



SIMEU position paper on non-invasive respiratory support in COVID-19 pneumonia

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Abstract

The rapid worldwide spread of the Coronavirus disease (COVID-19) crisis has put health systems under pressure to a level never experienced before, putting intensive care units in a position to fail to meet an exponentially growing demand. The main clinical feature of the disease is a progressive arterial hypoxemia which rapidly leads to ARDS which makes the use of intensive care and mechanical ventilation almost inevitable. The difficulty of health systems to guarantee a corresponding supply of resources in intensive care, together with the uncertain results reported in the literature with respect to patients who undergo early conventional ventilation, make the search for alternative methods of oxygenation and ventilation and potentially preventive of the need for tracheal intubation, such as non-invasive respiratory support techniques particularly valuable. In this context, the Emergency Department, located between the area outside the hospital and hospital ward and ICU, assumes the role of a crucial junction, due to the possibility of applying these techniques at a sufficiently early stage and being able to rapidly evaluate their effectiveness. This position paper describes the indications for the use of non-invasive respiratory support techniques in respiratory failure secondary to COVID-19-related pneumonia, formulated by the Non-invasive Ventilation Faculty of the Italian Society of Emergency Medicine (SIMEU) on the base of what is available in the literature and on the authors' direct experience. Rationale, literature, tips & tricks, resources, risks and expected results, and patient interaction will be discussed for each one of the escalating non-invasive respiratory techniques: standard oxygen, HFNCO, CPAP, NIPPV, and awake self-repositioning. The final chapter describes our suggested approach to the failing patient.

Keywords COVID-19 · CPAP · HFNCO · NIPPV · Non-invasive respiratory support · NIV

Roberto Cosentini, Paolo Groff, Anna Maria Brambilla and Rodolfo Ferrari equally contributed and should be all considered first author.

On behalf of SIMEU NIV Group collaborators included in Acknowledgement section.

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Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
BGA	Blood gas analysis
COPD	Chronic obstructive pulmonary disease
COVID-19	Disease caused by SARS-CoV-2
CPAP	Continuous positive airway pressure

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ETI	Endo Tracheal intubation
FIO ₂	Fractional concentration of inspired oxygen
HFNCO	High flow nasal cannula oxygen
ICU	Intensive care unit
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
NRS	Non-invasive respiratory support
OTSR	Oxygen target saturation range
PACO ₂	Partial pressure of carbon dioxide in arterial blood
PAO ₂	Partial pressure of oxygen in arterial blood
PEEP	Positive end-expiratory pressure
P-SILI	Patient self-induced lung injury
RCT	Randomized controlled trial
RR	Respiratory rate
SARS-CoV-2	Coronavirus-2 cause of the severe acute respiratory syndrome
SIMEU	Società Italiana Medicina d'Emergenza—Urgenza
SPO ₂	Saturation of arterial blood with Oxygen as measured by Pulse-oxymetry
WOB	Work of breathing

Introduction

In March 2020, after the SARS-CoV-2 infection spread from China to the rest of the world, the World Health Organization declared a pandemic [1]. The massive number of sick patients posed a unique challenge to every health system. The high frequency of respiratory involvement [2, 3] forced our hospitals to rapidly reorganize and redeploy doctors and nurses to acute care wards and adapt our protocols. To help our colleagues, we issued an early position paper on Non-invasive Oxygenation for COVID-19 patients at the beginning of the first wave [4, 5]. Since March 2020, several observational studies have been published involving thousands of COVID-19 patients treated for acute respiratory failure (ARF). It is time to give some suggestions based on this best available evidence, even though no randomized controlled trials (RCT) have been published to date.

Methods

We divided the topic into 8 chapters, 5 on different techniques of respiratory support and the last one focused on the failure of non-invasive support. Chapters are: 1. COVID-19 Pathophysiology; 2. Indication to oxygen therapy; 3. Conventional oxygen therapy systems; 4. The role of High Flow Nasal Cannulae Oxygenation (HFNCO); 5. Continuous Positive Airway Pressure (CPAP) efficacy and safety;

6. Non-invasive double level Positive Pressure Ventilation (NIPPV) efficacy and safety; 7. Awake self re-positioning; 8. When non-invasive respiratory support fails. Each chapter has been developed by 4 experts in Non-invasive Ventilation (NIV) techniques; recommendations have been made according to Evidence-Based Medicine (best evidence + clinical experience + patient values) and revised by the NIV SIMEU Faculty group. Each technique (chapters 2–6) is structured according to the following draft:

- (a) Why it may work (rationale)
- (b) What is known (the literature)
- (c) Our recommendation
- (d) Our experience (tips & tricks)
- (e) Resources (human/instrumental)
- (f) Risks and expected success
- (g) What I say to my patient

COVID-19 pathophysiology

In evaluating the use of Non-invasive Respiratory Support (NRS) in ARF secondary to COVID-19-related pneumonia, it is necessary to make some preliminary considerations. The pathophysiology of this condition is quite different from that of the main indications of NIV [6]. COVID-19 pneumonia is characterized by an initial phase of prevalent interstitial and microvascular involvement, which subsequently leads to a condition of diffuse alveolar damage with the formation of hyaline membranes, edema and fibrotic deposition [7]. Therefore, it is possible to believe that, at least in the first phase, lung compliance is not significantly compromised and that hypoxemia depends on the loss of the physiological mechanism of hypoxic vasoconstriction secondary to a dysregulation of the microcirculation induced by inflammation and the formation of microthrombi [8, 9]. It follows that the best treatment of this condition may be the progressive increase of oxygen support rather than the application of positive pressures, aimed at alveolar recruitment, which will be better reserved for the next phase of full-blown ARDS [10].

In this scenario, the role of NRS techniques, and NIV in particular, is controversial. The application of pressure support to a patient who breathes spontaneously can generate an excessive swing of transpulmonary pressure inducing a real risk of producing a patient-Self Induced Lung Injury (p-SILI) [11–14]. It should be noted that the concept of pSILI responds more to a theoretical assumption than to concrete experimental evidence and in particular this picture has never been directly observed in patients with COVID-19-related pneumonia. On this basis it has been debated by distinguished authors, especially insofar as the decision to intubate a patient would depend on it [15–17]. Besides, NIV

may delay intubation and worsening the patient's prognosis [11, 12]. Finally, NIV can involve the risk of environmental dispersion of droplets, with a consequent risk of contagion for healthcare workers [18–21]. However, CPAP applies a single level of pressure during the entire respiratory cycle, reducing the risk of excessive transpulmonary pressure. Furthermore, CPAP can determine an increase in resistance in the small vessels of the non-dependent regions of the lung, favouring the redistribution of perfusion to newly recruited depending areas in patients who have lost the mechanism of hypoxic vasoconstriction [22] and may reduce the likelihood of generating high transpulmonary pressure and tidal volume compared to NIPPV, as explained in chapter 6 [23].

Key concepts

- (a) COVID-19 pathophysiology is a continuum between an initial 'soft phase' with hypoxemia determined by deranged hypoxic vasoconstriction and a later 'heavy' phase with lung atelectasis resembling the classical ARDS
- (b) Hence, each phase needs an individualized therapeutic approach in terms of oxygenation and positive pressure application

Indications to oxygen therapy

The Literature. The use of supplemental oxygen in adults with COVID-19 has not been studied.

The target of SpO₂ in adults with COVID-19 is uncertain.

Oxygen therapy is recommended as the first-line therapy for treating COVID-19-induced hypoxemia by the World Health Organization and the Center for Disease Control and Prevention. [24, 25]

The current COVID-19 management guidelines by Surviving Sepsis Campaign suggest the use of supplemental oxygen if the SpO₂ is <92% and recommend its use once SpO₂ is <90% [26].

The current oxygen target saturation range (OTSR) for patients with COVID-19 recommended by the National Institutes of Health is 92–96% [27].

In non-COVID-19 pneumonia outpatients, oxygen saturations less than 92% are known to be associated with major adverse events [28].

Our recommendation

Start with oxygen therapy when SpO₂ <94%, obtained by an arterial blood gas analysis (BGA).

Choose high FiO₂ if SpO₂ <90 (e.g., non-rebreather mask 15 L/min).

Choose low FiO₂ if SpO₂ range is 90–93% (e.g., nasal cannula 3–6 L/min).

In patients with chronic pulmonary disease, start with oxygen therapy if SpO₂ <90–92%

OTSR is ≥94–98% (avoid hyper-oxygenation)

In patients with chronic pulmonary disease, OTSR is 90–92%.

All the indications refer to “SpO₂” and not to “PaO₂”; to start oxygen therapy look at SpO₂ and perform BGA: then repeat BGA at least daily and when patient worsens.

Caveats

1. These patients frequently show a marked respiratory alkalosis; this means that with the same SpO₂ the PaO₂ is lower. Perform a BGA before starting any treatment and at least once daily.
2. Mind hypercapnia or even a slight increase in PaCO₂ despite an increasing/high respiratory rate (RR).
3. Mind patients with chronic mechanical load (COPD, obesity, kyphoscoliosis etc.) who are at risk of hypercapnia and fatigue.

Conventional oxygen therapy systems

Nasal oxygen cannula

The nasal cannulae are the most common initial step for oxygen treatment in patients with mild hypoxemia. They are simple to use and inexpensive; furthermore, nasal cannulae are considered relatively safe due to the minimal generated aerosol with a low risk of SARS-CoV-2 spreading. The air dispersion depends on flow. With 1 L/min, the measured distance using a high-fidelity mannequin was 30 cm, and 40 cm with 5 L/min (Fig. 1).

Main drawbacks are: 1. the low maximal FiO₂ provided that can reach up to 40%; 2. the need for humidification if oxygen flow is >6 L/min; 3. The actual variable FiO₂ depends on the patient's inspiratory flow [28–30].

Simple mask

Flow rates with simple masks reach approximately 5–10 L/min. As with nasal cannulae, FiO₂ depends on the patient's inspiratory flow.

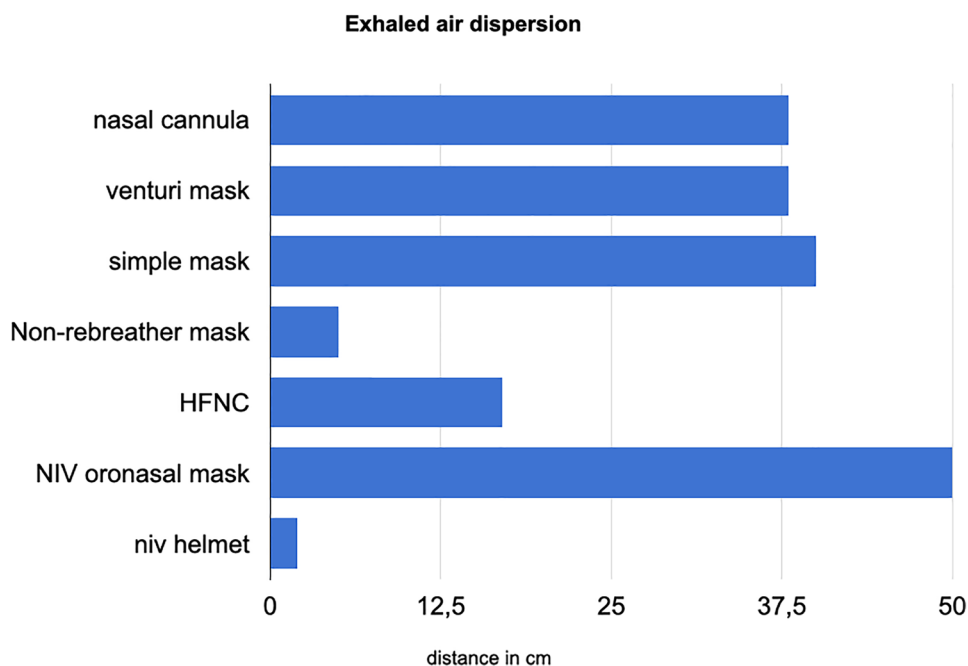
The increase of oxygen supplementation via simple mask is marginal when compared to nasal cannulae.

Air dispersion: the measured distance using a high-fidelity mannequin at 10 L/min was 40 cm (Fig. 1) [28–30].

Venturi mask

FiO₂ delivered by Venturi mask is more precise and ranges from 24 to 60% of oxygen. Typical pre-specified flow rates range between 2 and 15 L/min.

Fig. 1 Exhaled air dispersion distance according to oxygen device



Air dispersion: the maximal measured distance using a high-fidelity mannequin varied from 33 cm at FiO_2 40%, to 40 cm at FiO_2 24% [28–30].

Non-rebreather mask

The non-rebreather mask is a safer device to deliver oxygen to COVID-19 patients as the mask itself limits droplet dispersion. At 15 L/min, the FiO_2 can reach 90%.

Air dispersion: the maximal measured distance using a high-fidelity mannequin at 10 L/min was less than 10 cm (Fig. 1). These data suggest that the non-rebreather mask provides the least aerosol dispersion [28–30].

Use of surgical mask

The use of a surgical mask to cover the nose and mouth over a nasal cannula or an oxygen mask has been suggested by several authorities including the World Health Organization.

In a recent study, the use of the surgical mask over or under an oxygen Hudson mask in 3 volunteers gave a negligible FiO_2 difference measured at the lips [31].

OUR RECOMMENDATION. Choose the best oxygen system for your patients to obtain your target and the best comfort.

OUR EXPERIENCE. Patients generally increase their oxygen need gradually.

RESOURCES. Prepare in advance every type of device available for O_2 administration; be ready to change from one to another rapidly.

RISKS. Always ask the patient to wear a surgical mask over the oxygen device.

EXPECTED SUCCESS. The vast majority of patients progress over days. A small percentage of patients worsens in a matter of hours from breathing air to need of intubation [32].

WHAT I SAY TO MY PATIENT. ‘Your oxygenation is getting worse and this may damage your entire body. We need to start/change the device for oxygen administration’.

The role of high flow nasal cannulae oxygenation

Why it may work

As concerning the role of HFNCO in the non-intensive care setting, the available guidelines recommend its use before resorting to NIV [24, 33]. Actually, HFNCO can be the most suitable non-invasive support tool for treating COVID-19-related respiratory failure, at least in its earliest stage, due to the possibility of delivering fixed and known FiO_2 , thanks to the creation of high flows of humidified and heated air–oxygen mixture. Besides, HFNCO achieves a PEEP of 2.5–5 cm H_2O and a continuous wash-out of CO_2 of the dead space in the airways [34]. More recently, a Swedish monocentric experience conducted on a limited number of cases has shown how it is possible to improve the effectiveness of HFNCO simply by superimposing a conventional oxygen mask (without supplemental O_2) over the cannulas during treatment [35].

The literature

The analysis of the literature available on the subject allows us to detect studies that are very different from each other in terms of number and severity of patients enrolled, design, assessed outcomes.

In some experiences published immediately after the first pandemic peak, the use of HFNCO was conceived in the context of an oxygen escalation therapy in which the main outcome was to avoid resorting to the use of positive pressures, both by non-invasive and by conventional means, also with the aim of saving the use of ventilators in an Intensive Care Unit (ICU) resource constraint setting [36–38]. With this mode of use and selecting patients of moderate severity ($\text{PaO}_2/\text{FiO}_2 > 200$ mmHg) a success rate equal to two thirds of patients was described, while subsequent studies collected larger case series and more severe patients on average ($\text{PaO}_2/\text{FiO}_2 < 150$ mmHg), not excluding those with numerous co-morbidities or immunosuppression, again, in an operational context of severe ICU bed shortage [39–41]. With the limitations linked to a non-homogeneous definition of outcomes (escalation to positive pressures, intubation or intubation and death), these studies reported a lower percentage of success, around 50% of treated patients. Interestingly, the authors observed a high percentage of deaths among patients who failed the method and often higher than that of patients who were intubated directly without carrying out therapy with HFNCO, corroborating observations that appeared in the pre-COVID-19 era on the fact that patients subjected to this method delayed the use of tracheal intubation worsening their outcome [42]. Particular importance was, therefore, reserved in these studies to the analysis of the risk factors of failure which were identified in the male sex, older age, increased respiratory rate and lower oxygenation upon entry. Of note, the prognostic performance of the ROX index (the ratio between $\text{SpO}_2/\text{FiO}_2$ and respiratory rate), already validated in the pre-COVID-19 era by Roca, was tested [43]. Even with different values and timing of measurements (> 3.7 at 6 h; > 3 at 2, 6, 12 h from the start of treatment; values increasing in the first 3 days from the start of treatment) it was invariably correlated with a favourable outcome. One study in particular [44], in addition to confirming the prognostic utility of the ROX index, showed that, among patients who failed, the timing of intubation (within 48 h or beyond 48 h) did not influence intra-hospital mortality and other secondary outcomes. The Authors concluded that prolonged HFNCO trials were not clearly related to worse outcomes and that mortality was more likely to be attributed to a complex of factors related to the severity of the underlying disease.

An aspect that has often been pointed out in the discussion of the works cited so far is the fact that they are essentially cohort studies for the most part retrospective. They,

therefore, do not have a control population and this allows judgments to be made on the effectiveness of HFNCO only in a very indirect way. Using a case–control analysis method, Demoule and co-workers retrospectively compared 137 COVID-19 patients treated with HFNCO for hypoxemic respiratory failure with 137 patients who received conventional oxygen therapy in ICU [45]; in the results, HFNCO was associated with a reduced proportion of patients requiring invasive mechanical ventilation at day 28, while mortality at day 28 was similar between the two groups and this held true after adjusting for confounders.

The recent publication of the HENIVOT study by the Gemelli-ICU Study Group [46], has concretely contributed to the definition of the role of HFNCO and helmet-NIV in the treatment of hypoxemic ARF in patients admitted to the ICU for moderate to severe COVID-19 pneumonia, confirming the superiority of the latter in outcomes, such as the frequency of tracheal intubation at 28 days, correction of hypoxemia and dyspnea. However, it should be noted that while the level of monitoring obtainable in the ICU is difficult to generalize to other operational areas, the Same Authors Have previously reported an increase in endotracheal intubation in those patients who demonstrated an increase in trans-pulmonary pressure during helmet NIV [12]. In a large UK controlled randomized trial of 1272 patients, rapidly set up in the making of the pandemic, Perkins et al. compared CPAP and HFNCO to conventional oxygen treatment as to a combined primary outcome consisting of tracheal intubation or death at 30 days [47]. They found that CPAP, compared with conventional oxygen therapy, reduced the composite outcome, while there was no effect observed, compared to conventional oxygen therapy with the use of HFNCO. While some observations of a methodological nature, admitted by the authors themselves, lead to a cautious interpretation of these data, more generally, it must be considered that in particularly severe situations ($\text{PaO}_2/\text{FiO}_2 < 150$), i.e., when a lung damage corresponding to the ARDS type (high elastance, high recruitability) is conceivable, the use of positive pressure techniques may well achieve better results in terms of oxygenation. It remains to be investigated what the role of HFNCO may be in the patient with mild respiratory insufficiency (low elastance, low recruitability) in which this method could prevent the need for positive pressure techniques in the escalation of oxygen therapy. The COVID-HIGH international multicenter randomized controlled trial (COVID-HIGH trial, NCT04655638) that is completing patient enrollment as we write will certainly provide valid answers in this regard.

A final aspect to consider concerns the safety of health-care workers with respect to the possible airborne transmission of the virus during treatment with HFNCO. In this regard, it should be noted that already at the time of the SARS and MERS pandemics [48, 49], data had been

produced that showed that among the various devices that could be used HFNCO is one of those least correlated with the dispersion of potentially infected droplets. The use of a surgical mask placed on the patient's face during treatment significantly reduces this risk. It should also be said that among the studies cited so far, those that have dealt with this problem have reported a very low incidence of SARS-CoV-2 infection among health professionals during the study period and mostly not related to us of HFNCO.

OUR RECOMMENDATION. Considering the studies analyzed, the use of HFNCO may be effective in the treatment of moderate to severe respiratory failure secondary to COVID-19-related pneumonia, preventing the use of other support techniques, such as CPAP or NIPPV.

We recommend its use for 1 to 2 h in patients with $SpO_2 < 92\%$ or PaO_2/FiO_2 200–300 mmHg during treatment with a non-rebreathing mask at 15 L/min for at least 15 min, before sorting to CPAP in case of failure of the technique to correct these values.

We strongly recommend close clinical monitoring of the patient and check of gas exchange after 2 h of treatment in order not to delay the escalation of therapy in case of deterioration. The determination of a ROX index value > 4 at this timepoint correlates with a better outcome of the technique.

From a practical point of view, we recommend choosing a cannula size appropriate to the size of the patient's nostrils; adjust the flow to 60 L/min and titrate it down to patient comfort; adjust the temperature of the mixture to patient comfort starting from 31 °C; enrich the oxygen mixture by titrating it to the therapeutic target ($SpO_2 > 92\%$).

We also recommend placing a surgical mask on the patient's face during treatment.

OUR EXPERIENCE. The patients who seem to benefit the most are those with hypoxemia and respiratory alkalosis during conventional oxygen therapy without marked dyspnoea or respiratory distress. The ability to compensate the patient-generated inspiratory flows with the high flows generated by the device allows to precisely titrate the FiO_2 to the saturation target. Furthermore, HFNCO is particularly comfortable for the patient, even during maneuvers, such as awake pronation.

RESOURCES. One trained operator. One HFNCO device and its disposables. One non-invasive monitoring system.

RISKS. The greatest risk is to continue the treatment for too long without adequate monitoring, clinical and BGA improvement.

EXPECTED SUCCESS. HFNCO can be effective in up to two-thirds of patients with moderate respiratory failure if well selected.

WHAT I SAY TO MY PATIENT. ‘Your oxygenation is getting worse due to the COVID-19-related pneumonia you suffer from. The simple oxygen mask we are using is no longer sufficient for this purpose. Now, we will use a device

that, in addition to improving oxygenation, will make you feel very comfortable. In any case, we will continue to periodically check your values’.

CPAP efficacy and safety

CPAP systems are widely but heterogeneously used in the treatment of severe refractory hypoxemia that characterizes COVID-19, with a predominantly empirical approach in the Emergency Department.

Why it may work

Pathophysiologically, CPAP in COVID-19 can: a. Lead to increased resistance in the small vessels of non-dependent regions of the lung, favouring the redistribution of perfusion to newly recruited depending areas when the hypoxic vasoconstriction mechanism has been lost; b. Allow saving the inflamed lung parenchyma by the traumatizing phenomenon of recruitment and de-recruitment; c. Reduce the respiratory work and distress and avoid the reduction of the residual functional capacity; d. Improve the compliance of the thoracic–pulmonary system increasing the percentage of ventilated alveoli; e. improve the oxygenation even in refractory hypoxemia during conventional oxygen therapy with moderately preserved pulmonary compliance [9, 18, 50]. f. Reduce the risk of excessive transpulmonary pressure.

CPAP may cause delayed intubation and the need for emergency airway management [51], and increase the risk of viral spread into the environment with a major rate of infection and contamination of health workers.

The use of CPAP, as well as that of NIPPV, in respiratory pandemics, has been reported in the past in quantitatively and qualitatively poor studies; the effectiveness of NIV is, therefore, too limited to allow for any kind of widespread recommendation and rather requires serious caution [6].

Nowadays, the relationship between the potential benefit in cases of mild to moderate hypoxaemic ARF, the amount of droplet dispersion, the risk of inadequacy, waste of resources, and time in applying invasive and intensive measures, are still debated.

The clinical and ventilatory picture of COVID-19 is half-way between pneumonia and ARDS [7, 9, 10, 52–56], thus representing a very high risk of CPAP failure, even if in expert hands in an intensive/semi-intensive environment.

The literature

Most of the available studies in the literature are the results of observational retrospective monocentric experiences, and only a couple of them are prospective. Consequently, main considerations derive from theoretical assumptions

and there is still substantial uncertainty about the selection criteria, risk stratification, timing, defined indications, duration, and success or failure criteria for CPAP in COVID-19 [18, 57–77].

A meta-analysis on 3377 patients from 17 observational investigations treated with non-invasive respiratory support has been recently published. All patients were treated outside the ICU, 80% with CPAP, and the rest with NIPPV [78]. In-hospital mortality was 36% (30–41%). 26% (21–30%) of the patients failed NRS and required intubation, with an in-hospital mortality rising to 45% (36–54%).

More recently, an adaptive RCT has been published as an online preview (non-peer reviewed) by Perkins et Al. [47]. The Authors randomized 1271 patients with severe COVID-19 pneumonia (mean PaO₂/FiO₂ = 131–138 mmHg) into 3 groups, 380 CPAP, 417 HFNCO, and 475 conventional oxygen therapy. Primary composite outcome (ETI or death) was significantly lower in the CPAP Group (36%) vs conventional oxygen (44%), mainly by a reduction of ETI (33% vs 41%, adjusted OR 0.66 (95% CI 0.47–0.93) rather than mortality (16.7 vs 19.2%, OR 0.91 (95% CI 0.59–1.39)). If these data will be confirmed after the scientific review, the pendulum of efficacy will move significantly toward CPAP choice in severe COVID-19 pneumonia.

A pivotal issue is that of environmental safety and the risk of viral contamination [19, 79, 80]. Nowadays, the helmet seems the least dispersive interface [19, 21, 81–86]. Given the risk of airborne dispersion of droplets from devices with high oxygen flow, it is advisable to limit their use to isolated environments with negative pressure or to isolated and well-ventilated areas. To significantly reduce droplet dispersion, a certified antiviral/antibacterial filter should be mounted in series between the oxygen source and the interface, and a second between the interface and the interchangeable PEEP valve on the exhalation port.

It seems rational to recommend the early use of CPAP in hypoxaemic ARF in a moderate phase of the clinical course, for hemodynamically stable patients, with preserved neurological status (Kelly–Matthay scale = 1) [87], unscathed respiratory dynamics, RR ≥ 25 bpm, with SpO₂ < 90% or PaO₂ < 60 mmHg during standard oxygen with elevated FiO₂ via Venturi or non-rebreathing mask or HFNCO sustained at 50 L/min. The choice of high CPAP values, between 7.5 and 12.5 cm H₂O, and high FiO₂ is recommended to achieve the OTSR of 94–98% (69); the goal should be lower (90–92%) in patients at risk of hypercapnia.

The use of CPAP, also in COVID-19, can be recommended, where monitoring is guaranteed with trained medical and nursing staff, and with rapid access to invasive ventilation without any delay in case of failure. CPAP can be safely and effectively delivered outside ICU in some dedicated Emergency Department settings, built as High Dependency Respiratory Units with appropriate

staff and monitoring, along with ensuring cross-specialty collaboration.

Age, baseline SpO₂, baseline PaO₂/FiO₂ ratio, and comorbidities can be considered as main outcome predictors for success or failure.

Response to CPAP cannot be expected to be rapid and any signs of deterioration should be monitored at the beginning and the following days. In the interval phases in which CPAP is temporarily suspended, the decrease in SpO₂, an increase in RR, the appearance of respiratory distress with activation of the accessory muscles, and pump failure represent signs of treatment failure.

OUR RECOMMENDATION. Consider the use of CPAP in any case of severe hypoxemia unresponsive to conventional oxygen therapy. Place an antiviral and antibacterial filter both between the oxygen source and the patient and between the patient and the external environment. Minimize leakages.

OUR EXPERIENCE. Responders usually show quick improvement in SpO₂ and PaO₂/FiO₂ and reduction in work of breathing (WOB); the gain overtime is usually initially limited and then slowly gradually progressive, as well as that of the RR and the respiratory pattern. Even failure is usually slowly gradual and progressive over time.

RESOURCES. Choose from different CPAP devices based on the specific range of PEEP, FiO₂, and flows based on different patient targets. Choose the most comfortable interface based on the patient's preferences.

RISKS. Delay in ETI and invasive ventilation when needed and recommended, squandering of resources, interface drawbacks, aerosol generation, and droplet dispersion.

EXPECTED SUCCESS. Optimal adaptation to the interface, moderate hypoxemia (interpreted together with PaO₂/FiO₂), intact neurological status, improved BGA and RR in the first hours, low physiological score, absence of relevant chronic comorbidities are predictors of success.

WHAT I SAY TO MY PATIENT. “Pneumonia caused by the virus creates a kind of barrier that makes your response to oxygen-therapy unsatisfactory. We can step up with treatment by adding continuous pressure via a different device and a different interface. The first phase is slightly uncomfortable, but you will see that you will soon adapt and we will do our best to help you tolerate it and to optimize your comfort”.

NIPPV efficacy and safety

Why it may work

NIPPV is defined as intermittent positive pressure ventilation in two different alternating levels.

Most of what has been said about CPAP in COVID-19 in terms of pathophysiology also applies to NIPPV.

NIPPV provides: a. The addition of pressure support to inspiration; b. The improvement of tidal volume reducing the work of breathing and respiratory distress; c. The achievement of a wider range of PEEP and FiO_2 values; d. The stability of FiO_2 for a wider range of minute ventilation; e. Less dispersion of droplets (especially via the helmet) [19, 30]; f. The graphical monitoring of ventilator parameters, flow and pressure waveforms; g. The humidification of the circuit.

Compared to CPAP, NIPPV is less simple, positive pressures are less stable with increasing risk of patient–ventilator asynchronies, of generating excessively and unmeasurable swings of the intrathoracic pressure, and excessive tidal volume and total ventilation which ended in p-SILI.

The literature

The vast majority of patients treated with NIPPV have been described in the literature in observational studies [37, 61, 63–65, 70, 71, 75, 78, 88–92], accounting for more than 500 patients, a far lower number than CPAP patients described in the literature (> 2,500), with only one RCT on helmet NIPPV vs HFNCO and not standard O_2 in moderate-to-severe COVID-19 pneumonia ($\text{PaO}_2/\text{FiO}_2 \leq 200$ mmHg) [45]. In this only RCT on NIPPV, the authors found no difference in the primary outcome of respiratory support-free days.

Patients with COVID-19 can develop both interstitial pneumonia and ARDS, which is associated with high mortality; in this scenario, the role of NIPPV is uncertain and still debated, both for efficacy and safety. There is no shared evidence (it is, in fact, even lower than CPAP) to recommend NIPPV in ARF and ARDS due to COVID-19, and the risk of delaying an appropriate invasive mechanical ventilation must always be considered first and foremost: a clear decision on ETI must be made before initiating NIV in any patient affected by COVID-19.

NIPPV should be early preferred to CPAP in case of initial signs of muscle exhaustion and a trend towards respiratory acidosis, with a low threshold in the inclusion of patients with do-not-intubate and comfort-measures-only orders for which NIPPV may be preferred as a palliative ceiling treatment.

FiO_2 has to be set to achieve OTSR, PEEP should be high enough (7.5–12 cmH_2O) to obtain adequate alveolar recruitment and oxygenation under conditions of disadvantageous compliance, inspiratory pressure to get towards a lower than normal tidal volume (4 to 6 ml/kg of ideal body weight), inspiratory trigger must be maintained with maximum sensitivity, inspiratory pressure rise time must balance rapid pressurization and leakages in both restrictive

and obstructive scenarios (0.15–0.25 s), expiratory trigger cautiously at 30% of peak flow.

When choosing the helmet as the interface, instead of the oro-nasal or full-face mask [93], the possibility of non-invasive monitoring of tidal volume and minute ventilation is largely lost, and the setting of ventilator parameters requires particular caution and skills. FiO_2 is set as usual according to OTSR, PEEP should be set higher than usual, inspiratory pressure support higher than with face masks, inspiratory trigger must be maintained maximally sensitive (carefully observing the appearance of autotriggering phenomena), quicker inspiratory pressure rise time, earlier expiratory trigger. The advantage of helmet NIPPV is safety, since it is a closed circuit with an interface with minimal leakage when compared to the mask [94].

OUR RECOMMENDATION. Consider the use of NIPPV for concomitant COPD, a trend to respiratory acidosis (before the onset of muscle exhaustion), or the need to reach a wider range of FiO_2 , PEEP and flows. Place an antiviral and antibacterial filter in both inspiratory and expiratory ways. Minimize leakages.

OUR EXPERIENCE. Responders usually show slowly gradual and progressive improvement in RR, respiratory pattern, PaCO_2 , and resting of respiratory muscles. Even failure is usually slowly progressive over time.

RESOURCES. Ventilators must ensure high performances, such as to optimize synchronization, proportionality and servo-control, and the fine setting of all parameters including inspiratory and expiratory triggers, rise-time and alarms. Choose the most comfortable interface based on the patient's preferences and its sustainability by the ventilator.

RISKS. Patient–ventilator asynchrony, p-SILI, delay in ETI and invasive ventilation when needed and recommended, squandering of resources, interface drawbacks, aerosol generation and droplets dispersion.

EXPECTED SUCCESS. Optimal adaptation to the interface, moderate hypoxemia (interpreted together with $\text{PaO}_2/\text{FiO}_2$) and hypercapnia (with no signs of muscle exhaustion), intact neurological status, improved BGA and respiratory pattern in the first hours, low physiological score, absence of relevant chronic comorbidities (COPD excluded) are predictors of success. Expect a high failure rate in the very old, very low $\text{PaO}_2/\text{FiO}_2$ ratio and comorbidities.

WHAT I SAY TO MY PATIENT. ‘You are getting worse in both oxygenation and ventilation. We can intensify the treatment by adding some pressures that will actively support you in breathing. We will use different interfaces and devices that will follow you in your spontaneous breath. We will need your help to bring you maximum tolerance and comfort’.

Awake self re-positioning

Why it may work

It has been postulated [10] that the main mechanism of hypoxemia in COVID-19 pneumonia is the loss of hypoxic vasoconstriction. This may lead to blood maldistribution and shunt effect by the perfusion side (increased perfusion of non-aerated alveoli). The other effect of pronation is alveolar recruitment of basal regions and reduced dorsal over-distension. This leads to ventilation/perfusion mismatch improvement of non-dependent areas. These actions are probably more involved in the late phase of COVID-19 disease when the lung parenchyma is heavily consolidated, and therefore, atelectasis is predominant.

In summary: a. Position changes might correct the blood maldistribution, thus improving ventilation/perfusion mismatch. b. Awake patients do it by themselves (self-rolling) when instructed to, as opposed to ETI pronation that requires many operators. c. Awake self-repositioning can be applied in every phase of the oxygen escalation and should be attempted at least before ETI.

The literature

To date, more than 300 patients treated with awake pronation with different O₂ treatment, from nasal prongs to HFNC or CPAP or NIPPV have been described in observational studies [95].

The only observational prospective study on the awake prone and lateral position was published by Retucci et al. [77] in 26 Respiratory Intensive Care Unit patients. After a median of 1 h, failure to improve was observed in 25% and 40% of pronated and lateral decubitus patients, respectively. Twenty-seven% of patients were intubated.

The largest case series was reported by Coppo et Al. [62] who described 56 patients pronated for a mean of 3.5 h. PaO₂/FiO₂ ratio was significantly improved (mean + 58%), and 32% were intubated.

The largest case series observed in the Emergency Department was reported by Caputo et al. [96]. After only 5 min of awake pronation in 50 patients, mean SpO₂ rose from 84 to 94%. Intubation was required in 14% of cases.

Longer pronation time (median 9.0 hs) was not superior to shorter time (median 3.4 hs) in a RCT performed by Rosen J et al. [97]

Overall, the heterogeneity of patients described in all the observational studies in terms of severity, oxygen treatment, and duration of pronation is well represented by the rate of intubation that ranged from 0 to 69% (mean = 28%) [94]. Considering all studies, where at least 10 patients

were described, awake pronation improved significantly the oxygenation (PaO₂/FiO₂) in two-thirds of cases [94], without any benefit when longer than 12 h.

OUR RECOMMENDATION. Start with positioning for ≥ 1 h, ideally 3–6 h. If clinical signs and oxygenation improve above 90–92%, go on.

OUR EXPERIENCE. Responders show SpO₂ improvement in the first 2 h. The success rate is higher in diffuse interstitial patterns than consolidations. Explain to the patients that their lungs will possibly benefit from the maneuver; start with the more affected side for lateral decubitus. The response is usually rapid, within 1 h. Sessions of at least 3–6 h.

RESOURCES. For patients on CPAP, one operator and a pillow are sufficient. Help the patient to turn with a pillow under the chest/ or hips/pelvis for pronation or behind the chest for the lateral decubitus. In patients in NIPPV, the manoeuvre may require more personnel and may be more troublesome.

RISKS. Tolerance may be an issue; some patient complains of a sensation of suffocation when pronated. Massive pulmonary embolism has been reported when intubated patients were first pronated.

EXPECTED SUCCESS. The overall reported success rate is moderate in terms of oxygenation improvement (2 out of 3), probably more with pronation than lateral decubitus.

WHAT I SAY TO MY PATIENT. Your oxygen is very low, and this is partly due to a maldistribution of blood into the lungs. To treat this, some studies suggest changing the position to improve blood distribution, either laterally or face down, as you do during sleep. If it works, we'll go on with this for 3–6 h a day for a few days.

When non-invasive respiratory support fails

The SARS-CoV-2 pandemic has posed a unique challenge to the world health system, not only in terms of diagnostics and treatment but also for hospital capacity and resources.

The key aim of the support is tissue oxygenation via sufficient oxygen saturation. If saturation cannot be achieved through non-invasive oxygenation, ETI is mandatory, although the patient has not received a do-not-intubate order, as in common clinical practice.

In these recommendations, we have proposed a step-by-step approach of non-invasive oxygenation to avoid both early intubation and the consequent ventilation-induced lung injury and delayed intubation for those who fail non-invasive oxygenation (Fig. 2, Non-invasive Respiratory Support escalation in COVID-19 pneumonia).

Then, the crucial decision is to define the criteria for non-invasive oxygenation failure.

Non invasive Respiratory Support escalation in COVID-19 pneumonia

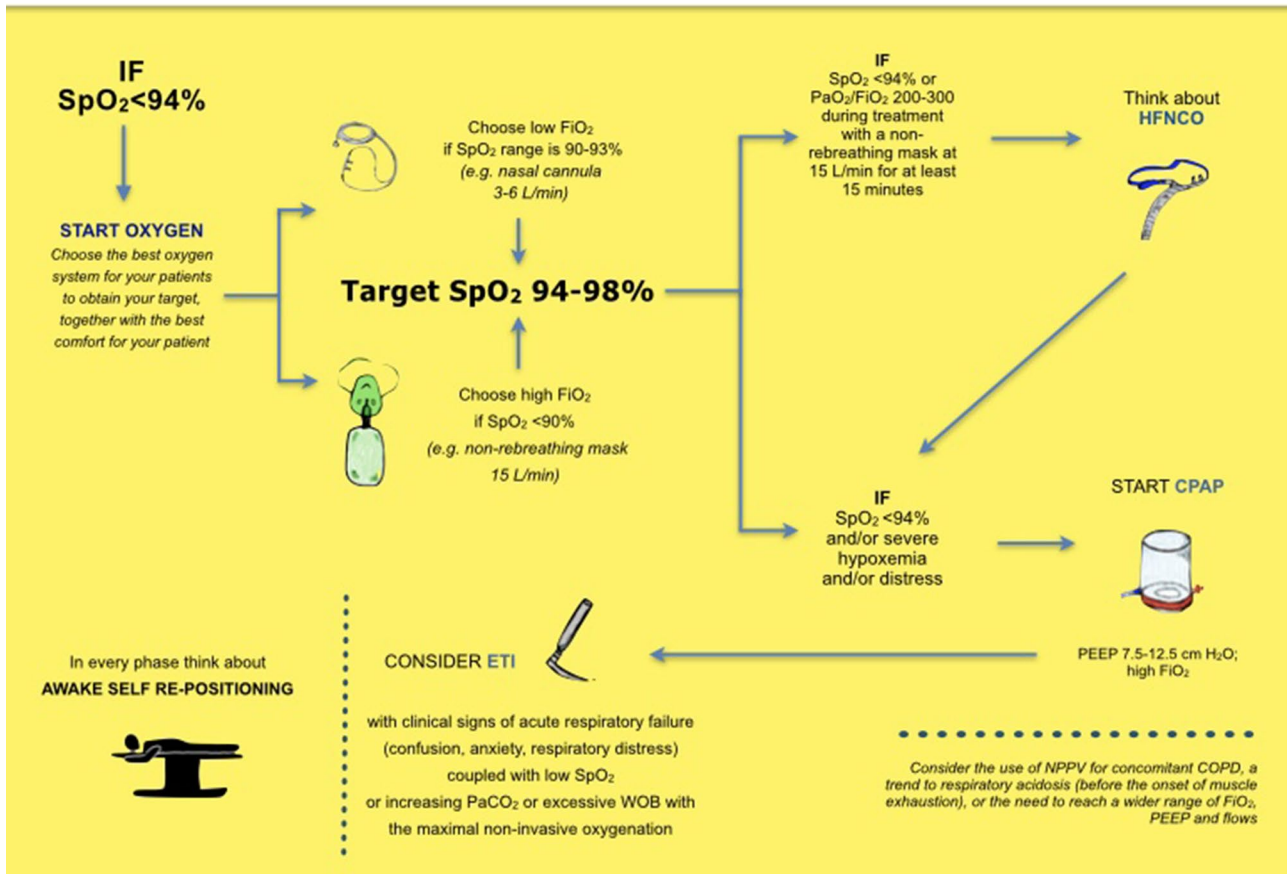


Fig. 2 Non-invasive respiratory support escalation in COVID19 pneumonia

As a rule, the further step to climb to ETI is when patients: a. failed to oxygenate; b. presented fatigue; c. increased their WOB.

We suggest clinicians to proceed to ETI whenever clinical deterioration ensues, such as confusion, anxiety or diaphoresis.

Let's define each-one of the three.

a. Hypoxemia.

Our patient failed to reach $SpO_2 \geq 92\%$ with maximal NRS oxygen. In this case, we suggest using SpO_2 instead of PaO_2/FiO_2 ratio because of its intrinsic limitations. In fact, PaO_2/FiO_2 depends on FiO_2 .

This means that: a. PaO_2/FiO_2 changes in the same patient according to FiO_2 if there is a shunt effect [78–80], such as in COVID-19 pneumonia. Furthermore, FiO_2 is reliable only if the patient is breathing room air or is invasively ventilated (no leaks).

b. $SpO_2 > 90\%$ is obtained whenever $PaO_2 > 60$ mmHg; this means that a wide range of PaO_2 , and therefore, PaO_2/FiO_2 ratios may represent an acceptable SpO_2 . For instance, if a patient's BGA shows a PaO_2/FiO_2 ratio of 120 mmHg,

while on CPAP with a FiO_2 of 60%, it means that PaO_2 is 70 with a saturation well above 92%. If the intubation algorithm considers a PaO_2/FiO_2 threshold below 150 mmHg, this patient should be intubated despite satisfactory oxygenation. If the patient is not in distress, the low PaO_2/FiO_2 means that the gas exchange is severely compromised, not that the patient is 'hypoxemic' despite the treatment.

In conclusion, PaO_2/FiO_2 represents the severity of gas exchange impairment and is very useful to compare case series. However, it should not be the only parameter to consider for intubation.

Therefore, it seems reasonable to wait for intubation until the patient's arterial saturation drops below 92% for at least 30 min while on maximal non-invasive oxygenation and develops signs of clinical deterioration, such as confusion, anxiety, or diaphoresis, and increasing respiratory rate rather than relying solely on the PaO_2/FiO_2 ratio.

Another interesting clinical score to classify the severity of acute respiratory failure is the ROX index ($SpO_2/FiO_2/RR$), formerly developed to predict intubation in patients treated with HFNCO [42]. In the original papers, the

recourse to intubation was significantly higher in patients with an index < 4.88. The ROX index may be attractive, because it combines the gas exchange impairment, expressed by FiO_2 needed to obtain a certain SpO_2 , together with the clinical sign of RR.

b. Fatigue

Patients who develop fatigue with an increasing PaCO_2 despite an increase of RR should be intubated. The intubation delay has been shown to lead to a worse prognosis [98–103].

The clinical picture of impending fatigue with PaCO_2 increase is presumably connected to the evolution to the final phase of COVID-19 disease with the typical ARDS picture [32].

c. Increased work of breathing

Patients with ARF may present with hypoxemia associated with increased WOB and hypocarbia. It's been postulated that the increased intrapleural negative pressure and its consequent increased transpulmonary pressure may have deleterious effects on the lung, the so-called p-SILI. The increase of transpulmonary pressure may lead to further lung damage and increased permeability with interstitial thickening and further gas exchange derangement [12, 99, 104, 105].

One major limitation is that WOB is an invasive measure via an oesophageal balloon, and therefore, it is not suitable for NRS. An interesting paper by Apigo et al. [106] measured non-invasively the WOB of consecutive patients with COVID-19 ARF treated with HFNCO. The WOB evaluation was performed clinically adding to the RR the use of accessory muscles (inspiratory via a. nasal flaring and b. sternocleidomastoid muscle; expiratory via c. abdominal muscles). The authors found that patients with increased WOB (WOB Index > 4 with a predominant use of accessory muscles) were more frequently intubated than those with tachypnoea and a lower WOB (≤ 4).

In patients treated with NIPPV, the exhaled tidal volume is related to intrapleural swings, and when expired tidal volume is higher than 6 mL/kg the risk of p-SILI increased.

In summary, Avoidance of p-SILI must be balanced with ventilation-induced lung injury due to early intubation [105, 107]. It is wise to stick to the clinical ground beyond numbers, looking for the very first signs of clinical deterioration of confusion, anxiety, or diaphoresis.

This aspect underlines the fundamental role of clinical and instrumental monitoring of these patients, as in every critically ill population. In particular, the main focus should be addressed to the circulatory function, which allows adequate oxygen tissue delivery. Perfusion is best checked clinically with mental status, urine output, capillary refill, and skin perfusion (temperature and color: cold extremities and/or mottling are clear-cut signs of hypoperfusion). In parallel, heart function may be monitored

non-invasively with point-of-care ultrasound, looking for inferior vena cava collapsibility, left ventricle contractility, and right ventricle performance by tricuspid annular plane systolic excursion, especially if patients are treated with positive pressure.

OUR RECOMMENDATION. Consider tracheal intubation in patients with clinical signs of acute respiratory failure (confusion, anxiety, respiratory distress) coupled with low SpO_2 or increasing PaCO_2 or excessive WOB with the maximal non-invasive oxygenation. Do not rely solely on numbers ($\text{PaO}_2/\text{FiO}_2$ or other scores, such as ROX index).

OUR EXPERIENCE. Look for PaO_2 and worsening clinical signs (confusion, anxiety, respiratory distress). Plan in advance; prepare a plan B; obtain a list of patients at risk and check it regularly.

RESOURCES. Time- and resource-consuming. If resources are limited (ICU beds, ventilators), consider a priority list according to the probability of success [108]. When intubate, wear personal protective equipment and remember that fewer people involved means less risk of contamination.

RISKS. To avoid the two clinical risks (too early vs too late intubation), refer to our recommendation, coupling numbers with clinical findings.

WHAT I SAY TO MY PATIENT. 'You're getting worse. The next step to treat you effectively is to sedate you to intubate your trachea and release your muscles and lungs'.

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