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Non-invasive ventilation in COVID-19-related acute hypoxemic respiratory failure: a narrative review

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Abstract

The high mortality rate and extended ventilator use associated with invasive mechanical ventilation in patients with severe COVID-19 have sparked a debate about the use of non-invasive respiratory support, such as high-flow nasal cannula, continuous positive airway pressure, and non-invasive ventilation (NIV), as treatment options. According to the European Respiratory Society and the American Thoracic Society clinical practice guidelines, NIV is recommended to prevent intubation in hypoxemic acute respiratory failure in patients with community-acquired pneumonia or early acute respiratory distress syndrome without major organ dysfunction. Central to this debate is the role of NIV in managing acute hypoxemic respiratory failure. However, there are concerns that NIV might delay the timely intubation and lung-protective ventilation in patients with more advanced disease, potentially worsening respiratory parameters due to self-inflicted lung injury. This review aims to explore the current literature, focusing on the rationale, patient selection, and outcomes associated with the use of NIV in COVID-19 patients with acute respiratory failure, to better understand its role in this context.

Key words: COVID-19, respiratory function, non-invasive ventilation.

Introduction

COVID-19, short for "Coronavirus Disease 2019," is caused by the novel coronavirus SARS-CoV-2 [1]. First identified in December 2019 in Wuhan, China, the virus quickly spread worldwide, triggering a global pandemic in early 2020. The pandemic has deeply affected human life and strained healthcare systems [2,3]. COVID-19 has led to millions of infections, deaths, and long-term health consequences. While many experience mild or no symptoms, severe illness leading to respiratory failure and hospitalization has been a major concern [4]. Managing acute respiratory distress syndrome [ARDS], and acute respiratory failure [ARF] in COVID-19 patients has been challenging [5-11]. Pathophysiological mechanisms of ARDS implicated in COVID include increased alveolar-capillary permeability which impairs gas exchange, whilst ARF occurs when the respiratory system fails to adequately oxygenate the blood or remove carbon dioxide, causing hypoxemia and/or hypercapnia [12]. Treating ARDS and ARF requires a variety of interventions to support lung function, mainly through oxygen delivery to prevent respiratory decompensation [12,13]. Initial treatment involves administering oxygen via an intranasal catheter or an air-entrainment mask. However, if conditions worsen, as seen in ARDS or ARF, higher oxygen levels are necessary. High oxygen levels are often delivered through helmet-based non-invasive ventilation [NIV], which reduces air leaks and the risk of aerosolization. NIV can improve lung health in patients experiencing respiratory distress and prevent the need for invasive mechanical ventilation.

SARS-CoV-2: molecular mechanisms of infection and cellular damage

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus from the Betacoronavirus genus [14]. We have learned that SARS-CoV-2 primarily infects cells via the angiotensin-converting enzyme 2 [ACE2] receptor, which is present on the surface of various human cells, particularly in the respiratory tract, but also in the heart, kidneys, testes, gastrointestinal tract, liver, vascular endothelium, and brain [1,15,16]. The infection and cellular damage caused by SARS-CoV-2 involve several molecular mechanisms, including attachment and entry, which have been extensively reviewed [1,15-17]. Once the virus enters the host cell and its genomic RNA is released into the cytoplasm, a series of defence mechanisms are initiated, triggering the expression of proinflammatory cytokines such as IL-1, IL-2, IL-6, IL-7, IL-10, TNF-α, and GCSF, leading to a phenomenon known as a cytokine storm [17-19]. Furthermore, the possible correlation with exposure to pollutants cannot be excluded, considering that particulate matter can be categorized by size and composition, with fine particulates posing the greatest health risk due to their ability to penetrate deep into the lower airways. Epidemiological evidence links fine particulate exposure to inflammation in the

alveoli, altered blood coagulability, and increased risk of respiratory and cardiovascular events [17]. Urban populations are particularly vulnerable due to higher exposure to vehicle emissions and other pollutants, which can interact with aeroallergens like pollen to promote allergic sensitization and airway obstruction, especially in predisposed individuals. since. PM1.0 +Allergens together exhibited the greatest capacity to induce type II lung epithelium (A549) cells cytokine responses and suggest the potential interaction between particulates and pollen is capable of forming micro compounds that can reach the acinar lung units and are able to activate cells of the immune system which may dysregulate the inflammatory response [17-21]. Uncontrolled hyperinflammation causes vasoconstriction, fibrosis, increased vascular permeability, and activation of the coagulation cascade, resulting in microthrombi formation blood clots that contribute to lung damage and [22,23] may promotes the onset of ARF, a critical condition that causes hypoxemia and requires complex treatments such as mechanical ventilation.

Pathogenic mechanisms of COVID-19-related acute respiratory failure

The primary mechanisms underlying acute hypoxemic respiratory failure in SARS-CoV-2 pneumonia include dysregulation of pulmonary perfusion, formation of microthrombi in the pulmonary circulation, intrapulmonary shunting, and alterations in gas diffusion across the alveolar-capillary membrane. Each of these factors contributes to the progression and clinical presentation of ARF, defined as a P/F ratio less than 300 mmHg [22-26]. Increased shear stress is implicated in causing vasoplegia and subsequently disrupting the regulation of pulmonary arterial flow [24]. ACE2, the primary receptor for SARS-CoV-2 entry into human cells [15], converts angiotensin II to angiotensin 1-7. The latter plays a crucial role in degrading bradykinin and regulating pulmonary arterial flow, so variations in ACE2 levels are associated with changes in lung perfusion regulation [27,28]. Intrapulmonary shunting, resulting from alterations in the ventilation-perfusion [V/Q] ratio, is one of the earliest mechanisms causing hypoxemia in acute respiratory failure in SARS-CoV-2 pneumonia patients. This is due to interstitial oedema caused by proinflammatory cytokine production, altered lung perfusion, surfactant loss, alveolar flooding, and collapse due to increased intrathoracic negative pressure required to increase tidal volume. These mechanisms result in the perfusion of large areas of parenchyma that are no longer ventilated, leading to significant hypoxemia due to a shunt unresponsive to oxygen therapy alone [29].

SARS-CoV-2-related acute respiratory failure management

During and after the COVID-19 pandemic, numerous studies proposed algorithms for effectively managing ventilation and oxygen support in virus-induced ARF. Key questions include the clinical characteristics that warrant respiratory support, the most suitable oxygen devices for these characteristics, and how to monitor the effectiveness and potential side effects of support. A short course of systemic corticosteroids for patients with moderate to severe COVID-19 has been shown to reduce the need for escalation of care, improve outcomes, and slightly reduce all-cause mortality [30-33]. Sampath Weerakkody et al. [28] analysed two randomized controlled trials and 83 observational studies on non-invasive respiratory support [NIRS] modalities, including high-flow nasal oxygen, continuous positive airway pressure [CPAP], and bilevel positive airway pressure [BiPAP] in COVID-19 patients. Contrary to initial WHO guidance, their findings suggest NIRS strategies such as face mask non-invasive ventilation or high-flow nasal cannula are safe and reduce the risk of death. These strategies also lessen the need for intubation in adults with ARF compared to standard oxygen therapy [34]. They proposed a decision-making flowchart for providing respiratory support to COVID-19-induced hypoxemic respiratory failure. Initially, standard oxygen therapy is recommended. If symptoms persist or there's increased work of breathing, persistent hypoxemia, or worsening of the PaO2/FiO2 ratio, SpO2, or ROX index, NIRS should be considered, such as BiPAP in the presence of hypercapnia, and CPAP or HFNC in the absence of hypercapnia. The SIMEU position paper [29] provides guidelines for NIRS use in respiratory failure secondary to COVID-19 pneumonia. Oxygen therapy should be initiated when SpO2 is below 94%, using high FiO2 if SpO2 is below 90%, and low FiO2 if SpO2 is in the range of 90–93%, except for patients with chronic pulmonary disease, where therapy should begin at SpO2 below 90–92%. HFNC is recommended before NIV [35]. The SIMEU flow chart suggests the target SpO2 should be between 94% and 98%. If SpO2 remains below 92% after 15 minutes with a non-rebreathing mask at 15 L/min or if the P/F ratio is 200-300 mmHg, HFNC should be used, starting at 60 L/min and titrating the oxygen mixture to achieve SpO2 > 92%. If there's no improvement after 1-2 hours, CPAP should be used. CPAP should start with a PEEP setting of 7.5-12.5 cmH2O if SpO2 remains below 94% or severe hypoxemia occurs. NIPPV is preferred early over CPAP in cases of COPD, initial signs of muscle exhaustion [36,37], and respiratory acidosis. NIPPV settings should include PEEP between 7.5-12 cmH2O, with the inspiratory trigger sensitivity maximized, a rise time of 0.15–0.25 seconds, and the expiratory trigger at 30% of peak flow. Patient-Self Induced Lung Injury [p-SILI] can be monitored using oesophageal pressure monitoring [35]. In ARF, the COVID-19 Treatment Guidelines Panel recommends HFNC as the first-line therapy over conventional oxygen therapy and NIV. NIV

should be used if HFNC fails or cannot be used, with a closely monitored trial [38]. Studies suggest HFNC is superior to NIV in therapy duration, intubation rate, and ICU mortality [39-42]. The Panel recommends a high PEEP strategy for mechanical ventilation with positive air pressure, as some patients benefit from high PEEP to prevent alveolar collapse and lung injury, while others may experience hemodynamic compromise [43-50]. Another algorithm for NIV use considers recommendations and contraindications [51]. Indications for NIV include obstructive sleep apnoea, COPD, congestive heart failure, cardiogenic pulmonary oedema, hypercapnic respiratory failure, and dyspnoea. HFNC is indicated when PaO2 < 65 or SpO2 < 90% on supplemental oxygen, RR > 25, and mild ARDS (PaO2/FiO2 < 300 but > 200). Contraindications to NIV include cardiac or respiratory arrest, encephalopathy, severe hypoxemia on admission (PaO2/FiO2 < 150), pneumothorax, pleural effusion, pulmonary embolism, gastrointestinal issues, aspiration risk, recent facial trauma or surgery, hemodynamic instability, multi-organ dysfunction, high SOFA score, and poorly controlled respiratory secretions. If a patient is a candidate for treatment, NIV, CPAP, or HFNC therapy should begin with constant monitoring for three hours, including hourly lab assessments, ABG, PaO2/FiO2 (target > 300), subjective improvement or worsening of dyspnoea, heart and respiratory rate trends, pulse oximetry, FiO2 requirements, and tidal volume measurement for CPAP or NIV. Failure parameters include primary (PaO2/FiO2 < 150 or inability to improve after 1 hour of NIV, worsening dyspnoea, tachypnoea > 25, failure to maintain PaO2 of 60 on FiO2 0.6, SpO2/FiO2 < 196, tidal volume > 9 ml/kg predicted body weight) and secondary (SAPS II > 35, APACHE II > 17, rising SOFA score, high peak pressure requirement, worsening bronchorrhea, mask intolerance). If symptoms worsen, invasive mechanical ventilation is considered. If there is no improvement and the patient is on HFNC, switch to NIV/CPAP. A proning trial may be attempted if the patient is on NIV/CPAP. If symptoms improve, continue NIRS with frequent reassessments. Based on prior experiences [37-40,42], and the algorithm proposed by Scala [50] for hospitalized ARF patients with COVID-19, a pathway for non-invasive assessment and ventilatory support can be proposed (Fig. 1). The criterion for starting conventional oxygen therapy (COT, with nasal cannulas, Venturi mask, or non-rebreathing mask) is SpO2 < 92%. The choice of support depends on the FiO2, and flow required to achieve a target SpO2 between 94% and 98% and a respiratory rate < 30 bpm. The patient should be re-evaluated within 4 hours during COT. If SpO2 < 93% and PaO2/FiO2 < 300 mmHg, trials can begin with HFNC at 30-60 L/min with a target SpO2 > 93%. If PaO2/FiO2 < 200 mmHg and/or RR > 30 bpm, CPAP therapy with a PEEP of at least 10 cmH2O is considered (to avoid S-ILI or barotrauma). In cases of PaO2/FiO2 < 100 mmHg and/or RR > 30 bpm with respiratory distress, NIV must be started with a PEEP of 12-16 cmH2O and a PS

to ensure a Vt of 4-6 ml/kg/PBW [50]. Reassessments during NIRS depend on the support used; HFNC patients should be re-evaluated every 2, 6, and 12 hours, while CPAP and NIV patients should be reassessed every hour. If SpO2 worsens or PaCO2 increases in NIRS, or if respiratory arrest, hemodynamic instability, or intolerance to CPAP/NIV occurs, invasive ventilation via endotracheal intubation (ETI) is indicated. The various aforementioned algorithms have been compared and summarized in *Supplementary Table 1*. It is also essential to acknowledge the studies by Prediletto and Marra [52,53] which contributes to the ongoing discussion concerning the clinical relevance of the standardized P/F (stP/F) ratio and the SpO_2/FiO_2 (S/F) ratio. Where they defined that, the PaO_2/FiO_2 ratio (P/F) does not account for compensatory respiratory efforts such as tachypnoea and hyperpnea, which often result in hypocapnia. Standard PaO_2, which adjusts PaO_2 for the individual's $PaCO_2$, more accurately reflects the underlying pathophysiology of hypoxemic ARF. In the first study they highlighted, in a cohort of 349 patients hospitalized with COVID-19-related ARF, STP/F demonstrated superior predictive accuracy for mortality compared to P/F [52]. These findings suggest that STP/F may provide a more physiologically relevant measure for assessing ARF severity in COVID-19 patients [53]. The second one [50], aimed to evaluate the correlation between the non-invasive SpO_2/FiO_2 (S/F) ratio and the PaO_2/FiO_2 (P/F) ratio, as well as their associations with radiological and laboratory severity markers. They find support of the utility of the S/F ratio as a reliable surrogate for P/F in clinical assessment, offering a non-invasive and accessible marker that also reflects overall disease severity [53].

Non-invasive ventilation usage in COVID-19 acute respiratory failure

During the COVID-19 pandemic, NIV has been utilized as both a first-line and rescue therapy for patients with varying degrees of disease severity [53-57]. It improves oxygenation, reduce dyspnoea, inspiratory effort, and work of breathing [58], and may lower endotracheal intubation and ICU mortality rates [58,59]. However, if NIV fails, it can delay intubation and worsen clinical outcomes. Success rates have varied, likely due to the different interfaces, settings, and protocols. Wang et al. reported an 11% failure rate for mild-to-moderate patients using NIV as first-line therapy [60], while failure in severe patients can reach up to 80% [61]. Observational studies have found failure rates between 40% and 50% [56,58,59]. Non-invasive procedures, such as NIV or CPAP with escalation to NIV, may be attempted for hypoxemic respiratory insufficiency, an inadequate response to oxygen therapy, or mild ARDS [60]. Arabi et al. [41,61] concluded that NIV can be effective for patients in early stages and milder forms of acute hypoxemic respiratory failure, but warned that without early improvement, NIV may merely delay intubation. Current literature supports this, as COVID-

19 patients can progress from initial symptoms to ARDS and intubation, necessitating timely ventilation decisions [41,61]. NIV's variable success is likely due to heterogeneous interfaces, settings, and protocols (*Supplementary Table 2*).

An Emergency Department in Northern Italy proposed a standardized procedure for monitoring patients on NIV, suggesting assessment of arterial blood gases, tidal volume, respiratory rate, accessory respiratory muscle use, hemodynamic, mental status, gastric distension and aspiration risk, organ failure, and patient compliance [54,62-65]. Predictive markers for NIV failure after two hours include lack of improvement in blood gases, lower bicarbonate levels, lower $PaCO_2$ [in hypoxemic ARF], higher lactate, and inability to maintain a PaO_2 of 60 mmHg on FiO_2 of 0 [62-66].

A significant concern is "silent hypoxemia," where marked arterial hypoxemia in COVID-19 patients may not present with obvious symptoms, potentially leading clinicians to underestimate severity [67]. SpO_2, used to measure oxygen saturation, should be interpreted cautiously; hypoxemia-driven tachypnoea and hyperpnea can cause respiratory alkalosis, shifting the oxyhaemoglobin dissociation curve to the left and yielding high SpO_2 despite low PaO_2 [67]. Secondary factors like diarrhoea, dehydration, and hypoalbuminemia can also produce falsely high SpO_2 and low respiratory rates. Therefore, respiratory support decisions should be based on the PaO_2/FiO_2 ratio rather than SpO_2 alone [67].

Factors associated with increased NIV mortality include moderate to severe ARDS, a PaO_2/FiO_2 ratio below 150 mmHg, high tidal volumes [>9.2 or 9.5 mL/kg], bilateral pneumonia, and progressive worsening on chest CT scans [68,69]. This is why many studies on COVID-19–related ARF target tidal volumes ranging from 5.8 to 8 mL/kg PBW [70-81]. Regarding PEEP, studies report values between 10 and 15 mmHg [59,64]. In the absence of randomized trial evidence, "higher" PEEP is recommended per the ARDS Network's higher PEEP/lower FiO_2 table [43,65,81-89], although variation reflects uncertainty in PEEP titration.

A recent review on COVID-19 pneumonia patients treated with NIV found that both CPAP and NIV were commonly used but linked to higher mortality rates (*Supplementary Table 2*). However, studies such as Faraone et al. [56] reported NIV to be effective for treating acute hypoxemic respiratory failure in 50 COVID-19 patients, with a 64% success rate. Similarly, Menzella et al. [90] found NIV successful in 48.1% of 79 COVID-19–related AHRF cases, with 25.3% requiring invasive ventilation and 57% of those patients discharged alive. The authors concluded that NIV can be safely applied and may prevent the need for invasive ventilation in about 50% of cases.

Recent evidence has highlighted the clinical benefit of the prone position as an adjunctive strategy during non-invasive respiratory support (NIRS), including both high-flow nasal cannula (HFNC) and non-invasive ventilation (NIV), in patients with acute respiratory failure (ARF) due to SARS-CoV-2 infection. Traditionally reserved for intubated patients with severe acute respiratory distress syndrome (ARDS), proning has been increasingly applied to awake, non-intubated patients during the COVID-19 pandemic, showing promising results in improving oxygenation and potentially delaying or preventing the need for intubation [89]. Furthermore, a novel variation of the prone position—termed the "Rodin's Thinker" position—has been proposed and described in the American Journal of Respiratory and Critical Care Medicine (AJRCCM) [91]. This modified position adapts the classic prone posture to enhance patient comfort while preserving the physiological benefits of dorsal lung recruitment. These developments emphasize the growing relevance of positioning strategies within non-invasive respiratory management protocols and suggest further investigation into their standardized application and outcomes.

Discussion and Conclusions

NIRS, in select COVID-19 patients, should be considered. When utilized with vigilance and under appropriate conditions, NIRS is an acceptable alternative to early IMV in the management of mild to moderate acute hypoxemic respiratory failure secondary to COVID-19. Although available evidence remains inconclusive regarding the impact of NIV on outcomes for patients with severe hypoxemia due to SARS-CoV-2, based on pre-COVID-19 experiences and limited studies in SARS-CoV-2 patients, nearly 50% of patients might avoid intubation with non-invasive respiratory treatment alone. Further large-scale trials are needed to identify which COVID-19 patients benefit most from non-invasive respiratory management with minimal risk. These considerations could potentially be extended to viral-induced lung injury processes in the context of similar pathophysiological damage. However, further studies are needed to corroborate the findings observed in SARS-CoV-2-related infection and disease, in comparison with acute respiratory failure (ARF) caused by other respiratory viruses. In the meantime, there is no reason not to use NIV when conventional oxygen strategies fail, provided there are no immediate indications for intubation and the patient is closely monitored to prevent delayed intubation and virus transmission. Appropriate use of NIV has the potential to successfully reduce the need for invasive mechanical ventilation and ICU burden.

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Online supplementary material:
Supplementary Table 1. A schematic and comparative table of clinical algorithms and guidelines cited.
Supplementary Table 2. Clinical trials of non-invasive ventilation in COVID-19-related acute respiratory failure.

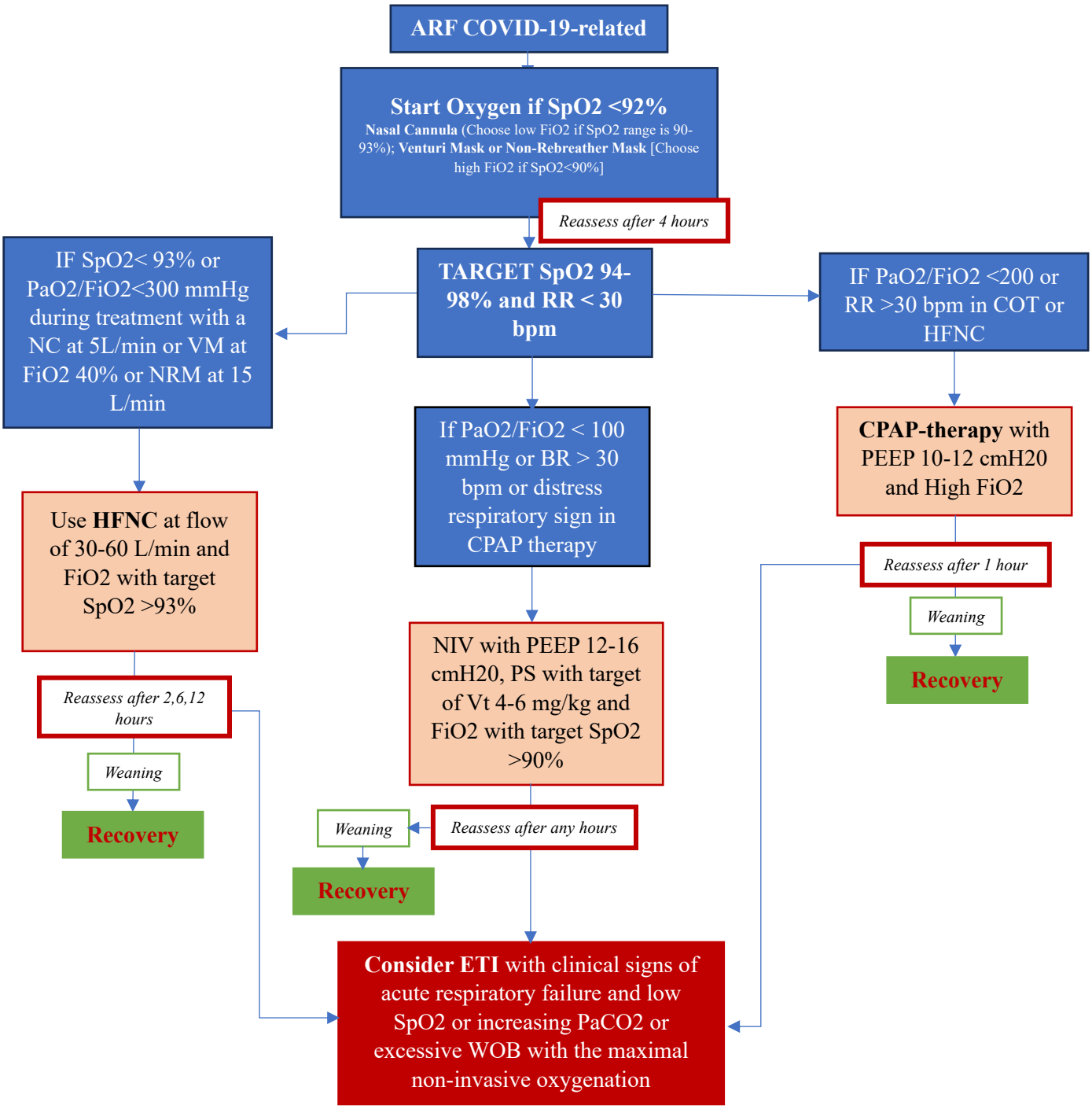

Figure 1. Proposed pathaway NIRS in COVID-19-reletad ARF. NC, nasal cannula; VM, Venturi mask; NRM, non-rebreather mask; HFNC, high-low-nasal-cannula; RR, respiratory rate; BPM, breaths per minute; COT, continuous oxygen therapy; PS, pression support; ETI, emergent endotracheal intubation; WOB, work of breathing.