Intensive Care Med (2023) 49:840–843
https://doi.org/10.1007/s00134-023-07048-1

EDITORIAL

Personalized noninvasive respiratory support for acute hypoxemic respiratory failure

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Physiological rationale

The last decade has witnessed major changes in the management of patients with acute de novo hypoxemic respiratory failure (AHRF). Noninvasive support may help avoid endotracheal intubation and reduce the detrimental effects of sedation and invasive mechanical ventilation. However, if noninvasive support fails and the patient is subsequently intubated (30–60% of cases), it can lead to increased mortality [1]. A more thorough understanding of the physiology of spontaneous breathing has led a new bedside conundrum: meticulously balancing the use of noninvasive devices to avoid intubation against the risk of exposure to delayed intubation combined to the newly described concept of self-inflicted lung injury (P-SILI). P-SILI occurs due to increased inspiratory effort (ΔP_{ES}) and trans-pulmonary pressures swings leading inhomogeneous lung inflation and local overstretch. Despite the existence of P-SILI remains debated, this physiologic concept may plausibly explain the adverse events noted in some patients failing noninvasive support.

In addition to standard oxygen therapy, high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), and pressure-support noninvasive ventilation (NIV) are the most extensively applied noninvasive respiratory support modalities in the acute care setting. The latter two modalities may be delivered by either a facemask or a helmet interface. The different devices have varying mechanisms that may impact oxygenation, ventilation, and cardiac physiology in patients with AHRF [2]. Below we summarize the most recent evidence for noninvasive respiratory support in de novo AHRF. The evidence summarized does not focus on the application post-extubation, on post-operative patients, respiratory failure due to cardiogenic pulmonary edema and acute exacerbation of chronic pulmonary diseases.

Clinical evidence

A series of meta-analyses have demonstrated a potential role of facemask NIV/CPAP in preventing intubation compared to standard oxygen therapy. These studies focused predominantly on AHRF of low severity and have not shown a consistent benefit [3]. Enthusiasm for facemask NIV was challenged by the results of the FLORALI trial, which suggested a possible higher risk of intubation and mortality in the most severely ill patients ($PaO_2/FiO_2 < 200$ mmHg) treated with NIV compared to HFNC [4]. Randomized trials of HFNC versus standard oxygen therapy have consistently shown reduced need for endotracheal intubation [5], but no effect on mortality [6, 7].

During the coronavirus disease 2019 (COVID-19) pandemic, a trial by Perkins and coworkers found that an initial strategy of CPAP, mostly delivered through a facemask with low levels of PEEP (8 cmH_2O), reduced a composite endpoint of endotracheal intubation or mortality within 30 days, compared to standard oxygen therapy [8]. Because of some limitations including early termination, a high frequency of crossover between the treatments and the lack of prespecified criteria for intubation, the results of this trial warrant further confirmatory investigations.

In a single-center exploratory trial, Patel and coworkers found lower rates of intubation and mortality with helmet compared to facemask NIV; the observed huge mortality benefit in the intervention group can be considered as surprising, especially because of the limited sample and the early termination of enrollment [9]. However,

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these intriguing findings led to further evaluation into the mechanisms by which the helmet interface could optimize the support of AHRF patients. These mechanisms include effective administration of higher PEEP (> 10 cmH_2O), which may improve oxygenation and mitigate the risk of self-inflicted lung injury by inspiratory effort modulation and more homogeneous lung inflation [2]. The first head-to-head comparison of helmet NIV alternating with HFNC compared to HFNC alone in patients with COVID-19 and PaO_2/FiO_2 < 200 mmHg (HENIVOT) found, as an exploratory outcome, lower rates of intubation in patients treated with the helmet, who received a median PEEP of 12 cmH_2O. However, a subsequent larger trial comparing helmet NIV to usual respiratory support (standard oxygen, facemask NIV or HFNC) did not find differences in intubation rate or mortality [10].

Taken together, these data highlight the uncertainty about the optimal initial strategy for noninvasive support in patients AHRF. Currently, due to its simplicity and reduction in intubation compared to standard oxygen therapy, HFNC represents the suggested initial treatment of AHRF by clinical guidelines [5]. High PEEP delivered through the helmet interface represents the most promising alternative strategy; ongoing clinical trials are evaluating this approach.

Physiologically based patient-targeted strategies

Emerging concepts around noninvasive devices have highlighted that (1) a one-size-fits-all approach is likely not beneficial in AHRF and (2) delayed intubation after prolonged exposure to spontaneous breathing may be associated with worse outcome. Given this, while studies surrounding individualized treatments of AHRF are underway, available tools capable of assessing the risk of self-inflicted lung injury and early identification of treatment failure are essential for clinicians at the bedside (Fig. 1).

From a physiological standpoint, AHRF is characterized by different degrees of hypoxemia combined or not with intense inspiratory effort [1]. Convincing evidence indicates that HFNC represents the most effective tool to treat patients with mild-to-moderate hypoxemia (PaO_2/FiO_2 > 150 mmHg) [5, 7]. For patients with moderate-to-severe hypoxemia (PaO_2/FiO_2 < 150 mmHg), in whom facemask NIV may potentially yield poor outcomes, it is uncertain whether a strategy of early CPAP (facemask or helmet), helmet NIV or either strategy combined with HFNC sessions may provide clinical benefit over HFNC alone. Recent data indicate that patients' phenotyping based on the intensity of inspiratory effort may aid clinical decision. A physiological study on AHRF patients with PaO_2/FiO_2 < 200 mmHg showed that high-PEEP helmet NIV and CPAP are both capable of improving oxygenation, compared to HFNC. NIV can decreases inspiratory effort by unloading the respiratory muscles but may increase trans-pulmonary driving pressure, especially in patients who have low inspiratory effort (< 10 cmH_2O) during HFNC. Conversely, CPAP does not usually affect inspiratory effort and does not increase trans-pulmonary driving pressure [2].

Importantly, in patients with AHRF and no metabolic acidosis, the intensity of inspiratory effort may be associated to hypocapnia. Accordingly, in a post hoc analysis of the HENIVOT trial, helmet NIV was shown to reduce the rate of endotracheal intubation and improve survival as compared to HFNC in patients with $PaCO_2$ < 35 mmHg. Helmet NIV had no effect on outcome in normocapnic patients ($PaCO_2$ > 35 mmHg) [11]. These data may suggest that patients with high effort (ΔP_{ES} > 10 cmH_2O with high tidal volumes and minute ventilation and thus $PaCO_2$ < 35 mmHg) may benefit from NIV. Patients with low effort (ΔP_{ES} < 10 cmH_2O and/or $PaCO_2$ > 35 mmHg) may be better treated with HFNC or CPAP delivered with either face mask or helmet, eventually combined with awake prone position to improve oxygenation [12, 13]. This observation however does not exclude that some patients with normal $PaCO_2$ could exhibit high effort (in case of, for instance, increased dead space/poor ventilation perfusion ratio) and thus benefit from NIV.

New technological developments to non-invasively assess inspiratory effort at the bedside are mandatory to allow us to optimize the use of the noninvasive techniques for respiratory support. Promising techniques may include diaphragmatic ultrasound and transcutaneous measurement of diaphragmatic activity.

Identification of treatment failure

During any treatment, the lack of improvement in gas exchange, persistent signs of respiratory distress and increased work of breathing (tachypnea and dyspnea) should indicate the need for endotracheal intubation and a high risk of P-SILI. Importantly, when PEEP is applied, the initial improvement in oxygenation should not be seen as conclusive sign of treatment success, as it may be falsely reassuring.

During HFNC, the ratio of SpO_2/FiO_2 to respiratory rate (ROX index) < 3.85 after 12 h of treatment and a worsening ROX index over time have been associated with increased risk of subsequent intubation [14]. During CPAP, there is a paucity of validated tools to identify treatment failure at an early time point. Recently, ROX index < 6 at 24 h has been shown to predict the need for endotracheal intubation [15]. During NIV, tidal volume > 9.5 ml/kg of predicted body weight and persistently high inspiratory effort (ΔP_{ES} > 10 cmH_2O)

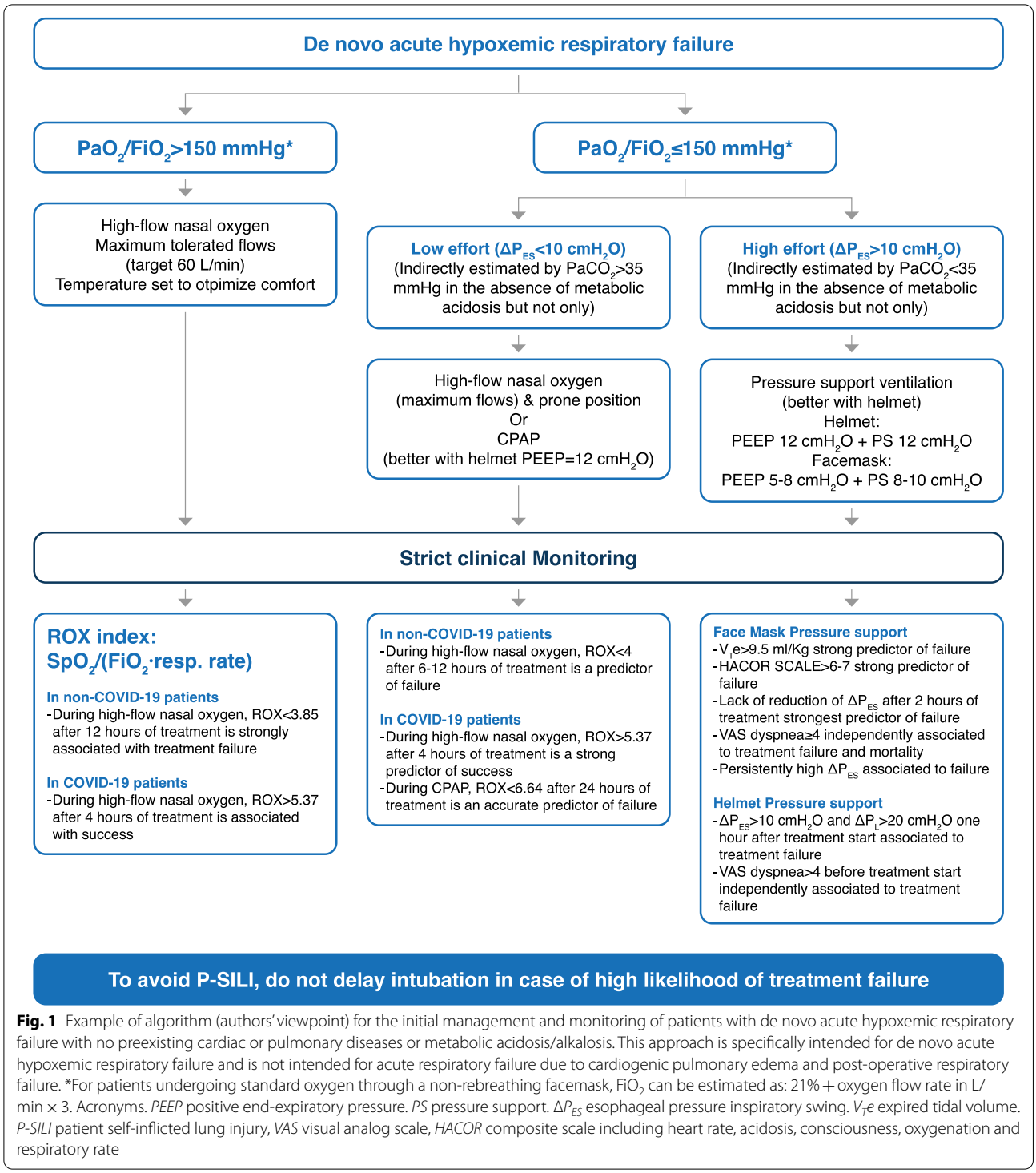

Fig. 1 Example of algorithm (authors' viewpoint) for the initial management and monitoring of patients with de novo acute hypoxemic respiratory failure with no preexisting cardiac or pulmonary diseases or metabolic acidosis/alkalosis. This approach is specifically intended for de novo acute hypoxemic respiratory failure and is not intended for acute respiratory failure due to cardiogenic pulmonary edema and post-operative respiratory failure. *For patients undergoing standard oxygen through a non-rebreathing facemask, FiO_2 can be estimated as: 21% + oxygen flow rate in L/min × 3. Acronyms. *PEEP* positive end-expiratory pressure. *PS* pressure support. ΔP_{ES} esophageal pressure inspiratory swing. $V_T e$ expired tidal volume. *P-SILI* patient self-inflicted lung injury, *VAS* visual analog scale, *HACOR* composite scale including heart rate, acidosis, consciousness, oxygenation and respiratory rate

are parameters strongly associated to subsequent failure. Unfortunately, tidal volume measurement may be difficult in the presence of leaks during facemask NIV and is impossible with conventional tools during helmet support. Similarly, inspiratory effort assessment currently requires esophageal manometry, which is not always feasible in non-intubated patients. Studies to identify noninvasive surrogates for inspiratory effort are ongoing. A composite scale (HACOR) including heart rate, acidosis, consciousness, oxygenation, and

respiratory rate has been shown to accurately identify patients prone to treatment failure 6 h after NIV initiation [16], and may aid clinical decision-making.

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Author contributions
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.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Outside of the submitted work, DLG is supported by research grants by ESICM and SIAARTI.

Data availability
Not applicable.

Declarations

Conflicts of interest
DLG has received payments for travel expenses by Getinge and Air Liquide, personal fees by Gilead, Intersurgical, Fisher and Paykel and GE, and discloses a research grant by GE. LP has received payments for travel expenses and/or lectures fees by Getinge, Air Liquid, Hamilton, GE and Fisher and Paykel. LP has received consultant fees from Löwenstein and Lungpacer.

Publisher's Note

Received: 28 January 2023 Accepted: 23 March 2023
Published: 28 April 2023

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