Effectiveness and applicability of Non-Invasive Ventilation (NIV) in the Emergency Department in acute respiratory failure due to Sars-CoV-2 pneumonia

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Abstract

Treatment of *de novo* acute hypoxic respiratory failure is not recommended by current Non-Invasive Ventilation (NIV) guidelines as it does not seem to improve patients outcome. Many cases of acute hypoxic respiratory failure associated with Sars-cov2 infection (SARI) have been observed during Sars-Cov2 pandemic. So far, data are missing regarding the use of NIV, but a correct identification of subgroups of patients based on different clinical, patho-physiological and radiological features, might be helpful for stratifying patients and choosing the correct respiratory support (invasive versus non-invasive). In case of NIV appliance, risk of environmental virus dispersion is particularly elevated; therefore, extreme attention by operators is required.

Introduction

A rapidly increasing number of critically ill patients who need intensive care treatment has been observed in the course of the new Sars-CoV-2 pandemic; this sudden emergency has led to a lack of ICU beds, especially in Italy. As a consequence, these patients have been treated in other settings and other healthcare professionals have been forcedly involved. This has expanded skills and knowledge also in the field of emergency medicine, acting as a didactic and organizational model also for the future when the pandemic will be over. In the past few months a lot has been debated regarding which respiratory support might be the best choice in case of Acute Respiratory Failure (ARF) related to Sars-CoV-2 pneumonia. As at the beginning of this new pandemic no clinical data were available, Evidence Based Medicine has become more and more relevant both for medical treatment as for oxygenation /ventilation techniques: clinicians have based their clinical practice mostly on personal experience and common sense.[1-7] In the first weeks of the pandemic, many patients have been precociously treated with mechanic ventilation similarly to other forms of ARF similar to Acute Respiratory Distress Syndrome (ARDS). Unfortunately, patient clinical conditions didn't improve after NIV as expected (data have not unfortunately been published so far in literature), probably because patients were hospitalized in severe clinical conditions after a prolonged period of untreated infection at home and because they were older patients with comorbidities, neuro cognitive disorders (Do Not Intubate Patients, DNI) and therefore with a worse outcome. Moreover, DNI order in this first period was related to the available resources, overcrowding, and lack of ICU beds.

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Background

ARDS represents a syndrome in which various pathological conditions lead to acute and severe lung damage. Although numerous papers on ARDS are published every year, a standardized diagnostic definition is still missing. Moreover, clinical and laboratory markers to identify patients at high risk of developing ARDS in order to start an early treatment have not been defined yet, as well as a definition of different phenotypes to better target patient's treatment.[8]

In ARDS, lung damage can be directly related to a lung insult (*e.g.* pneumonia, inhalation, contusion) or be indirectly caused by other pathological conditions (pancreatitis, sepsis, polytrauma, burn, overdose, transfusion). The damage begins with a first exudative phase (formation of hyaline membranes) followed by a proliferative phase which evolves in tissue fibrosis. ARDS is burdened by high morbidity and mortality together with high epidemiological and clinical variability, variability of clinical outcomes (depending on the care setting) and high percentage of diagnostic delay; moreover, during ARDS a high variability in supportive treatments, lack of specific treatment and a high percentage of severe physical, psychological and cognitive sequelae at 5 years in surviving patients are observed.

The most important consensus document for ARDS diagnostic criteria has been developed in 2012 in Berlin[9]; it defines ARDS as the onset or worsening of respiratory symptoms within 7 days of a known clinical insult associated with acute hypoxia (PaO2 / FiO2 ≤ 300 mmHg with a minimum PEEP of 5 cmH2O) and presence of bilateral opacities on CT scan not motivated by heart failure or fluid overload. Although an attempt has been made to standardize the diagnostic criteria, the Berlin definition has limits, and for this

reason some clarifications are worth remembering. First, the Berlin criteria do not represent a prognostic tool, data cannot be generalized due to epidemiological, diagnostic and therapeutic heterogeneity and bias due to selection of cohorts with missing data are possible; moreover, it is not always possible to identify higher risk categories, prevalence and outcomes can change depending on risk factors or patient management and finally, in some cases, some clinical conditions similar to ARDS can be defined as so without satisfying all Berlin criteria (ARDS mimics).

Defining patients with ARF due to Sars-CoV-2 pneumonia

The most important questions we would try to answer for optimal management of Sars-CoV-2 pneumonia is whether this condition can be defined as ARDS or not, as already reported in literature,[9] and if a non-invasive management of this clinical condition is safe and effective outside ICU setting, for example in the emergency departments.

ARF in Sars-CoV-2 patients generally occurs during the second week of the disease, after a period of viral replication characterized by fever and general symptoms.[10] In the following phase, an excessive inflammatory response is observed leading to a diffuse alveolar damage, inflammatory infiltrates, edema and exudate, endothelial damage (probably the main problem) with vascular thrombosis and disseminated intravascular coagulation.[8] Endothelial and vascular alterations seem to be crucial in causing lung (as well as kidney and heart) damage, and might explain the lack of response to mechanical (especially invasive) ventilation: the high pressures used might worsen the respiratory dynamics. Therefore, in the second part of the pandemic the treatment strategy has changed: patients have been treated precociously in order to avoid viral replication and to contain the exaggerated inflammatory response. As for respiratory support, patient's selection appears to be crucial for invasive treatment, whereas a non-invasive strategy seems to achieve a crucial role.

Patients with ARF related to Sars-CoV-2 pneumonia appears hypoxic, generally with respiratory alkalosis especially when no other ventilation issues are present, with a reduction of PaO2/FiO2 ratio and an increase of the O2 alveolar-arterial gradient. This last parameter appears to be extremely helpful to unmask a lack of gas exchange in patients with borderline values of PaO2/FiO2 ratio and to roughly quantify the problem entity and should be used routinely. Hypoxia is related to alteration in the ventilation/perfusion ratio due to the vascular damage with a part of shunt effect on alveolar areas excluded from ventilation. [11]

ARF in Sars-Co2 patients is generally characterized by a long course; therefore, patients undergo a long period of respiratory support. As a consequence, the correct choice of respiratory support becomes crucial in order to avoid side effects related to ventilation (especially invasive ventilation), avoiding it when unnecessary. It is well demonstrated how the use of *liberal* oxygen therapy and ventilation versus a *conservative* mode increase mortality in several clinical conditions.[11] We can generally state that indications for intubation and invasive ventilation are well defined but the same cannot be assert for SARI (Severe Acute Respiratory Infection) due to Sars-cov2. In this case, beside the usual indicators for intubation (such as lack of clinical and blood gas exchange

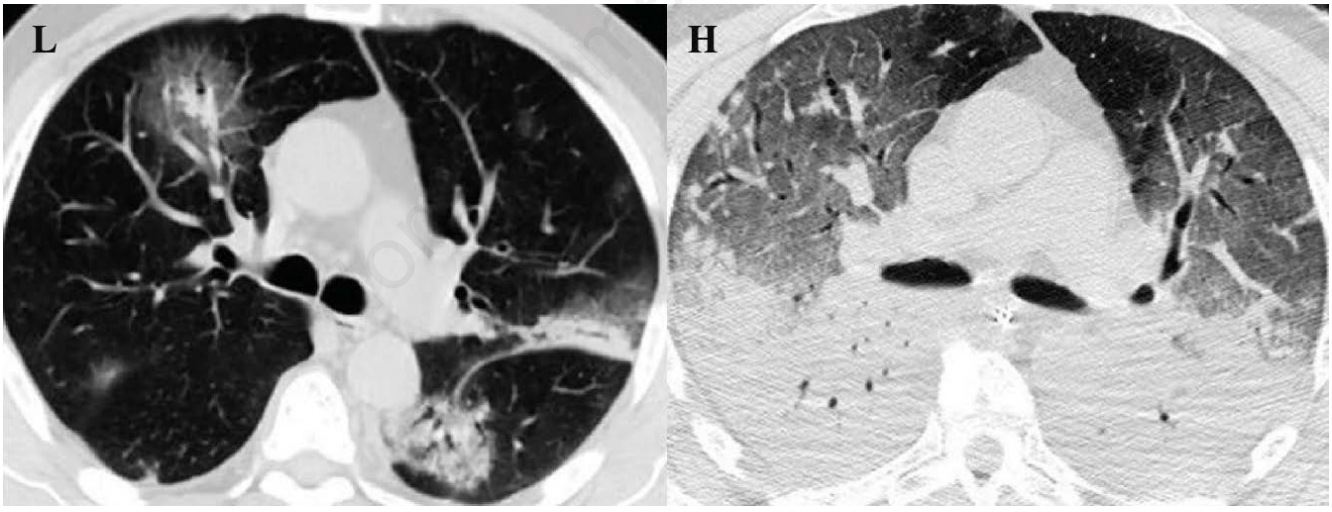

Figure 1. Phenotypes of lung injury in Sars-CoV-2 pneumonia. Modified from Gattinoni L. Chiumiello D, Caironi P *et al.* COVID-19 pneumonia: different respiratory reatments for different phenotypes? Intensive Care Med 2020;46:1099-102. doi: https://doi.org/10.1007/s00134-020-06033-2. Type L: - Normal or nearly normal compliance: gas lung content is normal or minimally altered. - Altered ventilation/perfusion ratio as firstly responsible for hypoxaemia. - Lung weight minimally increased: small ground glass areas are present together with little consolidation areas. - Low lung recruitability: amount of non-aerated lung is low (use of low PEEP). - No or mild respiratory distress, no recruitment of accessory muscle (*i.e.* no phasic contraction of sternocleidomastoid muscle); RR dose not relate to an increase respiratory effort - Good response to oxygen therapy / NIV. Type H: - Low compliance: gas lung content is decreased due to edema and consolidations. - Shunt effect as responsible for hipoxaemia: cardiac output perfusing the non-aerated tissue. - Lung weight hight: large areas of consolidation and edema. - High lung recruitability: amount of non-aerated lung is high (use of high PEEP). - Severe respiratory distress with recruitment of accessory muscle. - Poor response to oxygen therapy / NIV.

improvement during NIV, persistent respiratory distress with hypoxia and acidosis, hemodynamic instability, mental confusion, cardiac arrest, airways obstruction, abundant secretions, need for airway protection),[1-3,6,7] others are under evaluation in order to correct determine the proper ventilation strategy. Among these, respiratory effort based on oesophageal manometry, not easy to perform in the emergency setting, and quantification of well-ventilated lung areas using CT scan have been suggested.[12,13] The hypothesis that inspiratory effort might be a major determinant of NIV failure in these patients suggests the possibility to measure it through changes in oesophageal and dynamic transpulmonary pressure using a nasogastric tube with a dedicated pressure transducer: small variation of pression within the first 2 hours of NIV may be an early and accurate predictor of NIV outcome at 24 hours.[12]

Clinically, patients with ARF secondary to Sars-CoV-2 pneumonia, mainly male and elder, maintain a non-pathological breathing pattern: the respiratory rate is not elevated, the patient has a prolonged breath with high tidal volumes and no signs of both respiratory distress or use of accessory muscles (such as a phasic contraction of sternocleidomastoid muscle)[11] and easily tolerate compromised level of oxygenation. We must remember how the organ injury during hypoxia is due not only to PaO2 values but also depends on cardiac output and O2 tissue extraction. These last two elements usually increase with a compensatory mechanism during hypoxia therefore organ damage arises only for PaO2 values inferior to 40mmHg.[11] From a radiological point of view, CT scan shows a diffuse interstitial pneumonia, with ground glass areas, especially with areas of thickening and consolidation in the subpleura, with sometimes minimal pleural effusion. Thoracic US is characterized by a mixed pattern with asymmetric bilateral B lines together with white lung areas; at the same time irregularities in the pleural line can be observed together with sub pleural consolidations and pleural effusion. According to what has been published so far,[14-16] this pattern corresponds to phenotype L, characterized by normal/reduced lung compliance. This phenomenon might explain the absence of respiratory distress, differently from other forms of ARDS.

According to literature,[14-16] the second is phenotype H, in which lung compliance is reduced; this phenotype accounts for 20% of all patients with Sars-CoV-2 pneumonia and ARF and might represent the disease's evolution (meaning from phenotype L to H), because of the worsening of lung damage related to respiratory distress, usually present and severe. In this case a self-induced lung damage (SILI) is observed, related to an important negative intra-thoracic pressure during inspiration measurable by oesophageal manometry or to high airways pressure during mechanical ventilation (Ventilation Induced Lung Injury, VILI). CT scan of phenotype H patients is characterized by a more severe pattern with edema, diffuse consolidations, severe reduction of lung ventilation due to alveolar collapse and shunt effect. This condition is more similar to other forms of classic ARDS, according to 2012 Berlin Criteria Definition.

Choice of respiratory support for patients with ARF due to Sars-CoV-2 pneumonia

Currently, no univocal indications have emerged in literature regarding the correct timing for non-invasive (HFNC, CPAP, BIPAP) or invasive treatment. Even WHO only indicates the target saturation to be reached (92-95% in adults), specifying however how, in case of persistent respiratory distress, positive pressure treatments (NIV, and in case of early failure switch to invasive ventilation)[17] must not be delayed. The ITS / AIPO[18] statement suggests generic criteria (SpO2 and RR) for the choice of oxygenation methods. The Berlin definition for ARDS seems inapplicable in this type of ARF to select patients in need of invasive ventilation. Therefore, in the absence of literature evidence, the distinction between the two phenotypes described above, characterized by different pathophysiological mechanisms, could be useful for the overall management of the patient and also for the respiratory support choice[11,14-16] (Figure 1).

Phenotype L corresponds probably to an earlier phase of the disease and its treatment should be more conservative in a non-invasive way, avoiding intubation even in case of altered oxygenation parameters in order to allow medical therapy to obtain its effect. Therefore, in this case ARDS guidelines, recommending precocious intubation and no recurrence to NIV, should not be taken into consideration (Figure 2).[10] On the other hand, phenotype H, more severe and more similar to other forms of ARDS, should be treated accordingly to ARDS guidelines, with NIV but without delaying intubation when necessary. It must be added that, in many cases physicians do not proceed to intubation, although recommended by clinical, radiological and gas exchange data, because of patients features (old age, co-morbidities, chronic conditions) which candidate patient to a non-invasive approach outside of ICU.

Regarding the non-invasive respiratory support choice in patients with L phenotype, which are the majority of Sars-CoV-2 patients with ARF and are normally managed outside intensive care units and therefore also in emergency departments[5-7] we believe it could be useful to provide some practical indications.

The first approach is represented by conventional oxygenation systems, namely Ventimask, which guarantee high oxygen flows with specific and elevated oxygen fraction. In case of uncorrected hypoxia, it is necessary to progressively increase FiO2 being careful in maintaining a surgical mask on the ventimask in order to avoid droplets and virus dispersion. Nasal cannula dispenses lower flow and FiO2 with higher environmental dispersion and is therefore not recommended. In case Ventimask is not sufficient to guar-

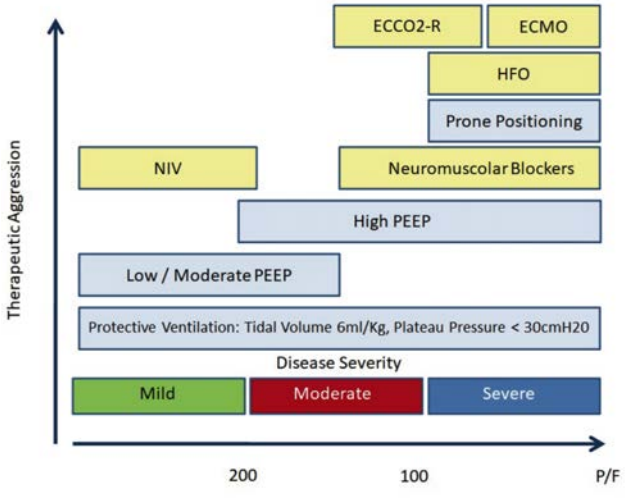

Figure 2. respiratory support in ARDS patients. PaO2 / FiO2 (P/F) values obtained in CPAP (continuous positive air way pressure). NIV non-invasive ventilation, PEEP end expiratory positive pressure, HFO high frequency oscillation, ECMO extra corporeal membrane oxygenation, ECCO2-R extra corporeal CO2 removal.

antee adequate levels of oxygenation a not rebreather mask should be considered (as it allows high FiO2 in low dyspnoeic patients) or High Flow Nasal Cannula (HFNC). These last systems, although facing risks of viral environmental dispersion and therefore recommended in negative pressure location, are very efficient as it delivers high flows, precise FiO2 and comfortable for the patient. Even in this case surgical mask is recommended. The next step, in case of inefficacy, is Non-Invasive Ventilation (NIV) with CPAP mode (continuous positive airways pressure) or double level of pressure (Table 1). CPAP should be applied, in order to limit clinicians' exposure, in negative pressure workplaces, mainly in critical areas with adequate monitoring, with highly trained staff with the possibility of rapidly intubate patients in case worsening of the general conditions. As already mentioned, no solid data are available in literature regarding NIV in these patients but it is of crucial importance to consider NIV ineffective as in other forms of ARDS because phenotype L patients are completely different and peculiar. Applying a positive pressure as in CPAP might reduce negative intra-thoracic pressure during inspiration and increase ventilation/perfusion ratio by recruiting new alveolar units with positive effects on oxygenation. Extreme attention needs to be paid to patients hemodynamic, as too high PEEP (positive end-expiratory pressure) might worsen lung injury by excessively expanding normal alveoli, reducing venous return and cardiac output, therefore compromising oxygen tissues delivery. Generally, in the inspiratory phase support pressures are not needed, as tidal volumes are usually preserved or increased and lung ventilation is normal, unless chronic ventilation problems are pre-existing. As a matter of fact, tidal volume must not be increased as it might worsen lung damage. CPAP can be applied in different ways: [5-7]

i) flow generators (Venturi-like): they can be integrated into the system, if disposable, or separated with an independent unit. These systems are extremely performing to apply CPAP, as they are able to generate high flows; unfortunately, they are associated to a major level of environmental dispersion because the exceeding flow is expelled through the PEEP valve. We therefore recommend them as a second choice associated with 2 anti-bacterial and anti-viral filters, one located on the main unit and circuit and the other right before the PEEP valve (namely between mask/helmet and valve).

ii) ventilators: generally, all NIV ventilators with turbine allow to apply CPAP. They use lower flows than Venturi generators and therefore are related to minor environmental dispersion but sometimes less efficacious in guaranteeing constant pressure during inspiration, especially if patient has high peak flow. Environmental dispersion can definitely be reduced by using a double limb circuit: 2 anti-bacterial and anti-viral filters are again recommended at the entrance of the inspiratory line, at the exit of expiratory line and between mask/helmet and circuit. Ventilators with a single tube with expiratory valve or intentional leaks are more dangerous in terms of environmental dispersion: again, it appears necessary to apply 2 anti-bacterial and anti-viral filters, one at the circuit entrance (between ventilator and tube) and the second between mask/helmet and the expiratory valve or intentional leaks.

The key point is the correct choice of the interface[5-7] which influences treatment outcome and the risk of environmental dispersion of the virus. We recommend generally the use of non-vented masks, that is to say without intentional leaks, already located on the circuit in case of single limb circuit. Face mask remains the best option in an emergency setting, as it allows constant pressures and FiO2, but it is burden by a high chance of air losses and subsequently environmental dissemination similarly to the total face mask. A better option therefore is represented by the helmet, although not all turbine ventilators are able to avoid CO2 rebreathing with subsequent hypercapnia. We must remember how, in case of helmet use with a double level of pressure, issues of trigger activation and tidal volume monitoring might arise. Helmet benefits include a high level of comfort for patients, especially in long lasting treatment; the helmet allows patients to drink and is provided with *holes* for different probes (*i.e.* nasal or gastric tube). By con-

Table 1. Choice of respiratory support in patients with ARF related to Sars-CoV-2 pneumonia, Target SpO2 92-96%.

SpO2 %*		RR	in	Therapy
<95	and	>20	AA	Ventimask or Reservoir
<92	and/or	>20	Ventimask or Reservoir	HFNC/CPAP/Bilevel
<92	and/or	>25	HFNC	CPAP/Bilevel
<92	and/or	>25	CPAP/Bilevel	Intubation / Intensive Care

*:88-92% in patients with pre-existing chronic ventilatory failure (obstructive or restrictive); SpO2: peripheral capillary oxygen saturation; RR: Respiratory Ratio; AA: Ambient Air; HFNC: High Flow Nasal Cannulae (warmed and humified); CPAP: Continuous Positive Airways Pressure.

Table 2. Practical indications for NIV use in ARF related to Sars-CoV-2 pneumonia.

First Choice	Dual limb ventilator with helmet (when applicable: adequate flow to avoid rebreathing) and 3 anti-bacterial / anti-viral filters (at the entrance of the inspiratory line, exit of the expiratory line and between helmet/expiratory line/Y circuit, to be substituted every 12/24 hours)
Second Choice	Single limb ventilator with expiratory valve/intentional leaks and helmet, 2 anti-bacterial and anti-viral filters, one at the circuit entrance, the second between interface and expiratory valve/intentional leaks
Third Choice	Venturi flow generator with helmet (and balloon reservoir), 2 anti-bacterial and anti-viral filters, one between main unit and circuit and the other among interface and PEEP valve
Second Choice	Face / total face non vented masks
Mode	CPAP / PEEP 8-10 max 12 cm H2O
FiO2	Aadequate to obtain SpO2 92-94%, non superior to SpO2 96-98%
In case of bilevel pressure ventilation	Pressure Support from 6 cm H_2O and non superior to 15 cm H2O (avoid high tidal volume, target 4-6ml/Kg body weight), short Rise Time, set inspiratory trigger to obtain synchronism, expiratory trigger set to 20% of inspiratory peak flow (40% if present flow limitation), maximum inspiratory time 1.25 seconds, back up respiratory rate 10/minute with inspiratory time 1 second
Arterial blood gases monitoring	At 2 hours form NIV appliance, in case of worsening (RR, respiratory pattern, SpO2, PaO2/FiO2, Kelly score) consider intubation and invasive ventilation
Patient Monitoring	Using MEWS or ROX index (SpO2/FiO2/RR). ROX index is a good predictor for HFNC treatment failure. ROX>4.88 after 2-6-12 hours of treatment = low failure risk / no intubation, ROX<2.85 after 2 hours, <3.47 after 6 hours, <3.85 after 12 hours = high failure risk / intubation. We hypothesis a routinely use of ROX index for NIV monitoring in ARF related to Sars-CoV-2 pneumonia

trast, inside helmet's sounds can be annoying (although ear plugs can be utilized) and two operators and some minutes are required to correctly place the device; lastly, the helmet is more expensive than any other device. Helmet removal might also be critical and this procedure needs to be performed with extreme caution, with operators behind patients when possible. In any case, before using the helmet with a turbine ventilator we strongly suggest to ask manufactures and verify carefully compatibility on the instruction manual. Practically, helmet is recommended in the first hours/days of treatment and face mask/total face masks for the weaning phase. In any case avoiding long ventilation pauses is crucial, as well as choosing the best device for each specific patient together with skin integrity, rotation in the use of different devices in case of pressure-related lesions. Literature data on the efficacy of the prone position during NIV are missing but this option has to be taken into consideration before admitting NIV failure.

Table 2 resumes some practical indications for NIV in patients with ARF related to Sars-CoV-2 pneumonia

In these patients, especially in case of positive pressure use, a continuous, non-invasive monitoring is needed.[5-7] The first parameter to be taken into consideration is SpO2, although especially at the beginning, it might be falsely reassuring. This happens because phenotype L patients, by hyperventilating, are able to correct hypoxia thus shifting the hemoglobin dissociation curve to the left due to hypocapnia and respiratory alkalosis. An important parameter is the Respiratory Ratio (RR) even if, similarly to SpO2, at the beginning it might be next to normal. Cardiac rate and blood pressure need to be frequently monitored. Fluid balance has also to be checked and must not be positive, as it might worsen alveolar edema. Arterial Blood Gas analysis (ABG) represents the gold exam. Nevertheless, ABG is crucial at time zero but has to be repeated every 24 hours unless clinical conditions change dramatically. In order to avoid ABG, ROX index[19] might be useful, easy to calculate and completely non-invasive, with the following form: (SpO2/FiO2)/RR. So far, its application regarded only patients affected by pneumonia treated with HFCN. In this study, a ROX index inferior to 4.8 was related to a worse prognosis. This index is useful in monitoring treatment efficacy and has to alarm physicians when inferior to 8. Last, even thoracic US appears to be crucial in monitoring patients.

As for the phenotype H, we have already stated how this severe condition should be treated in analogy to other forms of ARDS and therefore the use of NIV is very limited and should interest only mild cases with rapid passage to intubation if no response is obtained within the first 2 hours. It should be emphasized that in literature there is no uniformity on the indications regarding the ventilatory management of ARDS patients, although it is proven that the reduction in mortality is largely due to benefits related to protective ventilation (intubated, sedated and curarized patient).[20] The goal of protective ventilation is avoid worsening of lung damage. The recommended technical settings are: tidal volume not exceeding 6ml / Kg ideal weight, plateau pressure not exceeding 30 cmH2O, PEEP greater than 5 cmH2O and higher only in moderate / severe cases without compromising hemodynamics or worsening the pulmonary compliance. Recruitment maneuvers such as pronation are useful in patients with a P/F less than 150.

Conclusions

Generally, the use of NIV in *de novo* hypoxaemic patients such SARI, severe pneumonia, other pandemic related to viruses, and ARDS, is not recommended by guidelines as not effective in terms of prognosis (it does not reduce mortality and the need of intubation). In case of Sars-CoV-2, its role needs to be defined.

Distinguishing the 2 different phenotypes of Sars-CoV-2 pneumonia may not be easy because in the emergency departments we cannot measure negative intrathoracic swing or lung compliance, but radiological findings (CT, US) and clinical conditions (respiratory distress) may help us.

In Sars-CoV-2 SARI with phenotype L without severe respiratory distress HFNC and NIV might improve the breathing pattern and oxygenation when traditional oxygen therapy fails; in these patients, intubation should be avoided to prevent complications and worsening of lung injury.

Patients with severe respiratory distress and phenotype H should be treated invasively according to ARDS guidelines, in this case NIV plays a marginal role and intubation must not be delayed (protective ventilation). Ventilate in NIV *gently* with low pressure (PEEP 8-10 cm H2O), even phenotype L patients.

A correct choice of interfaces and the use of filters are highly recommended to limit environmental virus dispersion.

NIV and CPAP should be applied by highly trained personnel in negative pressure rooms if it's possible, based on local resources and organization. Consider weaning from NIV when respiratory distress is missing

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