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NARRATIVE REVIEW

Non-invasive ventilatory support and high-flow nasal oxygen as first-line treatment of acute hypoxemic respiratory failure and ARDS

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Abstract

The role of non-invasive respiratory support (high-flow nasal oxygen and noninvasive ventilation) in the management of acute hypoxemic respiratory failure and acute respiratory distress syndrome is debated. The oxygenation improvement coupled with lung and diaphragm protection produced by non-invasive support may help to avoid endotracheal intubation, which prevents the complications of sedation and invasive mechanical ventilation. However, spontaneous breathing in patients with lung injury carries the risk that vigorous inspiratory effort, combined or not with mechanical increases in inspiratory airway pressure, produces high transpulmonary pressure swings and local lung overstretch. This ultimately results in additional lung damage (patient self-inflicted lung injury), so that patients intubated after a trial of noninvasive support are burdened by increased mortality. Reducing inspiratory effort by high-flow nasal oxygen or delivery of sustained positive end-expiratory pressure through the helmet interface may reduce these risks. In this physiology-to-bedside review, we provide an updated overview about the role of noninvasive respiratory support strategies as early treatment of hypoxemic respiratory failure in the intensive care unit. Noninvasive strategies appear safe and effective in mild-to-moderate hypoxemia ($PaO_2/FiO_2 > 150$ mmHg), while they can yield delayed intubation with increased mortality in a significant proportion of moderate-to-severe ($PaO_2/FiO_2 \leq 150$ mmHg) cases. High-flow nasal oxygen and helmet noninvasive ventilation represent the most promising techniques for first-line treatment of severe patients. However, no conclusive evidence allows to recommend a single approach over the others in case of moderate-to-severe hypoxemia. During any treatment, strict physiological monitoring remains of paramount importance to promptly detect the need for endotracheal intubation and not delay protective ventilation.

Keywords: Acute hypoxemic respiratory failure (AHRF), Acute respiratory distress syndrome (ARDS), Patient self-inflicted lung injury (P-SILI), Noninvasive ventilation (NIV), Pressure support ventilation (PSV), Continuous positive airway pressure (CPAP), Inspiratory effort, Transpulmonary pressure, High-flow nasal oxygen (H-FNO)

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Introduction

Acute hypoxemic respiratory failure (AHRF) accounts for a prominent number of intensive care unit (ICU) admissions worldwide [1], as dramatically highlighted by the ongoing novel coronavirus disease 2019 (COVID-19) pandemic [2–4]. Direct or indirect lung injury accounts for essentially all causes of acute hypoxemic respiratory failure through different pathophysiological pathways. All AHRF causes, however, lead to pulmonary edema caused by lung inflammation that yields aeration loss with hypoxemia, altered respiratory mechanics and increased respiratory drive.

Acute respiratory distress syndrome (ARDS) is a subset of AHRF. ARDS definition requires the presence of bilateral pulmonary infiltrates on chest imaging, with hypoxemia not fully explained by fluid overload or cardiac dysfunction and assessed under positive pressure ventilation with at least 5 cmH_2O of positive end-expiratory pressure (PEEP) [5]. Hypoxemia severity is classified by the ratio of arterial partial pressure of oxygen (PaO_2) to inspired oxygen fraction (FiO_2), as mild (PaO_2/FiO_2 ratio of 201–300 mmHg), moderate (PaO_2/FiO_2 ratio of 101–200 mmHg) and severe (PaO_2/FiO_2 ratio $\leq$ 100 mmHg). ARDS has clinical outcomes comparable to AHRF with similar oxygenation impairment and equal number of involved lung quadrants [6]. Hence, AHRF and ARDS appear to belong to the same disease spectrum portrayed by lung injury, hypoxemia, altered respiratory mechanics and alveolar dead space fraction, and increased respiratory drive. Robust evidence indicates a direct relationship between the degree of hypoxemia and increased mortality [1, 5, 7], and preliminary data suggest that also the entity of dysregulated respiratory drive may be associated to worse outcome [8–10].

Non-invasive oxygenation strategies (high-flow nasal oxygen, helmet or face mask noninvasive ventilation and continuous positive airway pressure) compared with standard oxygen therapy have been shown to be capable of preventing endotracheal intubation in patients with mild hypoxemia [11]. However, the role of noninvasive oxygenation strategies in patients with moderate-to-severe hypoxemia remains unclear. Clinical outcome improves when non-invasive support successfully permits to avoid endotracheal intubation. Differently, if intubation is needed after a failing trial of non-invasive support, mortality is increased, possibly due to the prolonged exposure of injured lungs to the additional damage caused by the increased respiratory effort [12]. Current clinical practice guidelines have been unable to provide clear recommendations regarding the role of non-invasive respiratory support strategies in AHRF/ARDS [13]. Notwithstanding that, the use of non-invasive support is common also in moderate-to-severe cases, especially during the COVID-19 pandemic [14–20], as the shortage of equipment, ventilators and personnel has posed stress on healthcare systems worldwide.

Take-home message

In hypoxemic patients, non-invasive support may help avoid invasive mechanical ventilation but carries the risk of patient self-inflicted lung injury and delayed intubation that detrimentally affect clinical outcome. High-flow nasal cannula and high-PEEP noninvasive ventilation delivered through the helmet interface are the most promising tools for making spontaneous breathing less injurious and increase the likelihood of treatment success. Careful physiological monitoring remains mandatory during any treatment to promptly detect the need for endotracheal intubation and provide protective ventilation

We hereby report a physiology-to-bedside state-of-the art review about the role of noninvasive support in AHRF/ARDS. Our aim is to provide ICU physicians and researchers with an updated overview of the physiological mechanisms underlying the benefits and harms of non-invasive respiratory support, with the final purpose of allowing clinicians to best tailor interventions on patients' individual requirements.

A summary of several clinical trials on non-invasive respiratory support in AHRF/ARDS is shown in Table 1.

Benefits of maintaining spontaneous breathing with non-invasive support

Non-invasive respiratory support includes high-flow nasal oxygen (HFNO) and non-invasive ventilation (NIV) or continuous positive airway pressure (CPAP) delivered through facemasks or helmet. These devices are applied externally, and pressure and flow are delivered to upper airways with minimal invasiveness (Fig. 2).

Use of non-invasive oxygenation strategies preserves physiological pathways of airway protection (e.g. cough and clearance of secretions) [21, 22] and may directly reduce the complications related to endotracheal intubation (e.g. laryngeal and tracheal trauma) and invasive mechanical ventilation [11]. These include ventilator-induced lung injury [23], ventilator-associated pneumonia, sedation [24] and neuromuscular paralysis [25]. By preserving patients' alertness and interaction with the environment, use of non-invasive support reduces the risk of discomfort and delirium.

Maintenance of spontaneous breathing has further benefits related to lung, heart and diaphragm physiology. Specifically, spontaneous breathing prevents diaphragm dysfunction and atrophy [26, 27], allows maintenance of cardiac pre-loading and cardiac output [28, 29], and yields increased aeration of the dependent lung, which minimizes ventilation/perfusion mismatch [30–32]. As

Table 1 Clinical trials of noninvasive ventilatory support in acute hypoxemic respiratory failure

Publication	PMID	Patient population	Intervention	Control	Primary outcome	Other outcomes	Findings
Clinical trials of facemask NIV							
Antonelli et al. [22]	9700176	Mixed acute hypoxemic respiratory failure	Facemask PSV ($n=32$)	Endotracheal intubation ($n=32$)	Improvement in oxygenation	Complications during ICU stay	Same improvement in oxygenation, reduced complications in NIV group
Confalonieri et al. [122]	10556125	ARF due to community-acquired pneumonia	Facemask PSV ($n=28$)	Standard oxygen ($n=28$)	Endotracheal intubation	Hospital and 60-day mortality	Facemask NIV reduced endotracheal intubation but not mortality
Delclaux et al. [100]	11066186	ARF with $P/F \leq 300$ mmHg	Facemask CPAP ($n=62$)	Standard oxygen ($n=61$)	Endotracheal intubation	Hospital mortality	No difference in endotracheal intubation or mortality
Martin et al. [123]	10712326	Mixed ARF	Facemask ($n=32$)	Standard oxygen ($n=29$)	Endotracheal intubation	ICU mortality	Facemask NIV reduced endotracheal intubation but not mortality
Hilbert et al. [124]	11172189	ARF in immunocompromised	Facemask PSV ($n=26$)	Standard oxygen ($n=26$)	Endotracheal intubation	ICU and hospital mortality	Facemask NIV reduced endotracheal intubation rates and ICU/hospital mortality
Ferrer et al. [125]	14500259	Acute hypoxemic respiratory failure	Facemask PSV ($n=51$)	Standard oxygen ($n=54$)	Endotracheal intubation	ICU- and 90-day mortality	Facemask NIV reduced endotracheal intubation rates and ICU & 90-day mortality
Gunduz et al. [126]	15843697	Patients with Flail chest with $P/F \leq 300$ mmHg	Facemask CPAP ($n=25$)	Endotracheal intubation ($n=27$)	ICU mortality	ICU complications	Facemask NIV reduced ICU mortality and nosocomial infection rates
Hernandez et al. [127]	19749006	AHRF due to chest trauma, $P/F < 200$ mmHg	Facemask PSV ($n=25$)	Standard oxygen ($n=25$)	Endotracheal intubation	Hospital mortality	Facemask NIV reduced endotracheal intubation but not mortality
Wermke et al. [128]	21927036	ARF in allogeneic SCT	Facemask PSV ($n=42$)	Standard oxygen ($n=44$)	*P/F* ratio	Endotracheal intubation and hospital mortality	No difference in P/F ratio, endotracheal intubation, or mortality
Zhan et al. [129]	22020236	AHRF (200 mmHg > $P/F \leq 300$ mmHg)	Facemask PSV ($n=21$)	Standard oxygen ($n=19$)	Endotracheal intubation	ICU/hospital mortality	Facemask NIV reduced endotracheal intubation but not mortality
Lemiale et al. [130]	26444879	AHRF in immunocompromised	Facemask PSV ($n=191$)	Standard oxygen ($n=183$)	28-day mortality	Endotracheal intubation	No difference in mortality or endotracheal intubation
He et al. [131]	31484582	Mild ARDS due to community-acquired pneumonia	Facemask PSV ($n=102$)	Standard oxygen ($n=98$)	Endotracheal intubation	ICU mortality	No difference in endotracheal intubation or mortality

Table 1 (continued)

Publication	PMID	Patient population	Intervention	Control	Primary outcome	Other outcomes	Findings
Clinical trials of high flow nasal oxygen							
Azevedo et al. [132]	PMC4796500	AHRF	High flow nasal oxygen ($n=14$)	Facemask PSV ($n=16$)	Endotracheal intubation		No difference in endotracheal intubation rates
Frat et al. [85]	25981908	AHRF	High flow nasal oxygen ($n=106$)	Facemask PSV ($n=110$); Standard Oxygen ($n=94$)	Endotracheal intubation	90-day mortality	No difference in endotracheal intubation but twofold and 2.5-fold increase in mortality with standard oxygen and facemask NIV, respectively, in comparison with high flow nasal oxygen
Doshi et al. [133]	29310868	Mixed ARF	High flow nasal oxygen ($n=104$)	Facemask PSV ($n=100$)	Endotracheal intubation		High flow nasal oxygen was not inferior to facemask NIV to prevent endotracheal intubation
Bell et al. [134]	26419650	Mixed ARF	High flow nasal oxygen ($n=48$)	Standard oxygen ($n=52$)	Endotracheal intubation		High flow nasal oxygen reduced endotracheal intubation rates
Lemiale et al. [130]	26521922	AHRF in immunocompromised	High flow nasal oxygen ($n=52$)	Standard oxygen ($n=48$)	Endotracheal intubation or NIV within 2 h		No difference in endotracheal intubation rates
Jones et al. [135]	26577199	Mixed ARF	High flow nasal oxygen ($n=165$)	Standard oxygen ($n=138$)	Endotracheal intubation in ED	Hospital mortality	No difference in endotracheal intubation rates or mortality
Azoulay et al. [136]	30357270	AHRF in immunocompromised	High flow nasal oxygen ($n=388$)	Standard oxygen ($n=388$)	28-day mortality	Endotracheal intubation	No difference in mortality of endotracheal intubation rates
Clinical trials of Helmet NIV							
Cosentini et al. [137]	20154071	CAP	Helmet CPAP ($n=20$)	Standard oxygen ($n=7$)	Time to reach $P/F>315$		Helmet NIV rapidly improved P/F ratio
Squadrone et al. [138]	20533022	Acute lung injury in hematologic malignancy	Helmet CPAP ($n=20$)	Standard oxygen ($n=20$)	Endotracheal intubation		Helmet NIV reduced the need for endotracheal intubation
Brambilla et al. [139]	24817030	CAP	Helmet CPAP ($n=40$)	Standard oxygen ($n=41$)	Meeting endotracheal intubation criteria		Helmet NIV reduced the proportion of patients meeting endotracheal intubation criteria

Table 1 (continued)

Publication	PMID	Patient population	Intervention	Control	Primary outcome	Other outcomes	Findings
Patel et al. [87]	27179847	ARDS	Helmet PSV/CPAP ($n=44$)	Facemask NIV ($n=39$)	Endotracheal intubation	90-day mortality	Helmet NIV reduced endotracheal intubation rates and mortality
Grieco et al. [68]	33764378	AHRF due to COVID-19 with $P/F \leq 200$ mmHg	Helmet PSV ($n=54$)	High flow nasal oxygen ($n=55$)	Respiratory support-free days at 28 days	Endotracheal intubation	Helmet NIV did not increase respiratory support-free days but reduced the rate of endotracheal intubation

In this table, only randomized controlled trials which enrolled patients with de-novo hypoxemic respiratory failure and included either endotracheal intubation or mortality among the reported outcomes are reported

CAP community-acquired pneumonia, *ARF* acute respiratory failure; *NIV* non-invasive ventilation, *AHRF* acute hypoxemic respiratory failure, *SCT* stem cell transplant, *ARDS* acute respiratory distress syndrome, *P/F* PaO_2/FiO_2 ratio, *PSV* pressure support ventilation, *CPAP* continuous positive airway pressure, *ICU* intensive care unit, *ARDS* acute respiratory distress syndrome

such, non-invasive respiratory support is the less invasive strategy to improve hypoxemia in case of failure of conventional oxygen therapy [22, 33–35].

Nevertheless, maintenance of spontaneous breathing during moderate-to-severe AHRF and ARDS carries inherent risks, and the unwise use of noninvasive support may prolong the exposure of injured lungs to the harmful effects of increased respiratory drive, ultimately leading to delayed endotracheal intubation and worse clinical outcome.

Harms of spontaneous breathing

The potential harms of spontaneous breathing in non-intubated AHRF and ARDS patients derive from the vicious circle generated by hypoxemia, dysregulated inspiratory effort, altered respiratory mechanics and inhomogeneous lung inflation (Fig. 1).

Increased respiratory drive is caused by multiple mechanisms: impairment in gas exchange and respiratory mechanics, metabolic acidosis, inflammation, fever and agitation [36]. These result in intense inspiratory effort, high tidal volumes and tachypnea, with or without additional mechanical support [9, 10, 37, 38]. Injured lungs are exposed to higher risk of volu- and baro-trauma, which further worsen lung damage in a form similar to the ventilator-induced lung injury observed during controlled ventilation [39, 40].

Hyperventilation with intense inspiratory effort, high tidal volumes and inspiratory pressures may injure even healthy lungs [41]. However, the detrimental effects of intense inspiratory effort are magnified by the presence of lung injury, which makes the distribution of inspiratory forces inhomogeneous across the tissue [39]. The intense inspiratory effort (estimated by the inspiratory deflection in esophageal pressure-ΔP_{ES}) causes the inflation of large tidal volumes in an aerated compartment whose size is reduced by the edema, alveolar flooding and atelectasis. Moreover, the intense inspiratory effort interacts with the solid-like behavior of the injured lung, ultimately generating a vertical gradient in regional transpulmonary pressure. This mostly occurs at the beginning of inspiration (before fresh gas flow arrives from the non-invasive support) and may shift lung gas from non-dependent anterior lung zones to dependent posterior regions: this phenomenon is termed *pendelluft* and causes additional regional over-stretch in the dependent lung regions, worsening inflammation [42–44]. Finally, the pleural pressure negative deflections induced by intense inspiratory effort transiently decrease alveolar and lung interstitial pressure. This increases transmural pulmonary capillary pressure and facilitates transvascular fluid filtration, which exacerbates interstitial and alveolar edema [45].

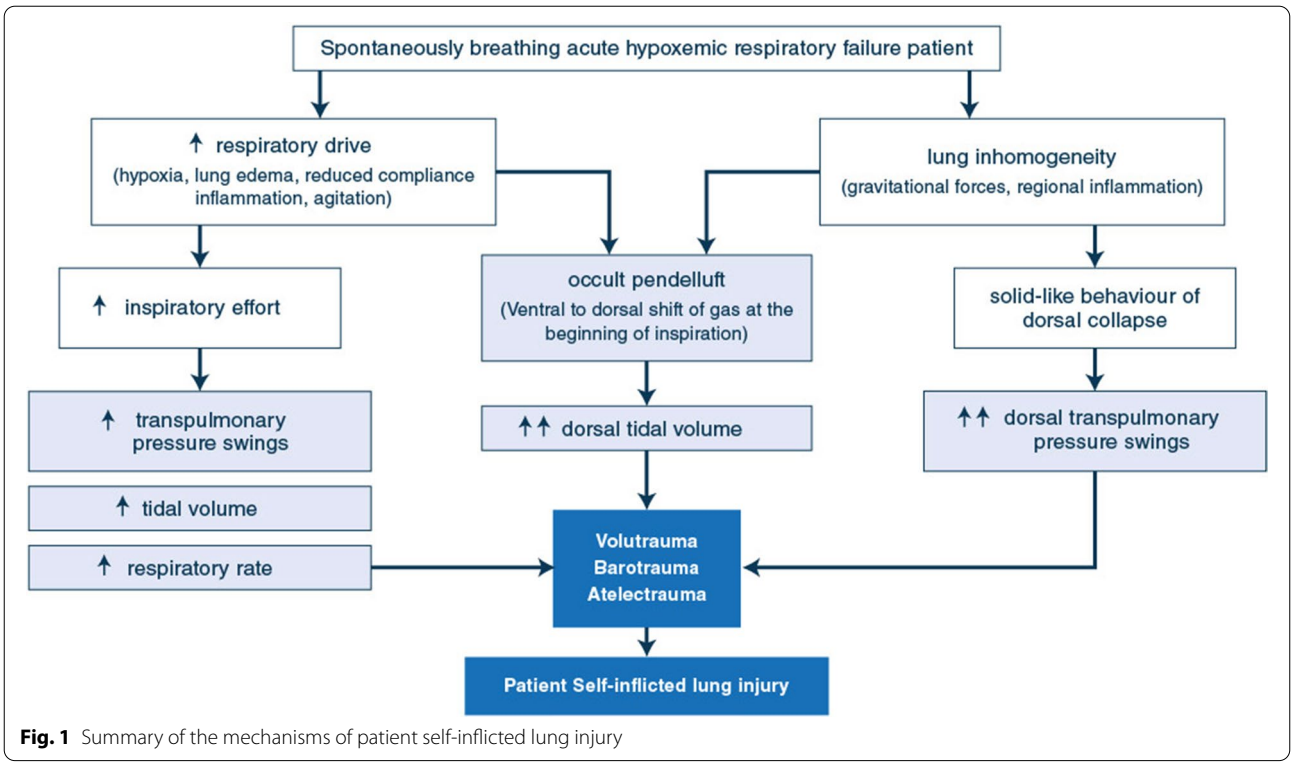

Fig. 1 Summary of the mechanisms of patient self-inflicted lung injury

Vigorous inspiratory effort can generate inhomogeneity and differences in regional strength of the diaphragm, which injure the diaphragm itself. Diaphragm injury results in sarcolemmal rupture, sarcomeric disarray and muscle inflammation. This causes diaphragm weakness, which detrimentally affects short- and long-term clinical outcome [46–48].

Through all these mechanisms, spontaneous breathing may result in patient self-inflicted lung injury (P-SILI) [40, 49, 50] (Fig. 1).

Clinical studies have demonstrated a causal relationship between persistent high respiratory effort and failure of non-invasive support [9, 10, 37]. Persistently high inspiratory effort [9, 10], respiratory rate [51] and tidal volume [37, 38] despite noninvasive support are associated to treatment failure and the need for intubation. Inspiratory effort may be proportional to patient's severity, and patient's susceptibility to P-SILI is magnified in case of most severe acute respiratory failure [34].

These considerations strengthen the hypothesis that increased mortality of patients failing noninvasive support might be explained by worse severity combined with prolonged exposure of injured lungs to the higher respiratory drive causing P-SILI [52–54].

Still, some controversy exists about the concept of P-SILI itself. Physiological data on endurance-trained healthy individuals showed that potentially extreme transpulmonary pressure swings (up to 60 cmH_2O) and tidal volumes (>3 L) did not result in lung damage [55, 56]. Accordingly, the mechanisms underlying P-SILI clinical effects remain to be fully elucidated [9, 10, 57], thus implying that not all patients may be exposed to the same risk of P-SILI.

How to make spontaneous effort non-injurious during non-invasive support

To limit the risk of P-SILI during noninvasive support, research has been focusing on strategies that could render spontaneous breathing less injurious [46, 58].

First, non-respiratory factors that may increase respiratory drive (i.e. pain, discomfort, metabolic acidosis, fever) should be assessed and corrected. Afterwards, pharmacologic agents to reduce respiratory drive may be used. Indeed, only propofol and benzodiazepines have been shown to reduce respiratory effort [59, 60], while opioids primarily reduce respiratory rate with mixed effects on tidal volumes and inspiratory effort [61, 62]. However, the use of propofol and benzodiazepines may have relevant side effect, which limit their use to highly selected critically ill patients. Opioids may improve dyspnea but also increase the risk of apnea and their use should always be accompanied by appropriate monitoring [24]. Dexmedetomidine seems to exert no direct effect on respiratory drive [63].

The application of high PEEP levels also shows promise for P-SILI prevention. The effect of PEEP on lung recruitment and oxygenation is well described [34, 64]. Recently, the application of moderate-to-high PEEP (10–15 cmH_2O) levels during spontaneous breathing and ARDS was suggested to improve ventilation homogeneity and prevent pendelluft phenomenon through a more balanced distribution of negative inspiratory pressure across the lung tissue [65]. Moreover, PEEP exerts a direct mechanical effect on the diaphragm by changing the force–length relationship of its fibers [66]. This yields electromechanical uncoupling, reduces the inspiratory effort and lowers tidal volume, finally rendering spontaneous breathing less injurious [67]. For these reasons, strategies to apply higher PEEP level (i.e. 10–15 cmH_2O) by means of non-invasive support are gaining growing attention for the non-invasive management of AHRF/ARDS [10, 11, 68].

Techniques

High-flow nasal oxygen

HFNO is provided by an air–oxygen blender directly connected to a flow meter (set up to 60 L/min), by a turbine connected to an oxygen flow meter or by a gas-compressed based ventilator and a heated humidifier. Continuous flow of heated and humidified gas with FiO_2 up to 100% is delivered to the patient through nasal cannula [69, 70].

HFNO allows accurate delivery of set FiO_2, provides low, variable levels of positive pressure in the airways generating a mild PEEP effect, and flushes the upper airways yielding washout of dead space [71–77]. As compared with standard oxygen, HFNO decreases inspiratory effort, work of breathing and respiratory rate, improves comfort and oxygenation [78–83]. In hypoxemic patients, the most beneficial effects are obtained as higher gas flow is applied (i.e. 60 L/min) [84].

These physiological effects make HFNO the optimal strategy for oxygen therapy in patients with high-flow demands, such as those affected by AHRF and ARDS [12].

Clinically, a randomized trial comparing HFNO with standard oxygen and intermittent sessions of facemask NIV showed no effects on the rate of endotracheal intubation in the overall population, but a reduction in the intubation rate among the subgroup of patients with $PaO_2/FiO_2 \leq 200$ mmHg treated with HFNO [85].

Concerning the P-SILI risk, physiological data have shown that HFNO could be more protective for the lung when compared to standard oxygen by favoring a more homogeneous distribution of tidal volume [80]. Moreover, it has been shown that HFNO results in some alveolar recruitment due to PEEP effect: this potentially yields reduced lung strain (i.e. ratio of tidal volume to function residual capacity, a major determinant of ventilation-induced lung injury) [80]. Importantly, during HFNO, this is accomplished with minimal additional risk of barotrauma, since there is no inspiratory assistance for tidal breathing.

Non-invasive ventilation

Mode of ventilation

In most studies and clinical practice, NIV is delivered as a means of biphasic positive airway pressure (mainly pressure support ventilation [PSV] = pressure support + PEEP) or continuous positive airway pressure (CPAP): unlike PSV, CPAP does not provide any inspiratory support. Despite the differences in physiological effect and mechanisms of action between CPAP and NIV, CPAP is classified as NIV because it is frequently used as an alternative to PSV [86, 87]. Although ICU ventilators can administer CPAP-NIV, in order to adequately fulfil patients' flow needs without additional increase in work of breathing [88, 89], the use of oxygen/air blenders, turbines or Venturi systems continuously delivering high flow are necessary during helmet CPAP, and could be encouraged also when facemasks are the chosen interfaces [90, 91].

Interfaces

Non-invasive ventilation may be delivered by facemasks or helmets. Both interfaces are characterized by peculiar features that are elucidated below.

Facemask Noninvasive ventilation

Facemasks (oronasal or full-face) are the most used interfaces for NIV. The main difference between oronasal and full-face masks is their internal dead space, but this difference does not affect carbon dioxide rebreathing, minute ventilation, patient's effort and clinical outcome [92]. Oronasal and full-face may be considered interchangeable even in the same patient, to optimize comfort and tolerance.

Facemask CPAP is usually delivered with pressure set between 5 and 8 cmH_2O. Noninvasive ventilation is usually applied in the PSV mode, with PEEP ranging between 5 and 8 cmH_2O and pressure support of 8–14 cmH_2O.

Both CPAP and PSV-NIV increase airway pressure, ameliorate arterial oxygenation, increase end-expiratory lung volume [93–96] and improve cardiac function by reducing left ventricular afterload and right ventricular preload [97, 98]. PSV-NIV also decreases inspiratory effort and work of breathing [94, 99].

However, studies conducted in the 2000s showed that CPAP is associated with only transient improvements in oxygenation and dyspnea, with no effects on intubation

rate [100]. Differently, use of PSV-NIV yielded more promising results [22]. The results of a recent meta-analysis that included patients with AHRF showed that the use of facemask PSV-NIV may associated with lower risk of intubation and mortality, as compared to standard oxygen [11].

Nevertheless, facemask NIV prevents endotracheal intubation in only 40–60% of the cases, and its failure is an independent factor associated to worse survival [53], which raises the following concerns about the use of facemask NIV: first, facemask NIV can be used only with lower PEEP levels (5–8 cmH_2O), because of the presence of air leaks [87]. This may be insufficient to correct hypoxemia [7] or reduce the inspiratory effort. Second, full inspiratory synchronization during PSV-NIV may increase transpulmonary pressure swings and tidal volume [101, 102], which may contribute to P-SILI and are associated with treatment failure and high mortality [37, 38].

From a clinical standpoint, two recent randomized clinical trials showed that facemask PSV-NIV may be less effective than HFNO and helmet NIV in preventing endotracheal intubation during moderate-to-severe AHRF [85, 87].

Helmet non-invasive ventilation

Air leaks, discomfort and skin breakdown [103] limit the tolerability of facemask NIV, making prolonged treatments with specific settings (i.e. high PEEP) difficult to apply [104].

The helmet interface represents an alternative to facemasks for NIV administration in hypoxemic patients. The helmet is a transparent hood that covers the entire head, sealed with a soft neck collar. The helmet has the advantage of better tolerability and less air leaks, enabling the possibility to deliver prolonged treatments with high PEEP [26, 68, 87, 105, 106]. Helmets can be used to deliver both PSV-NIV and CPAP.

For helmet CPAP, a continuous fresh gas flow (Venturi systems, gas compressed or turbine generators) is connected to the inlet port of the interface and a PEEP valve is connected to helmet outlet. Physiological studies suggest that a minimum fresh gas flow of 40–60 L/min (> 35 L/min) is required to substantially reduce the risk of CO_2 rebreathing [107].

In helmet PSV-NIV, pressure support level is usually set at 10–14 cmH_2O with the shortest pressurization time, and PEEP of 10–12 cmH_2O. Part of the pressure support is dissipated in the helmet and does not necessarily correspond to the pressure inside at airway opening and in the alveoli. These pressure-support settings, although sub-optimal for muscle unloading [10, 108, 109] and often associated with inspiratory desynchronization [101, 102], relieve inspiratory effort and may dampen swings in transpulmonary driving pressure, possibly reducing the risk of P-SILI. Moreover, the higher levels of PEEP improve lung recruitment and gas exchange, and may mitigate the risk of P-SILI when compared to HFNO and facemask NIV [10, 65, 106].

Patient-ventilator asynchrony may accompany the use of helmet PSV-NIV [110]. Trigger and cycling-off delays and errors may occur due to increased compliance of the helmet in relation to flow [10]. However, the helmet's large internal volume (approximatively 18 L) acts as a reservoir and allows the patient to receive inspiratory flow also in case of poor patient-ventilator interaction.

The use of helmet has a learning curve. Importantly, the large internal volume of the helmet can expose patients to CO_2 rebreathing, which is directly related to patient CO_2 production and inversely to the fresh gas flow passing through the interface [107, 111].

Helmet PSV-NIV with specific settings (10–14 cmH_2O with the shortest pressurization time, and PEEP of 10–12 cmH_2O) was shown to improve oxygenation, dyspnea, inspiratory effort in comparison to HFNO, particularly in patients with intense baseline inspiratory effort and more severe oxygenation impairment (PaO_2/FiO_2 ratio < 150 mmHg) [10].

Given the physiologic effects of helmet PSV-NIV, severe AHRF-ARDS patients (e.g. with a PaO_2/FiO_2 ratio < 150) may benefit from the use of this interface and may tolerate sustained application of higher PEEP to improve oxygenation and reduce inspiratory effort, especially if the inspiratory effort remains high with HFNO [10]. The risk of CO_2 rebreathing necessitates monitoring fresh gas flow rates, adjustment of pressure support parameters, and periodic arterial blood sampling.

Monitoring during non-invasive support

Non-intubated patients with AHRF undergoing a trial of non-invasive support must be closely monitored to identify early signs of failure and avoid delayed intubation [54, 112]. Impairment in gas exchange, signs of high respiratory drive/effort and composite scores are used to assess the response to noninvasive support and guide the decision to intubate (Table 2).

Oxygenation should be continuously monitored by pulse oximetry (SpO_2), which however, could overestimate the real arterial oxygen content in the presence of low arterial $PaCO_2$ [113]. Arterial blood gas analysis provides more accurate although intermittent assessment of patient's oxygenation (PaO_2/FiO_2 ratio) [113]. Moderate–severe hypoxia predicts the need for intubation early after NIV initiation [37, 38, 114, 115] and low SpO_2/FiO_2 ratio is associated with risk of failure in patients supported with HFNO [51]. Severe hypoxia may not be per se an absolute indication for intubation, while trend over

Table 2 Relevant physiological measures for monitoring of hypoxemic patients on noninvasive respiratory support

Parameter	Monitoring technique/score calculation	Clinical thresholds associated with risk of failure	Limitations
SpO_2/FiO_2	Pulse oximetry	< 120 and/or worsening trend	Underestimation of severity with low $PaCO_2$
PaO_2/FiO_2	Arterial blood gas analysis	< 150–200 mmHg and/or worsening trend	Intermittent
Respiratory Rate	Clinical examination	> 25–30 and/or not decreasing with support	Poorly correlated with effort
Expired tidal volume	Ventilator	> 9–9.5 ml/kg PBW	Not feasible during HFNO, standard helmet NIV
ΔP_{ES}	Esophageal balloon catheter	> 15 cmH_2O and/or reduction < 10 cmH_2O during NIV	Needs some expertise
ROX	(SpO_2/FiO_2)/Respiratory Rate	< 2.85 at 2 h of HFNO initiation < 3.47 at 6 h of HFNO initiation < 3.85 at 12 h of HFNO initiation	Validated only for HFNO
HACOR scale[a]	Heart rate, acidosis, consciousness, oxygenation and respiratory rate[a]	> 5 at 1 h of NIV initiation	Intermittent, time consuming, validated only for NIV

PBW predicted body weight, *NIV* noninvasive ventilation, *HFNO* high-flow nasal oxygen, *DeltaPes* inspiratory effort

[a] The HACOR score is calculated as the sum of the scores for each individual variable, assigned as follows. Heart rate: ≤ 120 beats/min = 0, ≥ 121 beats/min = 1; pH: ≥ 7.35 = 0, 7.30–7.34 = 2, 7.25–7.29 = 3, < 7.25 = 4; Glasgow Coma Scale score: 15 = 0, 13–14 = 2, 11–12 = 5, ≤ 10 = 10; PaO_2/FiO_2 ratio: ≥ 201 mmHg = 0, 176–200 mmHg = 2, 151–175 mmHg = 3, 126–150 mmHg = 4, 101–125 mmHg = 5, ≤ 100 mmHg = 6; Respiratory rate: ≤ 30 breaths/min = 0, 31–35 breaths/min = 1, 36–40 breaths/min = 2, 41–45 breaths/min = 3, ≥ 46 = 4

time may be a more sensitive marker: improving oxygenation is associated with NIV success [87, 115], likely because worsening oxygenation indicates clinical deterioration and/or P-SILI.

Inspiratory effort may be a specific predictor of the need for intubation, as it reflects the underlying severity, and it is the main determinant of P-SILI. Despite not being a reliable index of effort [116], respiratory rate remains the most used surrogate of respiratory drive because of its simplicity to use. Low or decreasing respiratory rate is associated with success of noninvasive support [117, 118]. During facemask PSV-NIV, expired tidal volume > 9–9.5 ml/kg PBW indicates lack of relief of inspiratory effort and is a predictor of NIV failure [37, 38]. Differently, during helmet PSV-NIV, it is not possible to monitor tidal volume, as the value displayed by the ventilator includes the amount of gas needed to distend the interface. In this case, the volume inhaled by the patient cannot be measured or estimated without additional equipment, routinely not available at the bedside [119]. Precise values of inspiratory effort associated with high risk of failure of non-invasive support are not defined, although a ΔP_{ES} threshold of 15 cmH_2O seems reasonable [120]. Also, lack of ΔP_{ES} reduction over time has been shown to be an early and accurate predictor of NIV failure in a recent physiologic study [9].

Since the power of a single parameter to predict the subsequent need for intubation is low, composite scores have been tested. The ROX index, defined as the ratio between SpO_2/FiO_2 and respiratory rate accurately predicted the outcome of HFNO [51]. Repeated assessment of the HACOR scale (which includes heart rate, acidosis, consciousness, oxygenation, and respiratory rate) allows dynamic monitoring of the risk of intubation during facemask NIV [118]. To date, no validated score exists to predict failure during helmet NIV.

Clinical evidence

A summary of the advantages, disadvantages and main technical specificities of the discussed non-invasive support tools is displayed in Figs. 2 and 3. The oxygenation improvement generated by non-invasive support may help avoid endotracheal intubation and permit maintenance of spontaneous breathing. However, spontaneous breathing in patients with lung injury carries the risk of delayed intubation and P-SILI during the treatment. Non-invasive strategies appear safe, effective and essentially equivalent in mild-to-moderate hypoxemia ($PaO_2/FiO_2 > 150$ mmHg), while no conclusive evidence exists regarding whether and which noninvasive strategy should be applied in the management of moderate-to-severe ($PaO_2/FiO_2 \leq 150$ mmHg) cases.

In 2015, Frat et al. [85] showed that patients with moderate-to-severe AHRF treated with HFNO were burdened by lower risk of intubation compared to those receiving facemask NIV. These results may be due to, at least in part, the increased comfort and relief of dyspnea produced by HFNO.

A clinical comparison between helmet NIV and facemask NIV was performed by Patel et al. [87]: a significant

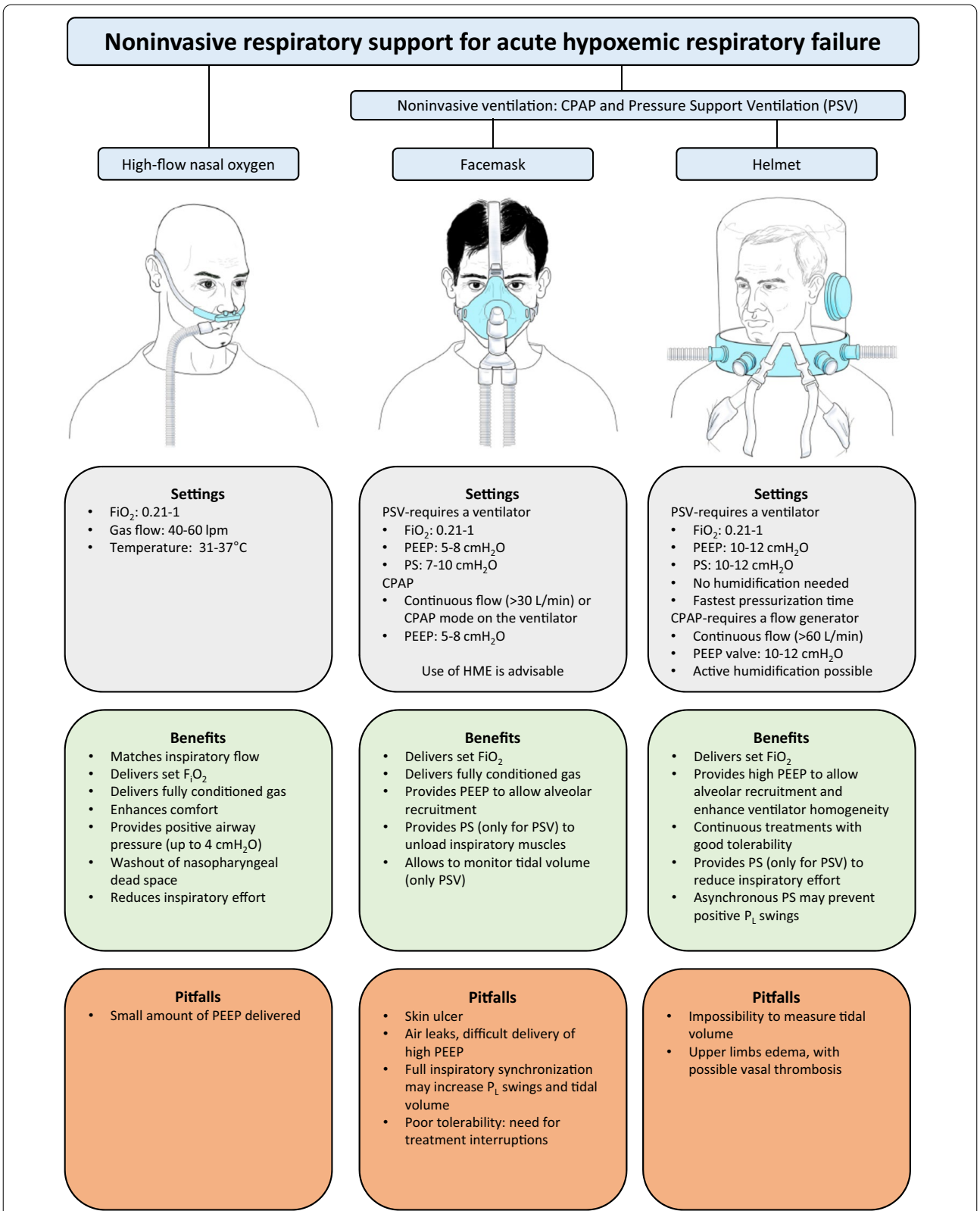

Fig. 2 Benefits and risks of the tools for non-invasive respiratory support in AHRF/ARDS. *PSV* pressure support ventilation, *CPAP* continuous positive airway pressure, *PS* pressure support, P_L, transpulmonary pressure, *HME* heat and moisture exchanger

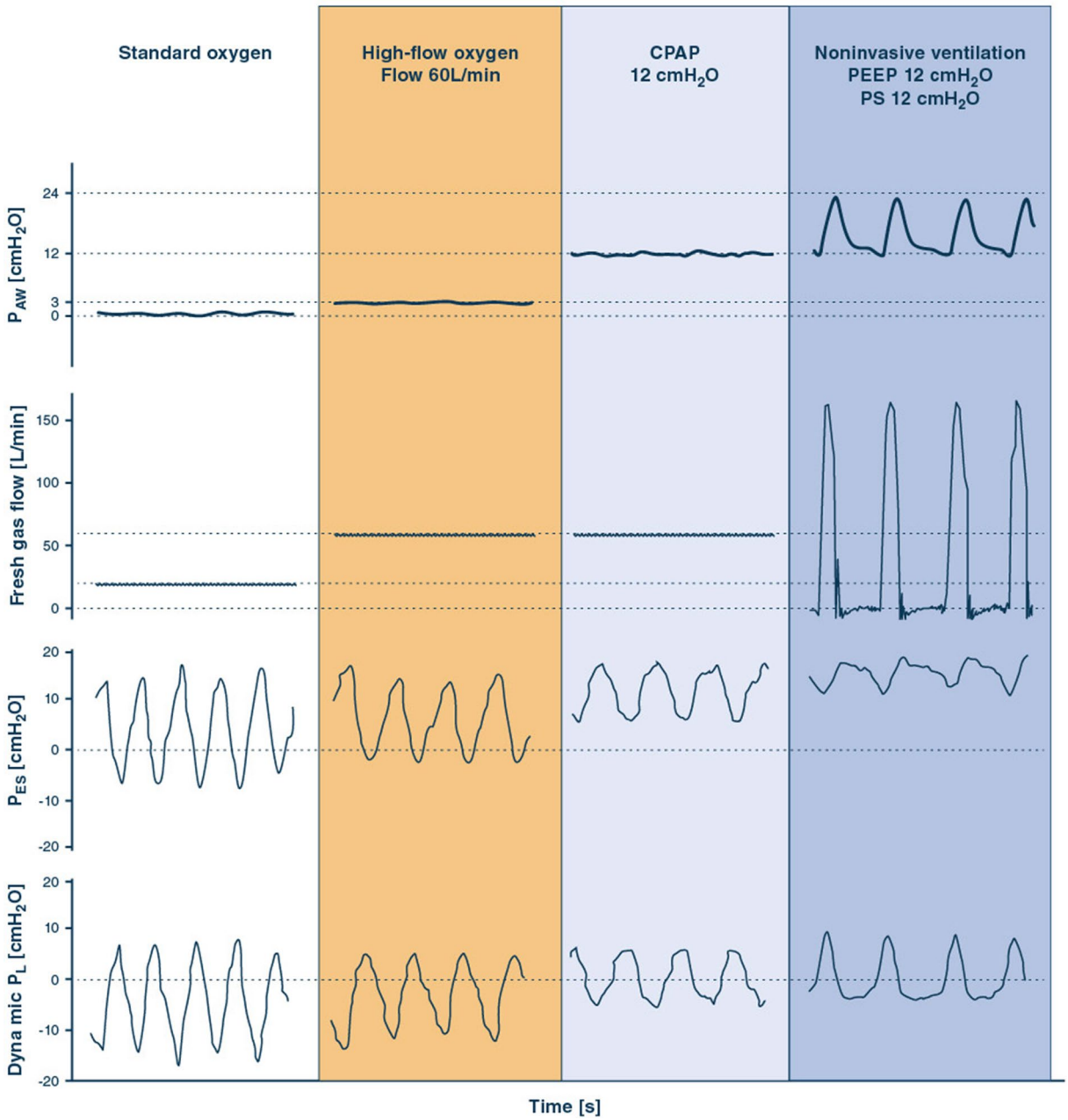

Fig. 3 Mechanisms of action of standard oxygen therapy, HFNO, CPAP and PSV-NIV in a representative patient with AHRF. Tracings of pressure at airway opening (P_{AW}, a continuous pressure 3 cmH_2O is assumed for HFNO [80]), inspiratory flow, esophageal pressure (P_{ES}) and dynamic transpulmonary pressure (P_L, calculated as $P_{AW} - P_{ES}$) are displayed. P_{ES} negative deflection during inspiration is the inspiratory effort (ΔP_{ES}). P_L positive deflection is the dynamic transpulmonary driving pressure (ΔP_L), which is an estimate of the static transpulmonary driving pressure [121]

reduction in intubation rate and mortality was detected in the helmet group. This was probably due to the physiological advantages of helmet, namely delivery of higher PEEP in continuous sessions with enhanced comfort.

In a meta-analysis, Ferreyro et al. showed an aggregate reduced risk of endotracheal intubation and mortality with helmet NIV compared to both HFNO and facemask NIV, acknowledging however, the lack of large-scale conclusive data on the clinical effects of helmet NIV [11].

Recently, the first head-to-head randomized trial compared first-line continuous treatment with helmet

PSV-NIV with specific settings (PEEP = 12 cmH_2O pressure and pressure support = 10–12 cmH_2O) vs. HFNO alone in patients with moderate-to-severe AHRF. Results showed no significant inter-group difference in the days free of respiratory support at 28 days, but lower intubation rate and increased 28-day invasive ventilation-free days the helmet group [68].

Conclusions

Because of its simplicity of use, physiological and clinical effects recent clinical guidelines suggest HFNO as the optimal first-line intervention in AHRF [12]. Early treatment with high-PEEP helmet PSV-NIV may represent a tool to further optimize the non-invasive treatment in most severe patients, but further adequately powered randomized studies are warranted to provide conclusive evidence.

The optimal interface for non-invasive support of AHRF/ARDS remains a debated topic. Personalized treatments based on patients phenotypes [3], clinicians' expertise, optimized interface, control of respiratory drive and strict physiological monitoring to promptly detect treatment failure represent the wisest approach for a safe clinical management.

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Author contributions
DLG, SMM and MA designed the review. All authors contributed to literature search and manuscript drafting. All the authors reviewed the final draft of the manuscript and agreed on submitting it to Intensive Care Medicine.

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Data availability Not applicable.

Declarations

Conflicts of interest
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