REVISTA DE PATOLOGÍA RESPIRATORIA
Volumen 24 • Número 2 • Abril-Junio 2021

REVIEW

Management proposal for non-invasive respiratory support in pneumonia caused by COVID-19. From pathogenesis to clinical practice

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Rev Patol Respir. 2021; 24(2): 54-60

Abstract

The new pandemic produced by a beta-coronavirus, SARS-Cov-2 presents some differential facts with the previous pandemics also produced by beta-coronavirus (severe acute respiratory syndrome--SARS and Middle East respiratory syndrome--MERS). The respiratory support consists of conventional oxygen therapy, high-flow nasal oxygen therapy, non-invasive mechanical ventilation, CPAP (continuous positive airway pressure), and invasive mechanical ventilation. May be this type of treatment has saved more lives than other treatments used during the pandemic. Although some components of noninvasive support such as high-flow nasal oxygen therapy, noninvasive ventilation, and CPAP had uncertainties regarding their efficacy at the beginning of the pandemic, they have been used widely throughout the world. On the other hand, COVID-19 presents distinctive pathological findings that probably cause physiological changes different from the classical respiratory distress of the adult and consequently can lead to different scaling and adjustments of respiratory support. In these lines we will review the clinical evidence of the efficacy of non-invasive respiratory support in hypoxemic acute respiratory failure before the pandemic, the pathological, pathogenic and functional changes described in this pneumonia and how these can affect the application of respiratory support as well as the way in which today we must apply respiratory support.

Key words: Noninvasive ventilation; Noninvasive respiratory support; CPAP; High flow nasal oxygen.

APOYO RESPIRATORIO NO INVASIVO EN NEUMONÍA CAUSADA POR COVID-19. DE LA PATOGENIA A LA PRÁCTICA CLÍNICA

Resumen

La nueva pandemia producida por un beta-coronavirus, SARS-CoV-2 presenta algunos hechos diferenciales con las pandemias anteriores también producidas por beta-coronavirus (síndrome respiratorio agudo severo - SARS y síndrome respiratorio de Oriente Medio - MERS). El soporte respiratorio consiste en oxigenoterapia convencional, oxigenoterapia nasal de alto flujo, ventilación mecánica no invasiva, CPAP (presión positiva continua en las vías respiratorias) y ventilación mecánica invasiva. Puede ser que este tipo de tratamiento haya salvado más vidas que otros tratamientos utilizados durante la pandemia. Aunque algunos componentes del apoyo no invasivo, como la oxigenoterapia nasal de alto flujo, la ventilación no invasiva y la CPAP, tenían dudas sobre su eficacia al comienzo de la pandemia, se han utilizado ampliamente en todo el mundo. Por otro lado, COVID-19 presenta hallazgos patológicos distintivos que probablemente causan cambios fisiológicos diferentes a la dificultad respiratoria clásica del adulto y, en consecuencia, pueden conducir a diferentes escalas y ajustes del soporte respiratorio. En estas líneas revisaremos la evidencia clínica de la eficacia del soporte respiratorio no invasivo en la insuficiencia respiratoria aguda hipoxémica antes de la pandemia, los cambios patológicos, patogénicos y funcionales descritos en esta neumonía y cómo estos pueden afectar también la aplicación del soporte respiratorio, como la forma en que hoy debemos aplicar el soporte respiratorio.

Palabras clave: Ventilación no invasiva; Soporte ventilación no invasiva; CPAP; Oxigenoterapia nasal de alto flujo.

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Recibido: 16 de abril de 2021; *Aceptado:* 20 de junio de 2021

"Take home" message

COVID-19 presents distinctive pathological findings that probably cause physiological changes different from other similar diseases and consequently can lead to different scaling and adjustments of oxygen therapy and non-invasive mechanical ventilation.

Introduction

The so-called SARS-Cov-2 is the seventh beta-coronavirus that affects humans and the third that causes severe pneumonia[1]. Although it is genetically similar to the other two previous coronaviruses that also caused severe pneumonia, this one maintains a difference of 21% with SARS-Cov-0[2], which is the most similar. As a consequence, it is very risky to extrapolate both its behavior (SARS-Cov-2 produces less severe pneumonia, but is much more contagious) and the treatments that were effective in the previous two. At present we have pharmacological treatments that have either been shown to be ineffective or of moderate benefit for some subpopulations of patients, although there is still much potential treatment under investigation. Respiratory support has probably saved more lives than all the drugs we have used so far.

The NIRS groups the conventional therapy with oxygen delivered by nasal cannula, masks with Venturi effect to regulate the concentration of inspired oxygen and reservoir bag. These systems can enrich the inspired air from 21% of ambient air to approximately 60% or close to 100% using the reservoir bag, but the actual FiO_2 that will reach the patient will depend on the peakflow of air (in this case oxygen) needed the patient. The maximum flow of a typical flowmeter is 15 L/min and a critically ill patient may need higher flows (i.e., 30 L/min). In order to achieve this last flow, we need another type of support such as high flow nasal oxygen therapy (HFNOT) or non-invasive ventilation (NIV).

Although NIRS may be provided using a flowmeter for oxygen flow, to achieve high FiO_2 for patient (i.e. close to 100%) we need high pressure valves (on the wall). In respiratory intermediate care unit (RICU), two high pressure valves per bed for oxygen and also for air is recommended[3].

Noninvasive respiratory support in hypoxemic acute respiratory failure before the first wave of COVID-19

In June 2020, an important meta-analysis was published that summarizes and analyzes the publications made on non-invasive support from 1995 to 2019[4]. This study concludes that NIV, delivered by mask or Helmet interfaces, is superior to standard oxygen therapy in terms of avoiding intubation and survival. NIV by Helmet was superior to NIV by mask probably due to a its more continuous use[5] and less air leaks[6]. The HFNOT was also superior to standard oxygen therapy in avoiding intubations, but not in survival, probably because the 5 studies included in this section of the meta-analysis enrolled seriously ill patients (mean $PaO_2/FiO_2 < 200$)[7-11] where perhaps both forms of supplying oxygen are not as effective as at a lower severity level.

Noninvasive respiratory support in acute hypoxemic respiratory failure during the COVID-19 era

First clinical practice guidelines

At the beginning of the pandemic, there was some uncertainty about the efficacy of non-invasive support (HFNOT and NIV) in hypoxemic acute respiratory failure (ARF) because the aforementioned meta-analysis was not published and it was feared that while using non-invasive support, vital time was lost for the application of invasive mechanical ventilation with intubation. On the other hand, contagion was feared for professionals by generating aerosols. Therefore, the first guidelines carried out either did not recommend non-invasive support or only HFNOT and NIV to try to avoid intubation[12-14]. However, subsequent studies have not endorsed the importance of aerosolization in infections, especially if it is placed a surgical mask over the point of aerosolization (nasal cannula, orifice of venturi effect or exhalation valve for mask, orifice of intentional leak for mask or orifice of expiratory valve)[15].

Noninvasive respiratory support use during the pandemic

HFNO had been widely used with apparent favorable results in observational studies[16-19] and its use has been recommended by some guidelines during the pandemic[13,14]. Failure rate seem be lower in patients with $PaO_2/FiO_2 > 200$ in comparison with those with $PaO_2/FiO_2 \leq 200$[20].

NIV by mask or "Helmet" has been widely utilized during the pandemic but also irregularly across centers probably depending on of the implantation of this therapy or the existence of RICU[21-29].

Anatomopathological alterations and pathogenesis

The autopsies that were carried out in Italy yielded many surprising data. Pseudo-emphysematous changes were observed, such as those that can be seen when there is increase of alveolar dead space, but mainly thrombosis of the capillaries, arterioles and medium-sized arteries, as well as damage to the vascular endothelium with an inflammatory component[30]. In addition, surely favored by hypoxia, the pulmonary capillaries divide in two by a mechanism known as intussusceptive angiogenesis, forming a "tangle" of newly formed pulmonary capillaries[31].

It is known that SARS-Cov-2 has a high affinity to bind to the angiotensin converting enzyme (ACE2) present in some cells such as type II alveolar pneumocytes. Once the virus enters the cell, a large inflammatory cascade is produced known as a "cytokine storm" that damages the capillary alveolus membrane, causing fluid exudation to the alveolus that leads to hyaline membrane syndrome or adult respiratory distress[32]. This also occurs in other viral lung infections. But in addition, the virus penetrates the cells of

the vascular endothelium, rich in ACE2, and causes a new inflammatory cascade at that level that leads to thrombogenesis and a decrease in fibrinolysis, that is, vascular thrombosis. On the other hand, this injury affects vascular tone leading to vasoconstriction. Both thrombosis and vasoconstriction result in pulmonary areas that are ventilated, but not perfused, which can be interpreted as increase in alveolar dead space[32]. The tangle of newly formed capillaries by intussusceptive angiogenesis prevents normal laminar blood flow, producing a turbulent flow that does not promote gas exchange and increases the lung areas that are ventilated and not perfused[31].

Physiological consequences

The consequences of the vascular alterations described can be evidenced in CT angiography, observing "buds" in the small arteries that have been called "budding tree". If we perform a dual perfusion CT scan, we can also observe the lung areas that are ventilated, but not perfused[33].

Pulmonary compliance increases when the lung has excess air with respect to other components of the lung tissue (increase of alveolar dead space), as in emphysema, and is reduced when the lung replaces air with other material such as inflammation or edema, which is what happens in the adult respiratory distress. It has been shown that lung compliance in patients with classical adult respiratory distress is lower than in COVID-19[34] distress and that this compliance is correlated with the degree of consolidation or pulmonary infiltrates seen radiologically[33]. The greater the lung consolidation, the less compliance and vice versa. That is, taken as a whole, the lung of adult respiratory distress of COVID-19 has more air (more areas that are ventilated and not perfused, more alveolar dead space) than adult respiratory distress produced by other causes, which can be a consequence of the "amputation" of the vascular bed caused by thrombosis, vasoconstriction and intussusceptive angiogenesis.

Repercussions on the application of non-invasive respiratory support

Two phenotypes of pulmonary involvement have been identified in COVID-19. The "L-low elastance" and "H-high elastance" phenotypes. Elastance is an opposite or inverse measure to compliance and can be translated as resistance to compliance or "stiffness", that is, the L phenotype would have easy compliance (it requires little inspiratory effort to introduce air into the lungs) and the H a reduced compliance (requires great inspiratory effort to introduce air into the lungs). The characteristics of the L phenotype are normal compliance, not very extensive or consolidated pulmonary infiltrates, and a predominance of vascular abnormalities (thrombosis, vasoconstriction, and intussusceptive angiogenesis). The H phenotype would have reduced compliance and extensive and consolidated pulmonary infiltrates[13,30]. The H phenotype is more like the classical adult respiratory distress.

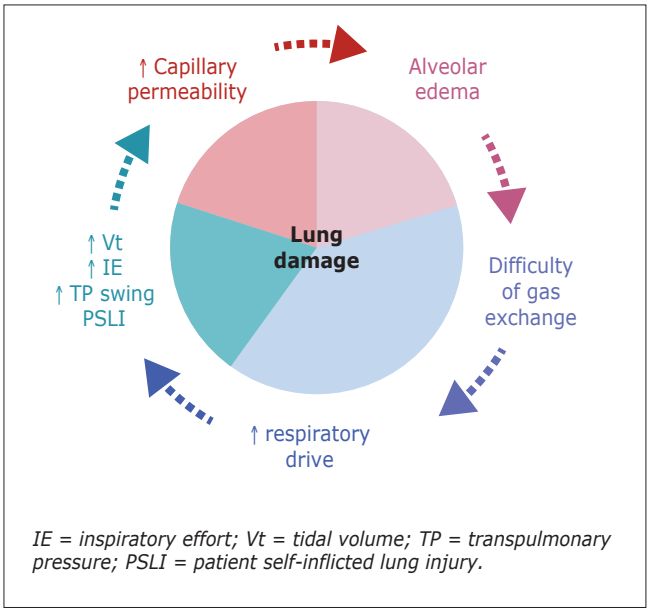
It is also likely that there are intermediate phenotypes and even not really phenotypes but evolutionary patterns within the same process. Consequently, the strategy for applying respiratory support would be different[35]. The L phenotype or pattern may not require mechanical ventilation and it would be sufficient to achieve adequate oxygenation, sometimes with HFNOT, which in turn produces a slight PEEP. The H phenotype would require mechanical ventilation similar to that usually used in adult respiratory distress. Due to the fact that in these conditions the lung is not very compliant or rigid, we cannot apply high volumes of inspiratory air because they would produce high pressures with the risk of "breaking" the lung, causing a pneumothorax. However, a high PEEP that recruits alveoli that are collapsed is very desirable. In the intermediate phenotype or pattern, "L/H", mechanical ventilation with higher inspiratory volumes than the H phenotype and intermediate PEEP would be necessary.

An important aspect is whether these evolutionary patterns or phenotypes are unique to COVID-19 or already existed without our knowing in other similar pathologies that also cause respiratory distress in adults. A study has examined a registry of patients with adult respiratory distress of 1,117 cases, observing that 12% seems to have an "L" phenotype, presenting these patients with a better prognosis[36]. This suggests that this phenotype can actually occur in other causes of distress, but it seems much more frequent in COVID-19 probably due to vascular alterations.

In recent years, the deleterious role of respiratory effort as a generator of lung damage has been revealed[37], which has become critical in the management of pneumonia caused by COVID-19[13,30]. As has been commented on the inflammation secondary to the storm of cytokines cause damage to the lung capillaries that exude fluid into the alveoli. This may be potentiated in COVID-19 with respect to other diseases due to damage to the vascular endothelium. These alterations inactivate the surfactant resulting in collapsed alveoli, which is also favored because healthy alveolar units compress ill and partially collapsed units[38]. The collapse and the alveolar fluid prevent the normal exchange of gases, leading to a serious depletion of oxygen in blood or hypoxemia. To try to counteract hypoxemia, the brain from its bulbar portion sends impulses to the respiratory muscles to produce more vigorous contractions that can increase lung volume. These contractions cause enormous negative pulmonary pressures that are greater the stiffer and less compliant the lung is. In a scenario of capillary damage, these negative pressures "suck" liquid into the alveolus, thus closing the vicious circle (Fig. 1).

Alveolar collapse is maximum at the end of expiration when lung volume is reduced to its maximum[38]. To distend these collapsed alveolar units at the end of expiration, enormous pressures are required that also affect the surrounding alveolar units, favoring the exudation of fluid through these alveoli which can extend the inactivation of the surfactant and collapse as an "oil stain". These pathophysiological alterations could be alleviated with mechanical ventilation by adding a high PEEP (i.e.,> 10 cmH_2O) and increasing the respiratory rate to prevent expiration from being deep and lasting.

NIV reduces this negative transpulmonary pressure, and consequently the respiratory effort, by almost half[39]. As we have mentioned, this negative transpulmonary pressure



IE = inspiratory effort; Vt = tidal volume; TP = transpulmonary pressure; PSLI = patient self-inflicted lung injury.

Figure 1. Lung injury produces capillary damage with leak of fluid into alveoli leading to pulmonary edema those results in gas exchange impairment. Consequently, the respiratory drive is increased with the subsequent increase in transpulmonary pressure, high IE and Vt, resulting in PSILI thus closing the circle.

necessary to distend the lung with each breath can cause lung damage. This damage can increase markedly as the respiratory rate is higher. To understand the importance of respiratory rate in lung damage, we can imagine a patient breathing with a high transpulmonary pressure, for example, −50 cmH_2O and at a respiratory rate of 30 times in one minute. Over 24 hours, this patient would do 43,200 breaths and each one could favor the passage of fluid from the pulmonary capillaries to the alveoli. This possibly explains the dramatic worsening seen in some patients within 24 or 48 hours.

Algorithms for the application of respiratory support today

Although the treatment gap of each component of the NIRS has not well established, in overall standard oxygen therapy may be the first step of NIRS for patients with not very high FiO_2 required (i.e. from 21% to 60%) to achieve the targets of adequate oxygenation and respiratory rate (RR) (SaO_3 > 93%)[13] and RR < 25) (Fig. 2). For higher FiO_2 patient requirement, HFNO or NIV/CPAP may be necessary. There is not a clear gap for using of these last components of the NIRS but probably, HFNO may be used when standard oxygen with high flow (i.e. FiO_2 close to 60%) became uncomfortable for patient or when the targets (SaO_2 > 93% or RR < 25) are no achieved[13,14,40]. This may happen in patients with not profound radiologic consolidation ("L" phenotype)[13,30] were the hypoxemia caused by high ventilation/perfusion areas is an important pathophysiologic component and a high PEEP may be not necessary. In cases were HFNO failure to attain the targets or probably in patients with more profound radiologic consolidation ("H")[13,30] or "L/H" phenotypes[35] (high shunt effect) were a PEEP can be important to recruit collapsed alveoli, NIV or intermediate to high CPAP, with high FiO_2, may be the alternatives. For "H" phenotype" a protective NIV may be required with low volume and plat pressure, high PEEP and high RR with high expiratory flow[13,30]. For "L/H" phenotype a more conventional NIV may be used with high volume, low RR and intermediate PEEP[13,30]. In both last phenotypes, intubation and invasive mechanical ventilation may be frequently necessary[13,30].

Conclusions

The NIRS plays an important role in hypoxemic acute respiratory failure and surely in that caused by COVID-19, although there is a lack of specific clinical trials to confirm this. Both HFNOT and NIV are superior to conventional oxygen therapy, although NIV is more powerful. It is likely that NIRS in overall can increase contagiousness among healthcare workers, but the risk is also likely to be minimized by wearing a surgical mask over the point of aerosol production. Given that many of the pathological changes of pneumonia caused by COVID-19 are distinctive, they surely produce specific physiological changes that in turn require modifying the way in which we apply the NIRS with respect to other similar diseases. The degree of oxygenation and the respiratory rate (as a surrogate respiratory effort) seem necessary markers to apply and scale the NIRS.

Acknowledgments

We are indebted to Verónica Rodríguez for her assistance in the translation of the manuscript and to Vanessa Iglesias for her technical assistance. Juan F Masa has full access to all data from the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial supports

Plan Regional de Investigación (PRI) 2020 Extremadura Government

Author contributions

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Conflicts of interest

The authors declare that they have no conflict of interest.

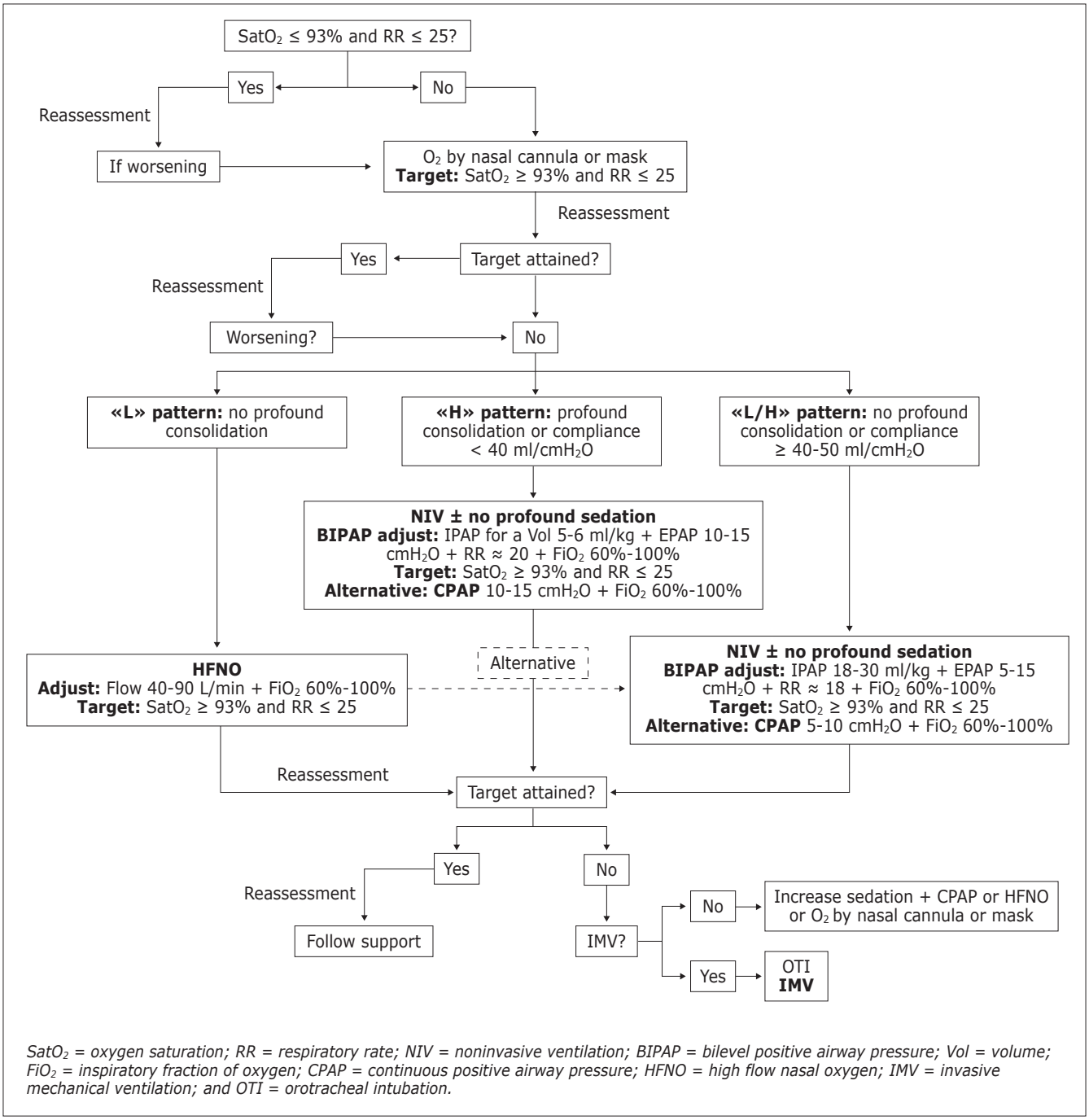

Figure 2. Patients with COVID-19 may be initially treated with conventional oxygen therapy if the $SatO_2$ is less than 93% using the necessary FiO_2 to achieve a $SatO_2$ ≥ 93% and RR ≤ 25. If this objective is not achieved, the patient should be classified into one of 3 groups based on the type of radiological pattern and compliance when available: 1) "L" pattern (no extensive consolidation); 2) H pattern (extensive consolidation or compliance < 40 ml/cmH_2O); and 3) L/H pattern (extensive non-consolidation or compliance ≥ 40-50 ml/cmH_2O). The Group 1 may initially receive treatment with HFNO with intermediate to high flow and FiO2 or NIV with intermediate to high pressures and RR ± non-deep sedation with an alternative of intermediate to high CPAP as it is also recommended in the Group 2. For the Group 3, NIV with low to intermediate pressures, high RR ± non-deep sedation with an alternative of high CPAP may be require. If the goal of an O_2 Sat ≥ 93% and RR ≤ 25 is not achieved we must ask ourselves if there is a contraindication to IMV. If there is no contraindication, intubation and invasive mechanical ventilation should be proposed. Otherwise, an attempt may be made to improve the patient's comfort by increasing sedation, if applicable, and non-invasive respiratory support with the best relationship between effectiveness and comfort.

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