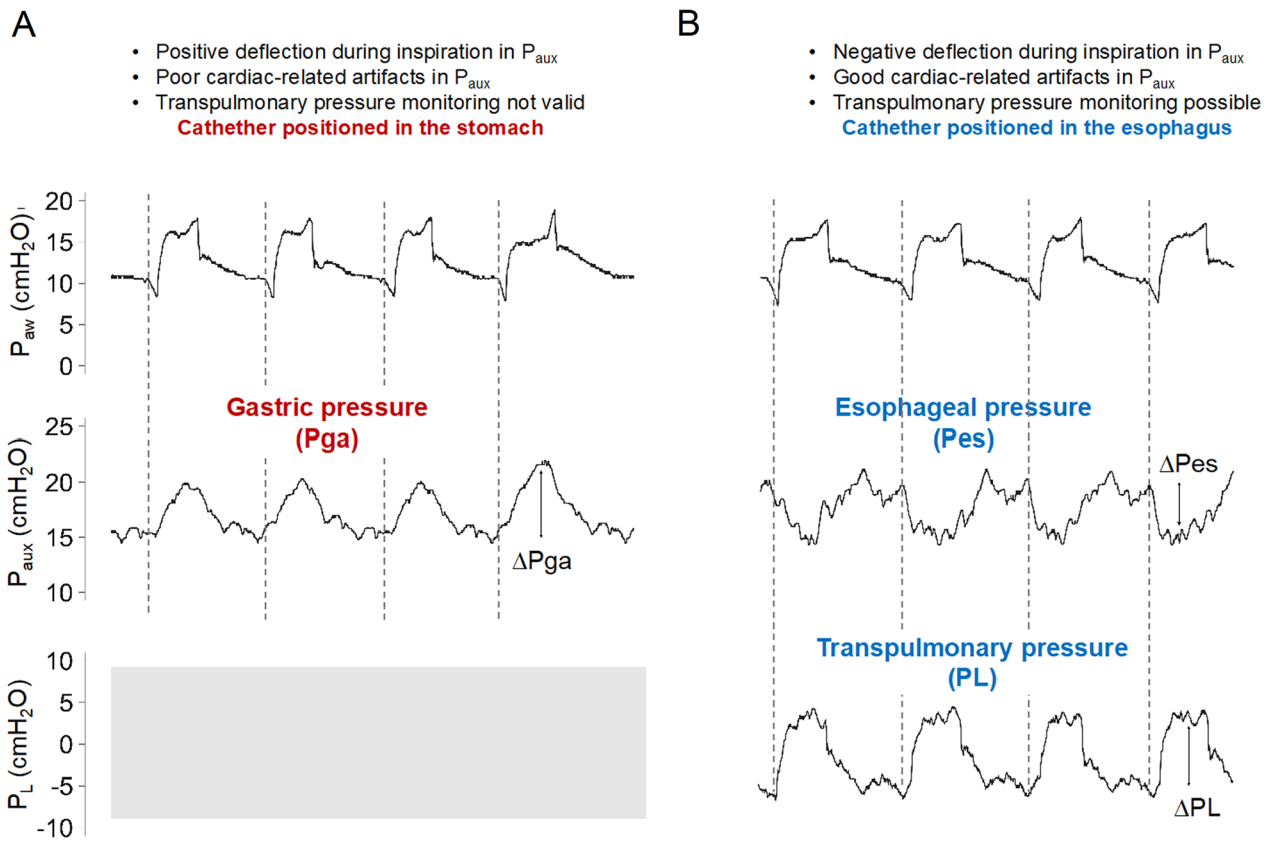

Fig. 2 Esophageal catheter insertion during non-invasive respiratory support. Respiratory recordings during non-invasive ventilation through facemask. Airway pressure, auxiliary pressure, and transpulmonary pressure (difference between airway pressure and esophageal pressure) are displayed (top, medium, and bottom respectively). Vertical dotted lines indicate separation between the respiratory cycles. Of note, during high flow nasal oxygen, there is no airway pressure monitoring and identification of individual respiratory cycles, inspiration and expiration require observation of the patient. Panel A) shows the initial position of the catheter in the stomach (approximately 60 cm from the nostril). Gastric pressure (Pga) is recognized by the characteristic positive deflection in auxiliary pressure (Paux) during relaxed inspiration due to the caudal displacement of the diaphragm. Panel B) shows positioning of the catheter in the lower third of the esophagus (approximately 40 cm from the nostril). Paux becomes negative during inspiration and cardiac oscillations become more noticeable. Measurement of esophageal pressure swing (ΔPes) and lung stress (ΔPL) are shown with vertical solid lines. Paw airway pressure; Paux auxiliary pressure; Pga gastric pressure; Pes esophageal pressure; PL transpulmonary pressure

important to distinguish between "delayed intubation" and "late intubation". While the former refers to a delay between the time of fulfilling intubation criteria (*i.e.,* NRS failure) and intubation, the latter illustrates that intubation occurred at an advanced stage from the initiation of therapy but was not necessarily delayed. Despite the distinction, observational studies have consistently shown that patients with de novo AHRF who failed HFNO or NIV have worse outcomes when intubation is performed beyond 24–48 h of the initial support [30, 79, 116, 117].

Future directions

Identification and prospective validation of thresholds for monitored variables to decide when to escalate respiratory support are needed. Novel study designs such as emulation target trials and collaborative adaptive platforms aim to close this gap [118–120]. In addition, further non-invasive and widely available monitoring tools to assess the respiratory effort (*e.g.,* P_{nose}) and lung stress may allow to achieve personalized NRS titration. The possibility of monitoring respiratory drive and effort using parameters derived from airway occlusion pressure, *i.e.,* P0.1 [88, 121] and ΔPocc [122] could help to achieve this goal. In this context, an integrated approach considering both drive and effort is essential, as certain clinical circumstances may modify the relationship between respiratory drive and inspiratory effort (*e.g.,* respiratory muscle weakness) [76]. Technical and clinical validation are required, and several research groups are currently performing these studies [123, 124]. One of the main challenges that arise when using these techniques

is to control leaks [123]. Under no-leak conditions, high P0.1 during facemask NIV (> 3 cmH_2O) was shown to detect respiratory distress shortly after extubation [125]. Besides, standardizing ventilator settings (*e.g.,* CPAP) to evaluate central drive and effort could enable a more accurate and unbiased comparison among patients [124]. Simple bedside techniques to quantify Vt, particularly during helmet NIV/CPAP, and HFNO, are also needed. Even though EIT offers the potential to become a bedside tool for Vt quantification, it currently requires calibration with a known tidal volume measured by other devices (*e.g.,* ventilator) and clinical validation before bedside implementation [43, 113, 126].

Conclusions

Non-invasive respiratory support has consistently shown variable efficacy across different scenarios in preventing the harmful effects of invasive ventilation and improving outcomes for patients with acute respiratory failure. A thorough assessment of the patients' initial characteristics, combined with close physiological monitoring to adjust settings is essential to tailor a personalized approach and minimize the risk of harm and failure. Importantly, applying non-invasive respiratory support in critically ill patients, particularly those with de novo acute respiratory failure, demands a delicate balance between avoiding invasive ventilation and ensuring timely intubation when clinically indicated.

Abbreviations

AHRF	Acute hypoxemic respiratory failure
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
AUROC	Area under the receiver operating curve
Bpm	Breaths per minute
BREF	Base excess, respiratory rate, PaO_2/FiO_2
COPD	Chronic obstructive pulmonary disease
CoV	Center of ventilation
CPAP	Continuous positive airway pressure
CPE	Cardiogenic pulmonary edema
ΔCVP	Delta central venous pressure
ΔPes	Delta esophageal pressure
ΔPL	Driving transpulmonary pressure
ΔPnose	Delta nasal pressure
ΔPocc	Delta oclussion pressure
EIT	Electrical impedance tomography
FiO_2	Fraction of inspired oxygen
GI index	Global inhomogeneity index
HACOR	Heart rate, acidosis, consciousness, oxygenation, respiratory rate
HFNO	High flow nasal oxygen
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
LUS	Lung ultrasound
NIV	Non-invasive bilevel positive-pressure ventilation
NRS	Non-invasive respiratory support
P0.1	Airway pressure decay at 100 ms
$PaCO_2$	Arterial pressure of carbon dioxide
PaO_2	Arterial pressure of oxygen
Paux	Auxiliary pressure
PEEP	Positive end-expiratory pressure
Pes	Esophageal pressure
Pga	Gastric pressure
PL	Transpulmonary pressure
PS	Pressure support
P-SILI	Patient self-inflicted lung injury
ROX	Ratio of SpO_2/FiO_2 to respiratory rate
RR	Respiratory rate
SpO_2	Pulse oxygen saturation
TFdi	Thickening fraction of diaphragm
VAS	Visual-analog scale
VILI	Ventilator-induced lung injury
Vt/PBW	Tidal volume to

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Ethics approval and consent to participate

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