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COVID-19 induced Acute Hypoxaemic Respiratory Failure: Respiratory Ventilatory Strategies

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ABSTRACT

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Respiratory failure due to Coronavirus 2019 (COVID-19) disease has triggered a debate about when and how to apply mechanical ventilation in these patients, as it has been proposed that severe "atypical" ARDS of COVID-19 cause an ARDS pandemic. As global database grows, it is evident that about 6% of patients will need admission to the ICU. About 75% of these will require invasive ventilation, and approximately 10% will need ventilation beyond 14 days. Different ventilation strategies are followed yet there is no strong evidence in favor of anyone. The present article attempts to gather the daily evolving evidence on the subject.

INTRODUCTION

As the COVID-19 pandemic evolves, is evident that around 6% of the patients will require ICU admission[1-4]. Around 75% of those will need invasive ventilation[4], and approximately 10% will require ventilation beyond 14 days[5-6].

Acute Hypoxaemic Respiratory failure (AHRF) due to Coronavirus disease 2019 (COVID-19) trigger a discussion on when and how to apply mechanical ventilation in these patients, as it has been proposed that severe COVID-19 causes "atypical" acute respiratory distress syndrome (CARDS)[7-8]. Though the heterogeneity of ARDS was long known before SARS-Cov2 appearance, COVID-19 pandemic reprovoked the interest about different subphenotypes[9]. Today, hypoxaemia stratification (mild, moderate, severe) of Berlin definition seems inadequate[10] and ARDS wider "space" is better reorganizing into smaller "parts" depending on cause (trauma, medical, high altitude, transfusion, e-cigarette, exercise induced,), anatomic distribution (local or diffuse) respiratory mechanics (driving pressure, dead space, compliance), inflammatory

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response (hyper~ or hypo inflammatory), patient's age, proteomics, metabolic or genetic factors[11].

Furthermore, the subset of observable characteristics (subphenotype) can be a result of one or more distinct biology (also referred as endotypes) and critically ill patients transition or combination of subphenotypesmay exist[12].

CARDS is no exception. The most popular was the clinical distinction of L (low elastance, low ventilation to perfusion ratio, low lung weight and little response to lung recruitment) and H (high elastance, high lung weight and height response to recruitment) subphenotypes[13]. Chest computed tomography (CT) patterns in COVID-19 may be divided into three main phenotypes: 1) multiple, focal, possibly over-perfused ground-glass opacities; 2) in homogeneously distributed atelectasis; and 3) a patchy, ARDS-like pattern[14]. Newer studies provide multi-omics (transcriptomic, metabolomics and proteomics) analyses of CARDS severity[15].

From the above, it is evident that, though general measures such as PEEP and prone positioning are able to improve oxygenation in CARDS[16], different ventilatory approaches are needed, depending on the underlying subphenotype.

The ventilatory protocols in patients with respiratory insufficiency due to COVID-19 have changed dramatically since its emergence and more and more controversies are being placed in the literature every day. The present article provides a short update of ventilatory strategies in COVID 19 -induced ARHF.

HIGH FLOW NASAL OXYGEN (HFNO) THERAPY

HFNO is a recommended therapy for AHRF in COVID-19 disease, especially for patients with non-hypercapnic acute hypoxaemic respiratory failure[17].The risk of airborne transmission to staff is low with well fitted newer HFNO systems when optimal PPE and other infection control precautions are being used. Negative pressure rooms are preferable for patients receiving HFNO therapy. Patients with worsening hypercapnia, acidaemia, respiratory fatigue, haemodynamic instability or those with altered mental status should be considered for early invasive mechanical ventilation if appropriate. There is debate about the degree to which high-flow nasal oxygen is aerosol-generating and the associated risk of pathogen transmission. Older HFNO devices may expose staff to greater risk, yet the risk of viral spread has not been studied[16].

In any case, results of HFNO use should not be carefully followed, in order not to delay escalation treatment when it is needed. Even when HFNO is used with combination of awake prone positioning, this does not seem to lower the incidence of intubation or mortality[18]. Thus, some authors suggest deploying dedicated HFNO units[17] in order to ascertain more efficient monitoring. In case of resource-constrained setting, HFNO for severe COVID-19 AHRF is a feasible alternative to manage these patients without the need for mechanical ventilation.[19-22].

NON-INVASIVE VENTILATION

Non-invasive ventilation (NIV) has long been used to treat chronic respiratory failure, but in more recent years it has increasingly been used to treat patients with various forms of acute respiratory failure[23]. Yet, although known for over 30 years, its use in ARDS is generally limited. Results from use of NIV in COVID 19 pandemic are controversial. Though reports from Italy suggested that use of NIV modes such helmet CPAP (hCPAP) combined with a prone positioning session may be beneficial and “buy time”[24]. Current guidelines suggest that cautious NIV 1 or 2h trials may be indicated only for selected patients. Otherwise NIV use is related to high failure rate, delayed intubation, and possibly increased risk of aerosolization with poor mask fit[25]. There also not clear data on which mode of NIV is better, apart from some reports in favor of HFNO over NIV[26-27]. In most cases CPAP is the reported mode, followed by bilevel positive airway pressure (BiPAP) ventilation[28-29].

Again, proper patient selection may be the key for a successful NIV application.

TRACHEAL INTUBATION

Intubation for ARHF is a high-risk procedure: around 10% of patients in this setting develop severe hypoxaemia ($SpO2 < 80\%$) and approximately 2% experience cardiac arrest. Critical incidents figures are likely to be higher for patients with severe COVID-19. The first-pass success rate of tracheal intubation in the critically ill is often < 80% with up to 20% of tracheal intubations requiring more than two attempts. Increased risk of Health care workers (HCWs) infection during multiple airway manipulations necessitates the use of airway techniques which are reliable and maximize first-time success. This applies equally to rescue techniques if tracheal intubation fails at first attempt.

Proper use of personal protective equipment (PPE) and possible problems is important during the procedure. Fogging of goggles and/or eyewear when using PPE is a practical problem for tracheal intubation in up to 80% of cases (personal communication Huafeng Wei, USA); anti-fog measures (such as iodophor or liquid soap) may improve the situation. Again, training and practicing PPE use before patient management is essential.

Rapid sequence induction should be used as the default technique, unless concerns with airway difficulty make this inappropriate[16,21,22]. Oxygenation via AMBU should be avoided if possible. Low-flow nasal oxygen (i.e. $< 5\ \mathrm{l.min}^{-1}$ via normal nasal cannula) may provide some oxygenation during apnoea and might therefore delay or reduce the extent of hypoxaemia during tracheal intubation. Still, there is no strong evidence regarding viral aerosol generating ability and its use in emergency setting. Other measures such as use of video laryngoscopes have been suggested. Yet, in any case, local settings and experience should be taken in account.

Timing of intubation is also a debate issue and a case-by-case decision seems to be the best strategy. A general rule for intubation could be PaO_2/FiO_2 ratio 120, or $PaO_2 < 70$mmHg when $FiO_2 >60\%$, but criteria vary depending on the respiratory strategy applied (early intubation or not), underline patient's diseases/condition and health care providing conditions (organization, staffing, equipment)[25].

INVASIVE MECHANICAL VENTILATION

The true impact of mechanical ventilation in COVID-19 will never be known. It depends on whether intubated patients truly required mechanical ventilation or whether they could have been sustained with oxygen supplied by less drastic methods. It is difficult to determine how many physicians have been influenced by patient self-induced lung injury (P-SILI) as a justification for preemptive mechanical ventilation as a preventive measure. Lung protective mechanical ventilation (MV) with use of a low tidal volume strategy (4-8ml/kg predicted body weight) and limiting plateau pressures (>30 cmH2O) is recommended for management for acute respiratory failure. Alternate modes of ventilation such as APRV may be considered based on clinician preference and local experience. Viral (rather than HME) filters should be utilized, and circuits should be maintained for as long as allowable.

Patients with type L CARDS, having good lung compliance, accept larger tidal volumes (7-8 mL/kg ideal body weight) than those customarily prescribed for ARDS without worsening the risk of VILI. Actually, in a 70-kg man, with respiratory system compliance of 50 mL/cm H_2O and PEEP of 10 cm H_2O, a tidal volume of 8 mL/kg yields a plateau pressure of 21 cm H_2O and driving pressure of 11 cm H_2O, both well below the currently accepted thresholds for VILI protection (30 and 15 cm H_2O, respectively). Higher VT could help avoid reabsorption atelectasis and hypercapnia due to hypoventilation with lower tidal volumes (table 1).

Table 1. Recommendations based in literature invasive mechanical ventilation-protocols.

INVASIVE MECHANICAL VENTILATION PROTOCOL IN ACUTE HYPOXAEMIC RESPIRATORY FAILURE (AHRF):
Sedation: midazolam, propofol, dexmedetomidine
Neuromuscular Blockade: rocuronium, vecuronium, atracurium, cisatracurium
Consider Prone Position
Start the patient on volume-controlled ventilation with high FiO_2
Tidal Volume 6 ml/Kg
PEEP $\geq$ 10 cm H_2O
Respiratory Rate < 30 BPM
Target Plateau Pressure, 30cm H_2O
Target Drive Pressure ideally,15cm H_2O

NEUROMUSCULAR BLOCKADE (NMB)

There is still no basis in the literature that supports indicating neuromuscular blockers during routine and anesthesia. However, we can use as reference the greatest experiences in ICU. The COVID-19 pandemic peak has significantly increased the workload in most ICUs and the frequency of TOF monitoring has been compromised at times. Even if one attempted quantitative monitoring in the ICU, validity of the results could be questioned because of the lack of standardization. Frequently asked questions are: shall one leave stimulating electrodes in the same place? How long could these stay on the skin without causing pressure damages? What position shall be used of the hand when monitoring is performed? Patients with COVID-19 who need intubation are predominantly suffering from multiple comorbidities. This leaves us with the eternal question which muscle relaxant is better for the 'can't intubate can't ventilate situation'. Despite best efforts of pre-oxygenation, patients with COVID-19 desaturate very quickly during the intubation process to alarming values of 70 or 60% or less within seconds. It is therefore important that intubation is provided by a dedicated team, and mostly by the very experienced physicians, predominantly using videolaryngoscopy. The procedure can be particularly challenging in patients with COVID-19.

NMB may be considered in the setting of worsening hypoxia or hypercapnia and in situations where the patient's respiratory drive cannot be managed with sedation alone resulting in ventilator dys-synchrony and lung decruitment Continuous use of neuromuscular blockade agents (NMBA), as another strategy to facilitate lung protective ventilation, implies some difficulties. Intended increase in patient-ventilator-synchronization with consecutively reduced ventilation-pressures to ease lung protection on the one hand, encounters procedural complications on the other hand. Inactivation of the diaphragm via NMBA in a time-period of ranging from 18-69h proved to cause ventilator-associated diaphragmatic dysfunction with consecutively hampered weaning from mechanical ventilation. Furthermore, a recent randomized controlled trial by the PETAL Clinical Trials Network on early application of NMBA was stopped for futility and recent meta-analytic data showed no improvement in ventilator-free days or mortality[19,20,21].

PRONE POSITIONING

The prone position is a well-established procedure in treating patients with moderate to severe acute respiratory distress syndrome (ARDS) in invasive mechanical ventilation under sedation and neuromuscular block. In the COVID-19 pandemic, this ventilation strategy has been widely adopted in patients on controlled ventilation and in those on spontaneous breathing (self-prone).

The effects of the prone position on the lung and chest wall mechanics depend on the respective complacencies. Chest wall compliance is directly related to stiffness of its anterior, posterior and abdominal limits. In the supine position, the anterior chest wall and abdominal wall are the main components of the compliance. In contrast, in the prone position, the posterior and abdominal walls are the most important. The chest wall's respiratory compliance is reduced in the prone position because the posterior chest wall is less compliant than the previous one. On the other hand, pulmonary compliance is mainly influenced by the opening of pulmonary alveoli and/or improvement in the mechanical characteristics of units already open, leading to better positioning on the volume-pressure curve. It is expected that with the prone position, lung compliance will overcome the decrease in chest wall flexibility to compensate for this change in prone position.

In the COVID-19 pandemic, this ventilation strategy has been widely adopted in patients on controlled ventilation. In those on spontaneous breathing, this is new management for patients with coronavirus pneumonia, still poorly established in the literature.

Prone position offers several physiological beneficial effects that may improve clinical conditions of SARS-CoV-2 patients submitted to surgeries. It increases functional residual capacity and oxygenation without changing airway resistance. Current reports suggest prone ventilation is effective in improving hypoxia associated with COVID-19. Prone positioning is in alignment with two major ARDS pathophysiological lung models. It improves gas exchange, respiratory mechanics, lung protection, and hemodynamics. Moreover, the prone position redistributes transpulmonary pressure, stress and strain across the lung, and unloads the right ventricle. Application of prone ventilation is highly recommended for adult patients and should be considered for paediatric patients with severe ARDS and P/F < 150 but requires sufficient human resources and expertise to be performed safely. In adult patients with severe ARDS, prone ventilation for 12 e16 h per day is recommended. The prone position should be used early (even in the first 48 hours, preferably in the first 24 hours), in patients with ARDS and severe gas exchange disorder, characterized by a relationship between partial arterial oxygen pressure - PaO2 and inspired fraction oxygen - FiO_2 (PaO_2 / FiO_2) less than 150 mmHg. When adopted, it must be maintained by at least 16 hours (possibly reaching 20 hours) before returning the patient to the supine position. It is also important to remind that there is no cross effect of PEEP and prone position. Thus, the adoption of prone position does not affect the PEEP strategy, as they both act synergistically to improve PaO_2/FiO_2. We must recalculate using the drecemental drive pressure and if available impedanciometry. We suggest that the strong indication for adopting a prone position is when the ventilation settings are: FiO_2: 0.6, PEEP: ~10 cmH_2O, VT: 6 ml/kg and PaO_2/FiO_2 remains <150[22]. However, the differences between classical ARDS and type L pneumonia are characterized by pseudo-normal lung mechanics that deteriorate during prone positioning[23.]

TRACHEOSTOMY

Surgical tracheostomies have a role in the weaning process of COVID-19 patients treated in intensive care units. This represents an aerosolizing procedure and must be considered in clinical decision making. Optimal PPE should be utilized at all times[31]. Surgical tracheostomy is an invasive procedure with potentially significant risks. Decision-making should be based on MDT consensus and with a protocol to get the maximum benefit whilst minimizing risk. Doing this in a carefully planned and executed manner with strict inclusion criteria has a positive effect for the patients and the team. Tracheostomy in patients admitted to the ICU, who are under orotracheal intubation and mechanical ventilation, is usually indicated between the fourth and the twenty-first intubation day. Most of the time it is done between 10 and 14 days. This indication may vary according to the severity of the disease and critical status of the patient. In critical ill patient, where the mechanical ventilation expectation is for more than 14 days, the tendency is to perform the tracheostomy earlier. Several reports show that the health condition of COVID-19 patients admitted to the ICU, under mechanical ventilation, is extremely severe and the mean time of intubation is of about two weeks. On the contrary, recent study results claim that early tracheostomy was noninferior to late tracheostomy and may be associated with improvement in some outcomes; it did not contribute to increased infections of clinicians.

SUCTIONING

Endotracheal suction is a procedure which aims to keep airways patent by mechanically removing accumulated pulmonary secretions, above all in patients with artificial airways.

Despite being a necessary procedure, it can lead to complications, such as lesions in the tracheal mucosa, pain, discomfort, infection, alterations of the hemodynamic parameters and of the arterial gases, bronchoconstriction, atelectasis, increase in intracranial pressure, and alterations in cerebral blood flow, among others.

Considering this procedure's complexity, a prior evaluation of the need for suction is indispensable, as this is an invasive, complex procedure that must be undertaken by judicious indication, as it can cause harm to the patient[32]. For this procedure, it is important that the nurse has knowledge based on valid scientific evidence concerning the different methods of endotracheal suction and aspects related to it. Closed in-line suction catheters are recommended. Any disconnection of the patient from the ventilator should be avoided to prevent lung decruitment and aerosolization. If necessary, the endotracheal tube should be clamped, and the ventilator disabled (to prevent aerosolization).

NEBULIZATION

Given the importance of disease management in the era of COVID-19, it is essential to translate the dilemma of using aerosol devices into an evaluation of not only the device but also the patient to recommend an appropriate device tailored specifically to patients' abilities and clinical conditions. Therefore, it is vital to train patients and clinicians on the risk of contamination during device preparation and viral transmission while providing suggestions on how to use each device safely and effectively in patients with COVID-19. Each aerosol device has advantages, limitations, and risks for device contamination and viral transmission

G. Reychler and the aerosol therapy workgroup (GAT) of the Sociétéde Pneumologie de Langue Française decided at SARS-CoV2 pandemic preparedness to suggest avoiding a drug delivery via nebulization to reduce the risk of spreading the virus by this way. Indeed, some arguments suggested[33]:

1. The nebulizers are a source of contamination.
2. The aerosolized droplet are dispersed.
3. The SARS-CoV2 is stable in aerosols

Use of nebulizers is not recommended and use of metered dose inhalers is preferred where possible.

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

The use of ECMO in COVID-19 is a rescue treatment if mechanical ventilation cannot guarantee appropriate gas exchange. ECMO therapy is also indicated when the negative effects of invasive mechanical ventilation are considered unacceptable. During emerging infectious disease outbreaks when resources are exhausted, inhaled nitric oxide and prostacyclin may be considered as a temporizing measure when patients develop refractory hypoxemia despite prone ventilation, or in the presence of contraindications to prone ventilation or ECMO[36] (table 2).

Table 2. Contraindications for ECMO support in COVID-19 patients[36].

ABSOLUTE CONTRAINDICATIONS	RELATIVE CONTRAINDICATIONS
Rejection by the patient	Age >65 years a (depending on the biological age)
Pre-existing severe neurological deficit, advanced dementia	Ventilation duration prior ECMO >7 days
End-stage disease (life expectancy <1 year)	Relevant immunosuppressive therapies
Known severe brain injury	Systemic hematologic disorders
Age >75 years or age >70 plus ≥2 relative contraindications a	Additional organ failure (except kidney)
End-stage lung disease	Frailty
Disseminated malignancy	Severe aortic regurgitation (VA ECMO)
Child-Pugh C liver cirrhosis	Severe peripheral vascular disease (VA ECMO)
<1 year after allogeneic stem cell transplantation	Chronic heart failure NYHA IV (without option for heart transplantation or ventricular assist device)

BRONCHOSCOPY

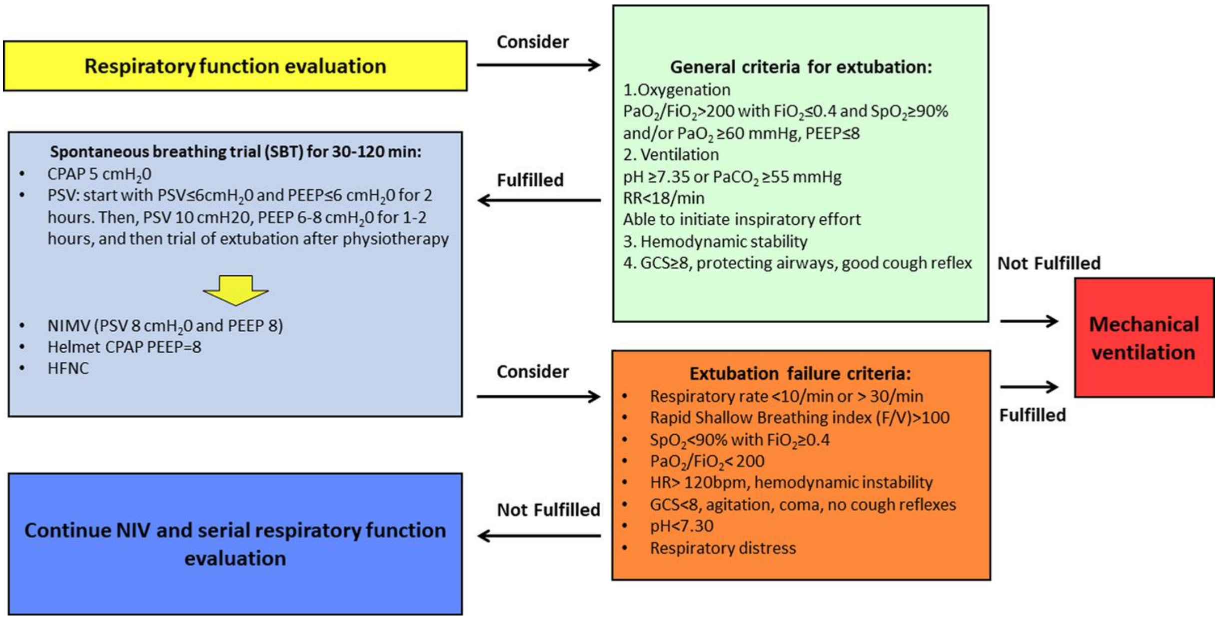
Diagnostic bronchoscopy is not recommended. It is not necessary for the diagnosis of viral pneumonia and should be avoided to minimize risk of aerosolization. Tracheal aspirate samples for diagnosis of COVID19 are sufficient and BAL is not usually necessary[34]. Bronchoscopy in critically ill patients with COVID-19 has been required to manage complications (atelectasis, hemoptysis, etc.) as well as to obtain samples for microbiological cultures and to assist in the management for intubation and percutaneous tracheostomy[35]. In critically ill, mechanically ventilated patients with COVID-19, thick hypersecretion in the airway is the most common complication observed, and these patients can benefit from specific bronchoscopy management.

LIBERATION FROM MECHANICAL VENTILATION

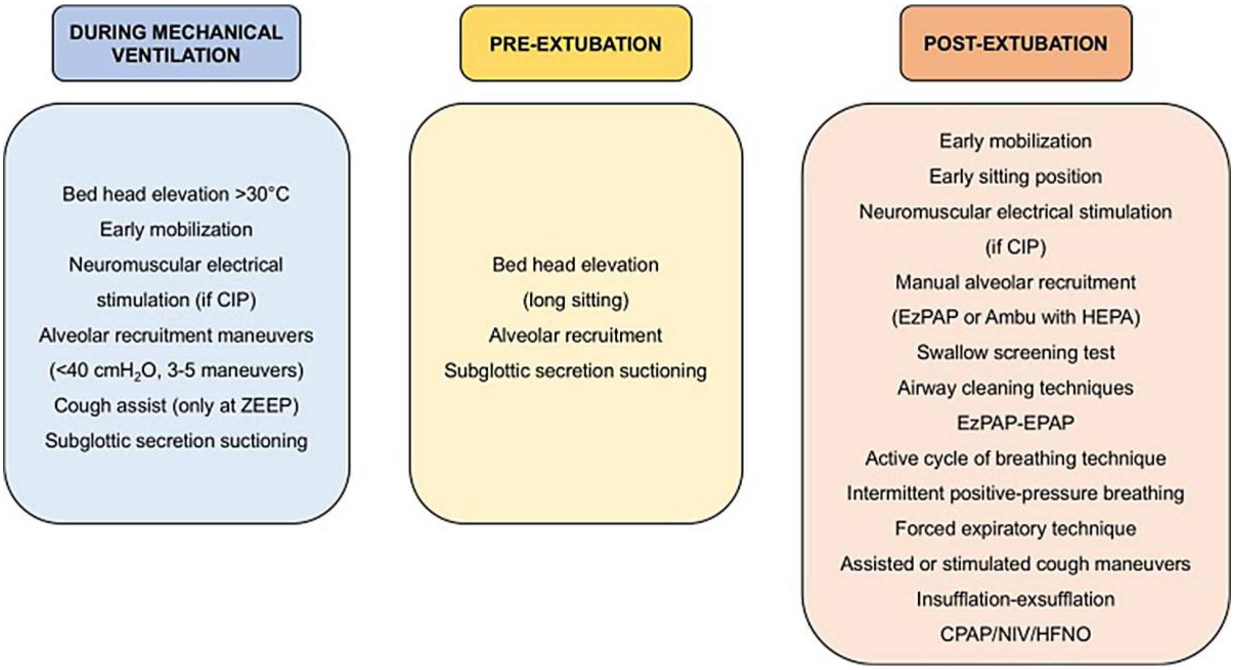
Standard weaning protocols should be followed. HFNO and/or NIV (well fitted facemask with separate inspiratory and expiratory limbs) can be considered as bridging therapy post-extubation but must be provided with strict airborne PPE. A case-by-case strategy should be decided as several factors can influence liberation from mechanical ventilation. Increased age, SOFA (Sequential Organ Failure Assessment) score at ICU admission, C_{rs}(respiratory static compliance) < 40 mL/cmH_2O, low PaO_2/FiO_2, renal and cardiovascular complications, and late-onset ventilator-associated pneumonia (VAP) are some of them[24]. However, since the phenotypes of respiratory failure in COVID-19 patients vary and no specific guidelines exist, multiple weaning indices could be used (Graph. 1)[25].

Early chest physiotherapy during mechanical ventilation, as well as pre- and post-extubation respiratory physiotherapy is also important for the weaning procedure (Graph 2)[26].

Graph. 1. Genoa algorithm for weaning of COVID 19 patients[26].



Graph 2. Genoa−COVID-19 algorithm for respiratory physiotherapy[27].



Lung ultrasound is useful asset during mechanical ventilation and results of large studies (e.g. INVICTUS), are expected to clarify more its role during weaning process[28,29].

Finally, a plan for respiratory follow up of these patients should be set before ICU discharge, in order to ascertain close surveillance and early management of possible complications (interstitial fibrosis, thromboembolic incident, etc). Long term effects of COVID -19 (i.e. "Long COVID") are still under investigation and rare respiratory complications, such platypnea - orthodeoxia syndrome, may arise. Several general algorithms have been proposed; yet case special characteristics along with local settings and capabilities of healthcare system should be keep in mind when planning post-extubation respiratory monitoring[30].

CIP, critical illness polyneuropathy; ZEEP, zero PEEP; PEEP, positive end-expiratory pressure; HEPA, exhalation/expiratory filter; EPAP, expiratory positive airway pressure; CPAP, continuous positive airway pressure; HFNO, high flow nasal oxygen; NIV, non-invasive ventilation

DISCUSSION

ARDS is a syndrome defined by a numerous physiopathological criteria. It is therefore not surprising that lung-protective ventilatory strategies that are based on underlying physiological principles have been shown to be effective in improving outcome. Lung protection strategy can be provided in patients with ARDS, resulting in better pulmonary function and higher rates of weaning from the ventilator. Therefore, lung-protective strategy should be applied to patients with ARDS who are on a mechanical ventilator.

The patients are placed on low tidal volumes and low FiO_2 to maintain acceptable oxygenation. Authors described that some patients do not respond well to high positive pressure and respond better to prone positioning in bed. The authors also mentioned that their study that their study findings may not be generalizable to all cases of COVID-19 associated ARDS, both due to the sample size and the fact that the study was not randomized. While they called their findings surprising; they wrote that any relation to body position and increased lung recruitability should be further explored. Prone positioning during general anesthesia affects respiratory mechanics while improving functional residual capacity and increasing oxygen tension. Prone position was initially introduced in healthy anesthetized and paralyzed subjects for surgical specific reasons.

Despite enormous efforts in research and medicine, the management of patients suffering from ARDS remains a big challenge in contemporary intensive care medicine. Due to the aforementioned problems in diagnostics and therapy, as well as far-reaching personal and social consequences of ARDS improvements in care are of highest interest both for the individual patient and for society. Therefore, various approaches to solve these issues have been discussed in the recent past but have predominantly shown moderate effects. These include audit- and feedback-sessions, educational measures for health-care practitioners, improvement of teamwork among providers and decision support measures[37-41].

CONCLUSION

The evidence about COVID-19 is evolving, and at present, the focus should be on the best supportive standard of care with compliance of infection control principles for the safety of patients and HCWs, but many indications are still without scientific evidence and are very controversial. New studies are needed for rationality. In conclusion, the main features of respiratory mechanics, the response to treatment (such as oxygenation response to LRM or prone position) and prognosis are similar in COVID-19 and non-COVID-19 ARDS. The oxygenation response to LRM and a high PEEP appear to be very heterogeneous in COVID-19 ARDS; this would argue in favor of a personalized ventilation strategy.

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