Use of non-invasive ventilation in acute respiratory failure due to SARS-CoV-2 pneumonia: typing of patients and choice of respiratory support, the role of internal medicine

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Key words: Acute respiratory failure; non-invasive ventilation; SARS-CoV-2.

Conflict of interests: the authors declare no potential conflict of interest.
Abstract

The use of non-invasive ventilation (NIV) during de novo acute hypoxemic respiratory failure is not recommended by the guidelines because NIV does not improve the prognosis. With the advent of the new coronavirus, many cases of acute hypoxemic respiratory failure associated with the infection (severe acute respiratory infection) have been observed: data are missing regarding the use of NIV in this particular clinical condition, but a correct typing of patients based on different clinical, pathophysiological and radiological characteristics, could help in prognostic stratification and in the choice of respiratory support (invasive versus non-invasive). During NIV in these patients particular attention is paid to the possibility of environmental dissemination of the virus and consequently adequate technical precautions are taken.

Introduction

The choice of respiratory support during acute respiratory failure (ARF) due to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pneumonia is a topic widely debated in the last months: lacking solid data in the literature in this new pandemic, the Evidence Based Medicine paradigm has been reversed and, as well as for medical treatment, also for oxygenation / ventilation techniques we rely on the experience gained in similar clinical conditions and on good clinical practice.1-7 In the first weeks of the pandemic, many patients were managed early with invasive ventilation as for other similar forms of ARF such as acute adult respiratory distress syndrome (ARDS) and then subsequently we verify that patients did not improve substantially in most of the cases; however, these patients often arrived in hospital in severe conditions after a first prolonged phase of untreated disease.

ARF typically occurs in the second week of illness in these patients. After an initial period of viral replication with fever and general nonspecific symptoms, a subsequent phase follows in which the excessive inflammatory response in some patients contributes to lung damage with diffuse alveolar damage, inflammatory infiltrates, edema-exudate, endothelial damage (perhaps the main problem)
with vascular thrombosis and disseminated intravascular coagulation. Among these, endothelial and vascular alterations seem to be decisive in the genesis of organ damage (also in other districts such as kidney, brain and heart) and as regards ARF this would explain the poor response to mechanical ventilation especially the invasive one that, if applied with high pressures, it could also worsen the respiratory failure. In a subsequent moment of the pandemic it was therefore understood that perhaps the disease had to be treated early trying to limit viral replication and containing the exaggerated inflammatory response and, as regards the choice of respiratory support in patients with ARF, we understood that it was fundamental a careful selection of patients to treat with invasive ventilation, while non-invasive strategies took on an increasingly important role.

**Typing of patients with acute respiratory failure due to SARS-CoV-2 pneumonia**

Patient with respiratory failure secondary to SARS-CoV-2 pneumonia typically presents with hypoxemia, generally with respiratory alkalosis if ventilation is preserved, a reduction in the PaO2 / FiO2 ratio, an increase in the arterial alveolar O2 gradient (the latter parameter is very more useful both for slatentising a gas exchange defect in patients with borderline PaO2 / FiO2 values and for roughly quantifying its size, therefore it should be used routinely). The mechanisms of hypoxemia are linked to alterations in the ventilation / perfusion ratio (primarily for vascular damage) with a variable share of shunt effect in the alveolar areas completely excluded from ventilation. The duration of respiratory failure is generally prolonged whereby patients who need respiratory support are usually treated for a long period. It is crucial to know how to choose the appropriate respiratory support (non-invasive *versus* intubation) because the best way to minimize complications related to ventilation (invasive in particular) is to avoid it if it is not absolutely necessary. And it has long been proven that the *liberal versus conservative* use of oxygen and ventilation has increased mortality in various clinical conditions. If in general we can claim to know the indications for intubation and invasive ventilation in other forms of ARF, this is not yet clarified for the severe acute respiratory infection (SARI) due to the new Coronavirus: to traditional indicators that orientate
towards intubation, (such as lack of clinical and gas exchange improvement during NIV with persistence of respiratory distress, hypoxemia and acidosis, hemodynamic instability, cardiac or respiratory arrest, airway obstruction, abundant and unmanageable secretions, worsening of neurological status, need to protect the airways)\textsuperscript{1,2,3,6,7} for SARS-CoV-2, the literature is evaluating other prognostic indicators that direct towards the choice of treating the patient in an invasive or non-invasive way (respiratory work evaluated for example with esophageal manometry, quantification of ventilated areas of the lung at CT scan).\textsuperscript{10,11}

Clinically the patient with ARF due to SARS-CoV-2 pneumonia, more often middle-advanced aged man, may not be clearly dyspneic: in general the respiratory rate is not excessively high, the breathing is deep, with high tidal volumes, there are not signs of respiratory distress or use of the accessory respiratory muscles (for example, absence of phasic contraction of the sternocleidomastoid muscle\textsuperscript{9}) and the patient can easily tolerate compromised oxygenation values. The organ damage during hypoxemia depends not only on the absolute values of PaO2 but also on the cardiac output and tissue oxygen extraction which usually increase in a compensatory way during hypoxemia, making evident the organ damage for PaO2 values lower than 40 mmHg.\textsuperscript{9} Radiological findings (High Resolution CT scan, HRTC) are generally a widespread interstitial thickening, ground glass areas (preferably perisepctic at the beginning), consolidation more frequently sub pleural, sometimes minimal pleural effusion. The ultrasound shows a mixed pattern with bilateral non-symmetrical B lines and white lung areas, irregularities of the pleural line, sub pleural thickenings and pleural effusion will also be highly appreciable. According to the indications of literature,\textsuperscript{12-14} a patient of this type can be classified as phenotype L, in which lung compliance is normal and this could explain the absence of respiratory distress by differentiating it from other forms of ARDS.

The second phenotype described in the literature\textsuperscript{12-14} is phenotype H in which lung compliance is reduced and it represents approximately 20\% of patients with SARS-CoV-2 pneumonia and respiratory failure. This phenotype can be the evolution of the disease (from phenotype L to phenotype H) due to the worsening of lung damage which can also be due to respiratory distress
which in these cases is usually present and severe (patient self-inflicted lung injury, SILI, due to the significant negative values of intrathoracic pressure during inspiration measurable with esophageal manometry) or even caused by high pressures in the airways during mechanical ventilation (ventilatory induced lung injury, VILI). In these patients, the HRTC scan shows more severe findings with worsening of edema, large consolidation areas, severe reduction of the pulmonary ventilation due to alveolar collapse and shunt effect. This condition is very similar to other forms of ARDS and meets the criteria of Berlin Definition.\textsuperscript{15}

The distinction of the two phenotypes described above, characterized by different pathophysiological mechanisms (Figure 1), is essential for the overall management of the patient and also for the choice of respiratory support.\textsuperscript{9,12,13,14} Patient L is probably a patient at an earlier stage of his respiratory disease, less severe, and should be managed conservatively, non-invasively, avoiding intubation even for compromised oxygenation levels with the aim of giving time to disease and medical treatment to take the natural course. Its management would therefore deviate from the indications proposed by the guidelines on ARDS which indicate early intubation and marginal role of NIV (Figure 2). The more severe H phenotype, on the other hand, looks much more like other forms of ARDS and therefore should be managed as such, preferably invasively without delaying intubation.\textsuperscript{16} It is true, however, that in many cases, even if intubation would be indicated on the basis of clinical, radiological and gas-analytical criteria, in practice it is not feasible because the patient is elderly, suffering from comorbidities and important chronic diseases, thus remaining only suitable for non-invasive management outside of intensive care units.

### Choosing respiratory support

We now provide some practical indications for the choice of non-invasive respiratory support in patients with L phenotype, which are the majority of SARS-CoV-2 patients with respiratory failure and are normally managed outside of intensive care units.\textsuperscript{5-7}

The first approach to manage hypoxemia should be through \textit{standard oxygen therapy}, such as the
Venturi mask that guarantees high flows as well as precise and high FiO2. It is appropriate to increase FiO2 progressively if hypoxemia is not corrected and take care to maintain a surgical mask over the Venturi mask to limit the viral dispersion. Nasal prongs are less effective in acute patients in terms of flow and FiO2 and increase the environmental dispersion so they would not be indicated. If the Venturi mask is not sufficient to guarantee adequate oxygenation, you could switch to the reservoir mask that provides high FiO2 in patients without high inspiratory flow (slightly dyspnoic) or to the high flow nasal cannulas with heated and humidified mixture (HFNC): although this system is also burdened by the risk of viral dispersion (and therefore can be used preferentially in environments with negative pressure), it is effective because it guarantees high flows, precise FiO2, and excellent patient comfort. Also in this case, the surgical mask correctly positioned above the cannulas is a must.

If oxygen therapy is ineffective, the next step in terms of therapeutic aggression is non-invasive ventilation (NIV) in CPAP mode (continuous positive pressure) or double pressure level (Table 1) which should also be practiced, to limit the exposure of operators, in environments with negative pressure and especially in critical areas with adequate monitoring, expert staff, rapid access to intubation and intensive care units in case of worsening. The application of CPAP reduces the negative intrathoracic pressure during inspiration, improving the ventilation / perfusion ratio recruiting alveolar units with positive effects on oxygenation. in this particular clinical condition we must pay attention to the patient’s hemodynamics status because if we use too high PEEP (positive end-expiratory pressures), as well as risking to worsen lung damage due to overdistention of alveoli not affected by exudate, we could compromise the venous return and cardiac output, and therefore the oxygen delivery to tissues. In general, pressure support during inspiration is not necessary in these patients because in most cases they maintain normal / high tidal volumes and good lung ventilation, in the absence of pre-existing ventilation problems. Indeed it is important not to increase the tidal volume which could worsen lung damage.

CPAP can be delivered with different systems:\textsuperscript{5,6,7}

- Venturi like flow generators: they can be integrated in the system (disposable) or external with
machine body. They are certainly the best performing systems for CPAP because they use high flows capable of satisfying the inspiratory needs of even the most dyspnoic patients, however they are probably the systems most burdened by the viral environmental dispersion because the high excess flow is generally eliminated in the environment through the PEEP valve. It is therefore advisable, in this situation, to use them as a second choice and combine at least 2 antibacterial / antiviral filters, one positioned between the machine body and the circuit (or at the entrance of the window that recalls ambient air) and a second immediately before the PEPEP valve (for example between mask or helmet and valve).

- **Ventilators**: generally all NIV ventilators with turbine technology offer the possibility of a CPAP mode. Because they are technologically different from Venturi flow generators, they generally use lower flows that adapt in real time to the patient’s inspiratory needs. For this reason they are certainly safer as regards the viral dispersion but less performing in keeping the pressures constant during inspiration if the patient has high peaks flow. With a dual limb circuit the environmental dispersion is probably less because the expiratory line conveys the exhaled into the machine with further filtering: however it is advisable to use antibacterial and antiviral filters at the entrance of the inspiratory line, at the exit of the expiratory line and between the mask or helmet and the circuit. Single limb ventilators with an expiratory valve or intentional leaks that eliminate the expired gases in the external environment are probably more risky for the viral dispersion: in this case it is advisable to use two antibacterial and antiviral filters, one at the circuit input (between ventilator and tube), the second between mask or helmet and expiratory valve or intentional leak (usually placed at the end of the tube, close to the patient interface).

The choice of interface is crucial as this affects both the effectiveness of the treatment and the risk of environmental viral dissemination. In general, it is advisable to use non-vented masks, *i.e.* without intentional leaks (which must be present on the circuit if a single limb ventilator is used). The face mask (oronasal) remains the most suitable in emergency, the best in terms of efficacy (constant pressures and FiO2) but can expose the risk of leaks and therefore of environmental dissemination as
well as the total face mask. From this point of view, the helmet seems to offer some more guarantees even if not all turbine ventilators provide adequate flows to avoid CO2 rebreathing with the consequent risk of hypercapnia. Furthermore, if used in bilevel pressure mode, the helmet could generate problems related to the activation of the triggers and the monitoring of the current volume with some ventilators. The helmet also offers the advantage of better comfort for the patient undergoing prolonged treatments, as usually happens in this clinical condition, allows the patient to drink and you can introduce probes through special openings, on the other hand the noise perceived by the patient can be annoying (but ear plugs can be used), it requires at least 2 operators and a few minutes to be positioned correctly and it has a higher cost than the other interfaces. The moment when the helmet is removed can be critical for the environmental dispersion of the virus; this procedure must be done with caution by the staff placing themselves if possible behind the patient. Anyway, before using the helmet with a turbine ventilator, contact the supplier / manufacturer of the machine and consult the instruction manual to check its compatibility. It may be advisable to start with a helmet in the first hours / days of treatment, then at the moment of weaning consider the possibility of switching to facial / total face masks, in this phase avoid long pauses from ventilation to avoid derecruitment, consider always the elective adaptation of each single patient to the different interfaces, always guarantee clean skin, the use of protective barriers and the rotation of different interfaces to prevent pressure injuries. In the literature there are few data on the effectiveness of pronation (even partial) during NIV in improving oxygenation parameters, however, it is an option to consider before sanctioning the failure of NIV.

In Table 2 we report some practical indications regarding the use of NIV in patients with ARF due to SARS-CoV-2 pneumonia.

**Monitoring**

Like all patients in oxygen therapy, and even more in those whose treatment involves the application of positive pressures, a continuous, simple and non-invasive monitoring is essential.⁵-⁷ Among the
parameters to be assessed, SpO2 is certainly fundamental even if, especially in the early stages, it can be falsely reassuring. This is because the patient with L phenotype L, hyperventilating, corrects the hypoxemia quite well and determines a shift to the left of the hemoglobin dissociation curve caused by hypocapnia and respiratory alkalosis. A very important indicator is the respiratory rate (RR) even if, like SpO2, at the beginning of the disease it can have values that deviate little from the norm despite severe hypoxemia. Heart rate and blood pressure are two other values to be measured regularly. Fluid balance must be absolutely measured in order to avoid that it is positive (situation that would worsen the alveolar edema). Arterial blood gas analysis represents, as in other forms of respiratory failure, the main examination. However, if the one at time zero is essential, too close checks should be avoided given the long duration of the respiratory support. Check-ups should be performed at least every 24 hours unless major changes in the patient's clinical condition. In this form of hypoxemic and non-hypercapnic respiratory failure, the frequency of blood gases could be reduced by monitoring the ROX index. The advantage of this index is that it is totally non-invasive and easy to apply. It is calculated using the following formula: (SpO2 / FiO2) / RR. Although it has been mainly analyzed in a study on pneumonia treated with high flows with nasal cannulas (where it was shown that values below 4.8 had a negative prognostic significance), this index can certainly provide a response trend to therapy and alert us when it drops below 8. Lastly, thoracic ultrasound is certainly very useful in monitoring the treatment.

Conclusions

In general, NIV in acute hypoxemic respiratory failure (de novo ARF) such as SARI, pneumonia, other pandemics due to respiratory viruses, ARDS, is not indicated by the Guidelines because it is not effective in reducing mortality and the need for intubation. For SARS-CoV-2, however, the role of NIV is still unclear and must be defined.

In patients with SARI COVID19 related and phenotype L without severe respiratory distress HFNC and NIV could have a role in improving dyspnea and oxygenation when traditional oxygen therapy
is not effective; in these patients we should try to avoid intubation in order to avoid a hasty procedure potentially causing complications and worsening of lung damage.

The most severe patients with respiratory distress and H phenotype should instead be managed invasively according to the ARDS guidelines, therefore the role of NIV is marginal and intubation should not be delayed.

Ventilate in a gentle way with low pressures (PEEP 8-10 cm H2O) also in NIV patients with phenotype L.

If possible, use systems, interfaces and filters that limit the environmental dispersion of the virus as much as possible.

NIV and CPAP would preferably be used in protected environments (critical care areas) with negative pressure and experienced staff.

Consider weaning the patient from mechanical ventilation, even NIV, if respiratory distress is not present in oxygen therapy (preferably at high flows).

References


Table 1. Practical tips for the choice of respiratory support in ARF due to SARS-CoV-2 pneumonia.

<table>
<thead>
<tr>
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<td>&lt;92</td>
<td>and/or</td>
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<td>HFNC</td>
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Target SpO2 92-96%, 88-92% (if chronic ventilatory failure is present); SpO2 partial saturation of oxygen, RR respiratory rate, AA ambient air, HFNC high flow nasal cannula, CPAP continuous positive airways pressure.

Table 2. Practical indication for the use of NIV in ARF due to SARS-CoV-2 pneumonia

- First choice: dual limb ventilator with helmet (if compatible = adequate flows to avoid rebreathing) and 3 hygroscopic antibacterial and antiviral filters (at the entrance of the inspiratory line, at the exit of the expiratory line and between helmet and expiratory line / Y circuit, to be replaced every 12/24 hours).
- Second choice: single limb ventilator with expiratory valve / intentional leaks and helmet, 2 antibacterial and antiviral hygroscopic filters, one at the circuit inlet (between fan and tube), the second between interface and expiratory valve / intentional leak
- Third choice: Venturi flow generator with balloon reservoir and helmet, 2 antibacterial and antiviral hygroscopic filters, one positioned between the machine body and circuit or at the inlet of the window that recalls ambient air and a second between interface and PEEP valve
- Second choice: non-vented face / total face masks
- Mode: CPAP / PEEP 8-10 max 12 cm H2O
- FiO2 adequate to maintain SpO2 92-94%, do not exceed SpO2 96-98%
- If a bilevel or pressure support mode is used: Pressure Support set at 6 cm H2O and not more than 15 cm H2O (avoid high tidal volumes, target 4-6ml / Kg predicted body weight), Rise Time short, inspiratory trigger set to avoid autotriggering or ineffective effort, flow cycling set at 20% of inspiratory peak flow (if present COPD with flow limitation, set at 40% of the peak), maximum inspiratory time 1.25 seconds, back up RR 10 acts/minute with inspiratory time of 1 second
- Clinical and gasanalytic control 2 hours from the beginning of NIV, if no improvement (RR, respiratory pattern, SpO2, PaO2 / FiO2, neurological score according to Kelly) consider intubation and invasive ventilation
- Use of scores during monitoring such as MEWS or ROX index (SpO2/ FiO2 / Respiratory Rate): the latter is a good predictor of HFNC treatment failure in patients with pneumonia. Reference values in this context are: ROX > 4.88 at 2-6-12 hours from the beginning of treatment = low risk of failure / intubation, ROX < 2.85 at 2 hours, < 3.47 at 6 hours, < 3.85 at 12 hours = high risk of failure / intubation. Its use is possible for the monitoring of non-invasive treatment in patients with ARF due to SARS-CoV-2 pneumonia.
Phenotype L: - normal compliance: the amount of gas in the lungs is almost normal or slightly altered. - impairment of ventilation / perfusion ratio as the main mechanism of hypoxemia. - Lung weight only slightly increased: only small areas of ground glass and small consolidations are present. - Recruitability low: the amount of non-aerated tissue is low (use of low PEEP). - absent or mild respiratory distress evaluable with the recruitment of accessory muscles (e.g. absence of phasic contraction of the sternocleidomastoid muscle), respiratory rate alone is not an expression of increased work of breathing. - acceptable response to oxygen therapy / NIV.

Phenotype H: - low compliance: the amount of gas in the lungs is reduced due to the presence of abundant amount of edema. - shunt effect as the main mechanism of hypoxemia, the cardiac output perfuses large areas that are not ventilated for edema. - Lung weight significantly increased due to the presence of large areas of consolidation and ground glass as in other forms of ARDS. - high recruitability: the presence of large areas of non-aerated parenchyma theoretically conditions a high possibility of alveolar recruitment (use of high PEEP and prone position). - respiratory distress: evaluable with the recruitment of accessory muscles (e.g. presence of phasic contraction of the sternocleidomastoid muscle) or with esophageal manometry which shows wide variations in intrapleural pressure. - poor response to oxygen therapy / NIV.
Figure 2. Respiratory support in ARDS. P/F PaO₂/FiO₂ (obtained in CPAP), NIV non invasive ventilation, PEEP end expiratory positive pressure, HFO high frequency oscillation, ECMO extra corporeal membrane oxygenation, ECCO2-R extra corporeal CO₂ removal.