

Hemodynamic and mechanical ventilation approach in patients with COVID-19

Abordaje hemodinámico y ventilatorio en pacientes con COVID-19

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a clinical entity generated by this new virus a Coronavirus (COVID-19). Disease called COVID-19 (Coronavirus Disease 2019) by the World Health Organization. Its presentation is acute respiratory failure characterized by hyperinflation of the lung that leads to an increase in capillaries and epithelial permeability, with loss of ventilation of lung tissue and increases lung stiffness. These disturbances lead to imbalances between ventilation and perfusion ratio, which ultimately result in hypoxemia and impaired carbon dioxide clearance. For this review, a search of PubMed and Trip Database was performed. Due to the scarcity of publications, a specific search algorithm was not used. The objective is to review, the evidence and the recommendations of national and international experts, of the hemodynamic and ventilatory management of these patients.

Keywords: COVID-19. Hemodynamics. SARS-CoV-2. Mechanical ventilation.

Resumen

El coronavirus del síndrome respiratorio agudo grave 2 (SARS-CoV-2, conocido previamente como nCoV-2019) es el agente causal de una nueva enfermedad denominada COVID-19 (Coronavirus Disease 2019) por la Organización Mundial de la Salud. Su presentación es la insuficiencia respiratoria aguda caracterizada por una hiperinflación del pulmón que conduce a un incremento de los capilares y permeabilidad epitelial, con pérdida de la aireación de tejido pulmonar e incremento de la rigidez pulmonar. Estas alteraciones conducen a desequilibrios entre la ventilación y la relación de perfusión, que finalmente resultan en hipoxemia y deterioro de la depuración de dióxido de carbono. Para la presente revisión se realizó una búsqueda en PubMed y Trip Database. Debido a la escasez de publicaciones no se utilizó un algoritmo de búsqueda específico. El objetivo es dar a conocer, de acuerdo con la evidencia y las recomendaciones de expertos nacionales e internacionales, el manejo hemodinámico y ventilatorio de estos pacientes.

Palabras clave: COVID-19. Hemodinamia. SARS-CoV-2. Ventilación mecánica.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has high affinity for angiotensin-converting enzyme 2 receptor in humans, which is expressed in type II pneumocytes in the lung. Reports from different countries show that the lung is the most vulnerable target, due to its high susceptibility to inhaled viruses. The distribution of angiotensin-converting enzyme 2 in other organs could explain the multiple organ dysfunction observed in critically ill Coronavirus Disease 2019 (COVID-19) patients¹.

In patients who require intensive care unit admission, hemodynamic, and ventilatory support are the cornerstone of treatment.

The purpose of this review is to present current recommendations on hemodynamic and ventilatory support for patients with COVID-19 at critical phase.

Method

A search was conducted in PubMed and Trip Database. Due to the scarcity of publications, a specific search algorithm was not used. The publications that were found are observational studies and expert recommendations; there are no meta-analyses or randomized trials.

Background

There are epidemiological reports of severe acute respiratory syndrome caused by SARS-CoV-2 where there is an increase in morbidity and mortality in patients with chronic lung disease, smoking, comorbidity (hypertension, diabetes, or cardiovascular disease) or advanced age², and it depends on the interaction of four factors:

- Infection severity
- Time elapsed since disease onset
- The host (response, physiological reserve, and comorbidity)
- Patient ventilatory response capacity to hypoxemia³.

Severe acute respiratory syndrome

Acute respiratory distress syndrome (ARDS) is a clinical syndrome defined by acute-onset hypoxemia ($\text{PaO}_2/\text{FiO}_2$ ratio < 300) and bilateral pulmonary

opacities in the absence of heart failure or volume overload (although they may coexist)⁴.

The Berlin definition stratifies ARDS into three subgroups according to the degree of hypoxemia (mild, moderate, and severe)⁵ as follows:

- Mild: $\text{PaO}_2/\text{FiO}_2 > 200$ and < 300 with the use of positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) $> 5 \text{ cmH}_2\text{O}$
- Moderate: $\text{PaO}_2/\text{FiO}_2 > 100$ y < 200 with PEEP use or CPAP $> 5 \text{ cmH}_2\text{O}$
- Severe: $\text{PaO}_2/\text{FiO}_2 < 100$ with PEEP use or CPAP $> 5 \text{ cmH}_2\text{O}$.

Mortality increases as $\text{PaO}_2:\text{FiO}_2$ decreases in patients with moderate to severe ARDS ($\text{PaO}_2:\text{FiO}_2$ ratio $< 150 \text{ mmHg}$).

Patients with COVID-19 may develop ARDS with this viral infection own characteristics. The lungs have higher compliance than that observed in ARDS. Hypoxia is severe and prevails as pulmonary perfusion regulation is gradually lost, significant hypoxic vasoconstriction occurs and pneumocytes with viral cytopathic effect cause an hyperinflammation that continues at advanced stages, which results in severe pulmonary compromise⁶. These patients with severe hypoxemia⁷ exhibit certain uniformity in their evolution: normal breathing, “silent hypoxemia” or dyspnea, hypocapnia, normocapnia or hypercapnia and, at severe stages, they may or may not respond to prone position; despite protective mechanical ventilation parameters, mortality within intensive care units is considerably high⁸⁻¹⁰.

According to symptom severity, patients can be classified as mild, severe, and critical (Table 1)¹¹.

Associated phenotypes (Fig. 1)

Little is known about the genetic interaction of the host with infection and its progression. Immune system-related data and genetic risk prediction models have been linked to immune and hematologic cell subtypes involved in viral defense, including lymphocyte count.

There is a transition between phenotypes. Patients with pneumonia with type L phenotype can remain without changes for a period and then improve or experience lung function deterioration, which determines evolution and severity of the disease¹⁰.

L phenotype

It is characterized by a decrease in the ventilation-to-perfusion ratio (V/Q). Pulmonary artery pressure

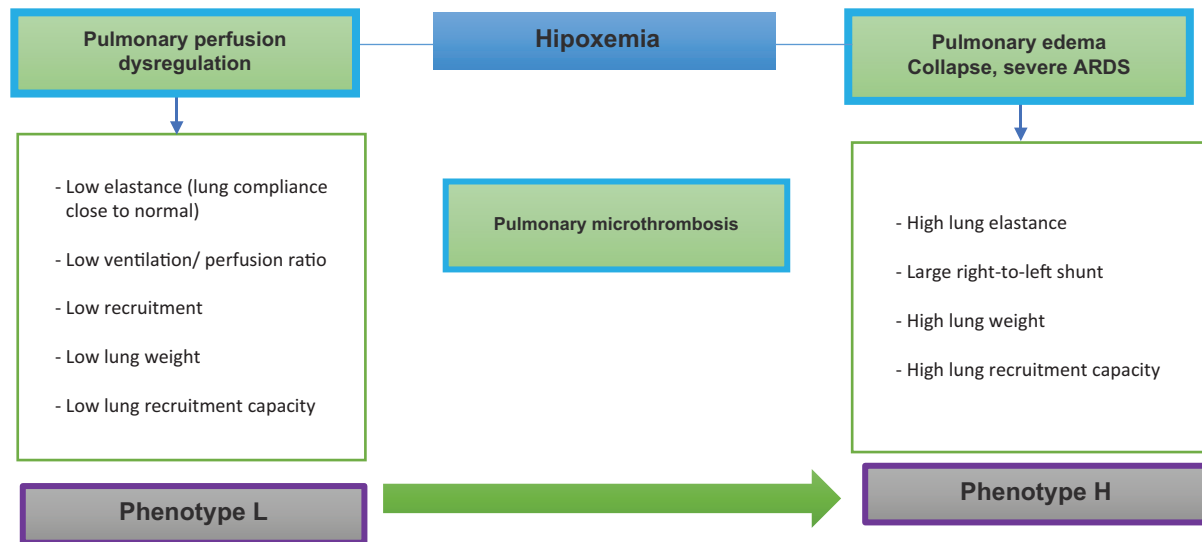


Figure 1. COVID-19, relationship of L and H phenotypes; Adapted from Repessé et al.⁵³

Table 1. Symptom severity. COVID-19 spectrum has been reported within a range comprising from asymptomatic infection to severe respiratory failure

Clinical types	Symptoms
Mild	Absence of pneumonia or mild pneumonia
Severe	Dyspnea, respiratory rate ≥ 30 , $SO_2 \leq 93\%$, $PaO_2/FiO_2 < 300$, or pulmonary infiltrates $> 50\%$ within 24/48 h
Critical	Respiratory failure, septic shock, or multiple organ dysfunction

does not show important changes, although associated cor pulmonale has been described in these patients and there is loss of perfusion regulation by hypoxic vasoconstriction.

Computed tomography (CT) can corroborate the presence of local sub-pleural interstitial edema and sub-pleural ground glass images along the lung fissures, which are related to low alveolar recruitment capacity.

At advanced stages, the patient presents with severe hypoxemia associated with intrathoracic inspiratory pressure negative increase, tidal volume increase with spontaneous breathing, and lung vascular permeability increase due to the severity of the inflammatory process with presence of interstitial edema. These alterations are the main cause of self-inflicted lung injury. Dyspnea and lung function deterioration develop at this stage, with increased

ventilatory work. Transition from type L to type H may be due to viral replication and self-inflicted lung injury¹².

H phenotype

It can occur in 20-30% of patients. At admission, they present with severe alveolar and interstitial pulmonary edema with criteria consistent with severe ARDS: hypoxemia, bilateral infiltrates, pulmonary elastance compromise caused by gas volume decrease, right-to-left shunt increase by an increase in the cardiac output fraction that perfuses unventilated pulmonary areas and has pulmonary recruitment high capacity.

Direct damage by the virus produces a hyperinflammatory injury, severe lung compromise, diffuse alveolar damage and a huge cytokine storm, and a marked increase in lung weight (> 1.5 kg) has been described on lung CT^{6,13}.

Inflammation stages

Stage I: viral phase

White blood cell count tends to be normal, lymphocytopenia is observed in 80% of patients, and there is mild thrombocytopenia; both recognized as a sign of poor prognosis, and evolves to thrombotic-type disseminated intravascular coagulation, which affects the lobular center of alveoli and increases

the V/Q alterations observed in critically ill patients. Inflammatory markers, such as C-reactive protein, are increased, and at this phase, it helps differential diagnosis with other pathologies that occur with severe respiratory failure and normal C-reactive protein. Elevated ferritin serum values help detect cytokine storm syndrome in patients with high fever¹⁴.

Stage II: pulmonary phase

Despite being stable for several days during Stage I, the patient can abruptly worsen and develop hypoxemic respiratory failure. Systemic inflammation markers are often moderately elevated (C-reactive protein and ferritin). An adaptive immune response occurs, which causes a reduction in viral titers. However, this also leads to higher inflammation and further tissue damage^{15,16}.

Stage III: hyperinflammation phase

Patients progressively deteriorate, and can develop disseminated intravascular coagulation and multiple organ failure syndrome. Laboratory anomalies include increased D-dimer (> 1500 associated with poor prognosis), C-reactive protein, and ferritin. Initially, patients may respond well to intubation and ventilation at stage II, but, subsequently, severe cytokine production and endothelial activation with a consequent activation of coagulation lead to clinical deterioration. The adaptive immune response becomes a storm of dysregulated immunopathological cytokines. This probably represents a form of hyperferritinemic syndrome, and whether it is a macrophage activation syndrome or a catastrophic antiphospholipid should be differentiated¹⁷. Microthrombosis and associated ischemic events are also common (including strokes). D-dimer, C-reactive protein, and ferritin levels increase according to severity and are associated with higher mortality¹⁸.

In observations at autopsies carried out at Hospital de Sacco, in Italy, on anatomopathological dissection, histologically, the lung has highly emphysematous areas with dilated blood vessels. Extensive diffuse alveolar damage is observed with the generation of hyaline membranes and considerable fibrotic exudate. The difference between ARDS and COVID-19 is that, on ventilation monitoring, its behavior is similar to that of emphysema, and there

is formation of vascular microthrombi and microhemorrhages, with small areas of diffuse alveolar damage^{19,20}.

Invasive mechanical ventilation (Fig. 2)

There is a relationship between viral pneumonia and higher predisposition to ventilator-induced self-inflicted lung injury, because mechanical ventilation subjects the lung to forces that alter its structure and elastic properties. In lungs injured by COVID-19, inflation pattern is heterogeneous and alveolar distension force can reach up to 140 cmH₂O, even with trans-pulmonary pressures of 30 cmH₂O, with the lungs being susceptible to cyclic damage by shear forces resulting from repetitive collapse and overdistension, which affects all structural and cellular components of the lung that contribute to ventilator-induced injury. Increasing alveolar pressure during inflation decreases interstitial pressure and increases transmural pressure in adjacent vessels; however, the opposite occurs in intra-alveolar vessels, because with lung volume increase, they are compressed and there is circulatory cessation, which modifies pulmonary vascular resistance and contributes to heterogeneity. Vascular permeability increase can lead to the formation of significant alveolar edema, thus compromising gas exchange. Hypoxemia should be treated in the first instance with high FiO₂, without rushing to achieve short-term goals; any intervention can be more harmful than gaining time (Fig. 2)^{21,22}.

- Tidal volume of 4-6 mL/kg of predicted weight
- Predicted weight: women, (height in cm – 152.4) × 0.91 + 45.5; men, (height in cm – 152.4) × 0.91 + 50
- Plateau pressure should be maintained below 30 cmH₂O
- Oxygenation goal of 88-92%^{23,24}.

PEEP should be limited to 8-10 cmH₂O, since higher levels will not increase lung pressure and will impact venous return with harm being greater than the expected benefit. It is recommended for PEEP levels be maintained low; tidal volume thresholds should not be limited to 6 mL/kg, in patients with significant dysoxia, volumes higher than 6 mL/kg can be considered, and respiratory rate should not exceed 20 breaths/min²⁵. The driving pressure value (plateau-PEEP pressure) should be managed at < 15 cmH₂O (patients usually do not respond to PEEP), which has been associated

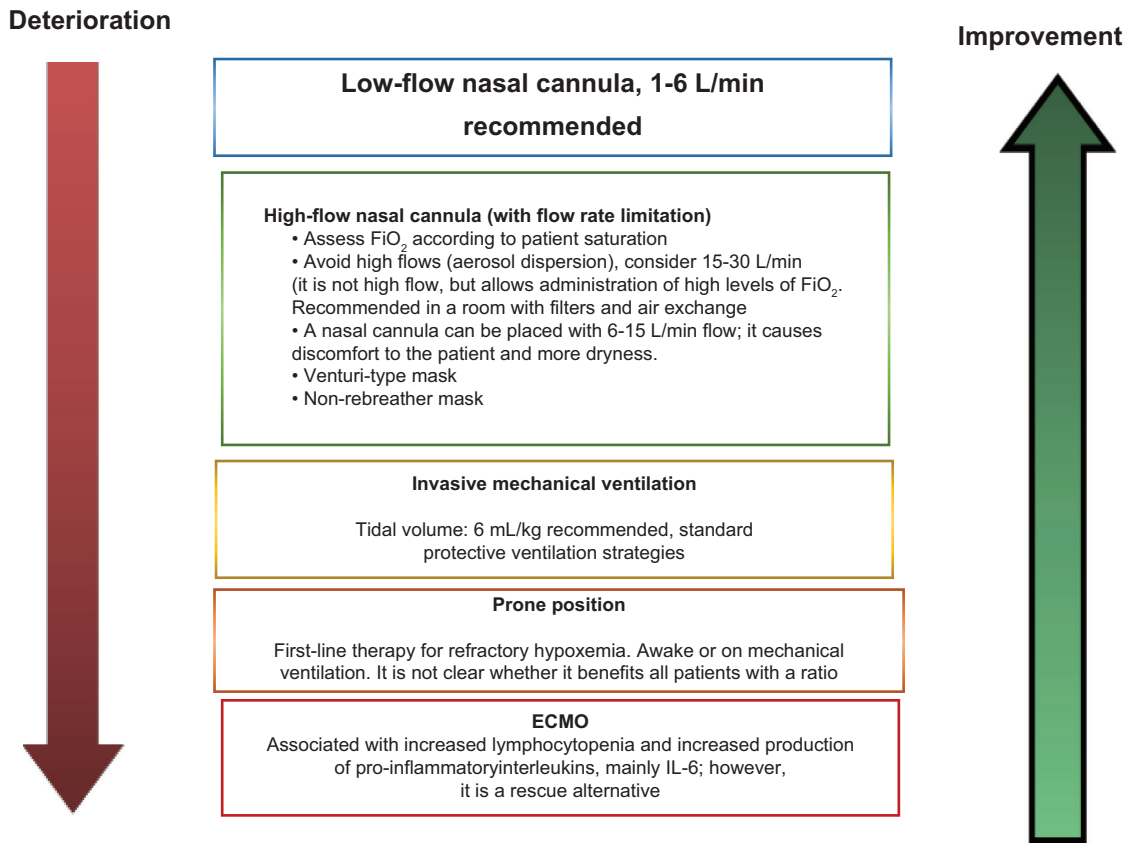


Figure 2. General diagram of ventilatory support for patients with COVID-19. Adapted from Marik.²¹

with lower mortality. A PaO_2 level > 50 mmHg suggests hypoventilation-associated atelectasis^{4,26}.

Recruitment maneuvers

Although of little value, moderate pressures of approximately 30 cmH_2O can be applied for 20-30 s; if the patient does not experience improved oxygenation or driving pressure, barotrauma, or hemodynamic instability, recruitment maneuvers should be discontinued. As for CT, it should be carried out (considering the high risk of contamination) to identify recruitable lung parenchyma. This fraction should be evaluated with two consecutive CT scans in a single session, with PEEP at levels of 5 and 45 cmH_2O , for the difference in the amount of parenchyma ventilation and recruitment potential to be measured²⁵.

Mechanical ventilation withdrawal

Mechanical ventilation withdrawal should not be rushed. According to current experience of specialized centers in China and Italy, it can be delayed for up to

2 weeks in the case of patients with slow evolution²⁷. Withdrawal should be gradual, with slow depressurization of the ventilatory system. This can be done with PEEP level gradual reduction verifying that oxygenation goals are met; early withdrawal can lead to further deterioration and worsen patient prognosis. With no doubt, mechanical ventilation is necessary as a life support for these patients, but we must limit its harms and use the least support that allows reaching the oxygenation goal²⁸.

Extracorporeal membrane oxygenation (ECMO)

Its use in patients with COVID-19 is limited. It is associated with higher levels of lymphocytopenia and higher production of pro-inflammatory interleukins, mainly interleukin 6, and patients with COVID-19 mainly show both these characteristics. In the EOLIA trial, ECMO early use did not significantly improve 60-day mortality in patients with severe ARDS²⁹; however, it is used as a rescue modality in extreme cases³⁰.

Other support measures

Nasal oxygen with high-flow cannula and non-invasive ventilation should only be used in selected patients with hypoxemic respiratory failure, and who are hemodynamically stable; they should be closely monitored in the critical care unit, and if the patient fails to respond within 1 h and acutely deteriorates, orotracheal intubation, and assistance with invasive mechanical ventilation should not be delayed^{30,31}.

In comparison with standard oxygen therapy, high-flow oxygen through nasal cannula reduces the need for intubation, but it should be considered that there is higher aerosol dispersion and it is associated with higher contamination, which is why it is essential for it to be carried out in a room with filters and air replacement. In patients infected with coronavirus, studies are limited and hardly recommendable.

Non-invasive ventilation guidelines do not recommend its use in hypoxemic respiratory failure; they suggest a high failure rate, delayed ventilatory support, higher hemodynamic instability, and patients with spontaneous or semi-assisted breathing (CPAP/non-invasive ventilation) for a long time have highly negative intrathoracic pressure, high pulmonary compliance, and deterioration even with ventilatory and hemodynamic support measures, given that ventilation-induced lung injury and bacterial superinfection are produced. In these cases, it may be more cautious to gradually increase PEEP. ScO_2 monitoring is recommended, as well as considering when SvO_2 starts to decrease, cardiac output is impaired, and PEEP levels are no longer useful for pulmonary recruitment; this is why right cardiac function should be evaluated while PEEP increases are managed³².

Use of dual ventilator

As an emergency measure and in disaster situations, with oversaturation of hospitals, but it are not advisable to use it due to several conditions. If all patients connected to a single ventilator have the same initial clinical characteristics, they might deteriorate and recover at different rates, and gas distribution to each patient would be uneven; therefore, in the scenario of the most severely ill patient, he/she would get the lowest tidal volume and the patient who improved would get the highest tidal volume. Pulmonary mechanics would be difficult to measure, thus increasing measurement errors. PEEP³³, which is critically important in these patients, would be

unmanageable; volumes would go to the most distensible lung segments. In case of cardiac arrest it would be necessary to stop all patients' ventilation. At the moment of ventilation switch, viral aerosol dispersion would expose health workers and other patients. Therefore, it is not a viable option, according to recommendations of the Association for Respiratory Care, American Society of Critical Care Medicine and American College of Chest Physicians³⁴.

Prone decubitus position

It should be considered as a rescue maneuver to facilitate pulmonary blood flow redistribution, rather than for opening collapsed areas. When, despite administering high oxygen concentrations, $\text{PaO}_2/\text{FiO}_2$ is < 150 , it is necessary to put the patient in the prone position as soon as possible and ventilate in this position for at least 16 h. Fluid balances should be negative to avoid excess fluid in the lung³⁵. A significant increase in lung weight can cause dorsal lung regions compression at 50% of lung height. Due to weight-related compressive forces when the patient becomes susceptible, the lung collapses at 50% of its height (ventral region), while regions above 50% of height (dorsal regions) will reopen. The effect on gas exchange will depend on the amount of mass present in the top 50% and bottom 50%.

Prone position

At this moment, there is scarce information on the ideal way to manage patients with ARDS associated with SARS-CoV, and on the specific role of prone positioning (PP) in those patients. However, early Chinese reports describe respiratory mechanics and lung recruitment capacity in a small cohort of patients with SARS-CoV-2-associated ARDS on mechanical ventilation. The main findings were that none of the included patients had complete airway closure or auto-PEEP, and conduction pressure was high (on average, 22 cmH_2O despite using 6 mL/kg of tidal volume). They used an index to directly quantify lung recruitment potential, called recruitment-inflation ratio (R/I ratio), which estimates how much increase in PEEP-induced end-expiratory lung volume is distributed between the recruited lung (recruitment) and "baby lung" inflation and/or hyperinflation when higher PEEP is applied. Most included patients were poorly recruitable with high PEEP, but recruitment capacity appeared to

change when body position was alternated. In those patients in the prone position, $\text{PaO}_2/\text{FiO}_2$ went from 120 ± 61 mmHg in supine to 182 ± 140 mmHg in prone position ($p = 0.065$ by Student's *t*-test)³⁶. Sun et al.³⁷ also described the use of PP in awake patients as an early critical care treatment in high-risk patients (heart rate > 120 or respiratory rate > 30 , or $\text{SpO}_2 < 93\%$ with room air) with high suspicion or confirmed SARS-CoV-2-associated pneumonia. Awake PP, together with fluid restriction and use of high-flow nasal cannula oxygen therapy or non-invasive mechanical ventilation to preserve PEEP, allowed them to maintain invasive mechanical ventilation rate below 1%, which was significantly low, especially in this specific population. There is still a lack of information on the best strategy and prone position implementation timing in awake patients, as well as ideal duration and the best way to assess success or failure for avoiding delays in invasive mechanical ventilation implementation³⁷.

Awake prone position

The benefits of PP in mechanically ventilated patients are well established; however, some authors have used PP in awake patients on non-invasive ventilation with promising results. Scaravilli et al.³⁸ addressed the benefits of awake PP in 15 patients at high risk of acquiring ventilator-associated pneumonia if invasive mechanical ventilation was established. Patients were managed with different devices and PEEP and FiO_2 levels. Pronation cycles median duration was 3 h (2-4), and the longest procedure lasted 8 h. An oxygenation improvement was observed in all patients, but they returned to baseline values 6 h after resupination, with several pronation cycles being necessary. Hemodynamic parameters and respiratory rate were not affected during PP. Survival rate was 80% and the need for invasive mechanical ventilation was 13%³⁹.

Gattinoni et al.⁴⁰ have issued a preliminary observation about the lung injury produced by this virus, in which two clinical scenarios stand out in their experience during the epidemic in Lombardy, Italy. In patients with high pulmonary compliance and isolated viral pneumonia, the main finding is the presence of hypoxic vasoconstriction, which explains severe hypoxemia. In these patients, the biggest problem is related to perfusion; the lungs are dilated and PEEP increase does not confer benefits. High PEEP and PP do not lead to collapsed areas recruitment, but may be beneficial for optimizing lung perfusion. CT patterns in this clinical scenario show that there are no

potentially recruitable areas in a significant proportion, and that there is presence of shunts larger than 50%.

Hemodynamic management

Patients with COVID-19 can develop ARDS and evolve into four critical moments at the hemodynamic level. In case of hypotension, a vasopressor challenge is recommended, based on a physiological principle:

- The first one is hypoxic pulmonary vasoconstriction, which can cause pulmonary hypertension and, in turn, right ventricular dysfunction. Both these situations can make for the patient to be highly intolerant to intravascular volume loads, which can be easily identified by ultrasound when a right ventricle of the same size or larger than the left ventricle is found, together with a dilated inferior vena cava without collapse⁴¹.
- The second type of hemodynamic crisis in these patients is when they are in a so-called “cytokine storm”⁴², which is characterized by high levels of interleukin 6, C-reactive protein > 100 mg/dL, ferritin > 600 μg and $> 38^\circ\text{C}$ fever events. This can cause a state of sepsis, vasodilation, or myocardial depression, including coronary arteries atheromatous plaque rupture, leading to acute myocardial infarction.
- The third one are crises related to thrombotic events, such as pulmonary thromboembolism, which has been associated with high D-dimer levels at admission of these patients^{43,44}.
- The fourth and most serious hemodynamic crisis event of these patients is the occurrence of cardiogenic shock caused by fulminant viral myocarditis⁴⁵.

Therefore, not performing any static or dynamic volume response test is recommended for two reasons. In the first place, patients with some degree of pulmonary hypertension are hardly volume-responders. In the second place, and more importantly, all dynamic or static volume-response tests lack physiological validity⁴⁶ in pulmonary hypertension scenarios. In fact, pulse pressure variability can be increased as a sign of right ventricular dysfunction rather than a sign of response to volume changes⁴⁷.

When the patient is not undergoing a cytokine storm event, the goal is to achieve negative balances. The fluids and catheters treatment trial (FACTT) volume restriction simplified protocol and use of a diuretic are recommended. The FACTT simplified protocol⁴⁸ consists of:

- Discontinuing maintenance fluids
- Dilution of medications on the least possible compatible amount
- Not limiting enteral nutrition requirements
- Use of vasopressors in case of mean blood pressure < 60 mmHg.

In the event of serum creatinine ≥ 3 mg/dL during the protocol, the need for hemodialysis should be evaluated.

Using the vasopressor challenge prior to the volume challenge is recommended in order to reverse hypotensive events.

Dynamic or static testing is not recommended for assessing fluid response.

We recommend the FACTT simplified protocol for volume management in COVID-19 patients who are not undergoing a cytokine storm.

COVID-19 patients undergoing a cytokine storm crisis may be classified within ARDS inflammatory phenotype⁴⁹. This group has been reported not to benefit from volume restriction. Based on fever duration, volume deficit is estimated⁵⁰ and a Ringer lactate solution bolus of 250 mL is initiated, at the same time as norepinephrine. Empirically, we recommend a volume challenge only as long as central venous pressure is < 8 mmHg.

Hemodynamic recommendations

Norepinephrine⁵¹ can redistribute pulmonary flow, which would decrease pulmonary hypertension, which is one of the causes of hypotension in these patients, but high doses of norepinephrine can exacerbate pulmonary hypertension, which is why we recommend, before using high doses of norepinephrine, to add vasopressin⁵², which has lower repercussions on pulmonary blood pressure.

On the other hand, from the hemodynamic point of view we recommend the use of induction drugs with minimal hemodynamic effects, which can be consulted in other papers on the subject.

It is important, to the extent possible, to have an echocardiographic evaluation. Hemodynamic management of these patients is considered to be appropriate if the degree of pulmonary hypertension is reduced or if right ventricle size decreases in response to each intervention. The presence of cor pulmonale (pulmonary hypertension) can be suspected using a scale designed by the Vieillard-Baron working group^{27,53}. The presence of more than 2 points on the cor pulmonale scale (Table 2) should warn about some degree of pulmonary hypertension, and this is the group with the

Table 2. Cor pulmonale prognostic scale¹⁵

Parameter	Points
Pneumonia as ARDS cause	1
Plateau – PEEP > 18 cmH ₂ O	1
PaO ₂ /FiO ₂ < 150	1
PaCO ₂ > 48 mmHg	1
Total	0-4

highest mortality in patients with ARDS. In these cases, a PaCO₂ balance < 48 mmHg should be maintained together with a plateau pressure < 27 cmH₂O and a plateau-PEEP ratio < 18 cmH₂O. This should be considered as part of the hemodynamic strategy for the right ventricle protection²⁷.

Suspected hypoperfusion

Clinical criteria:

- Mottling score > 2⁵⁴
- Capillary filling⁵⁵ > 4 s on knees and > 2.5 s on index finger
- < 36°C hypothermia events
- Shock index (heart rate/systolic blood pressure > 1)
- Heart rate < 60 + systolic blood pressure < 90 mmHg⁵⁶.

Blood gases low-output criteria:

- SvcO₂ < 65%
- Venous-to-arterial CO₂ tension difference⁵⁷ = CO₂ tension in venous blood (PvCO₂) – CO₂ tension in arterial blood (PaCO₂) > 6 mmHg.

When there is one clinical criterion plus one blood gas criterion, or three clinical criteria, or both blood gases criteria, the probability of hypoperfusion is very high. Using the algorithm as an approaching guide is recommended. In case echocardiographic or minimally invasive monitoring is not sufficient, and especially in cases where the use of pulmonary artery inodilators is considered, we suggest monitoring by pulmonary artery catheter.

Hemodynamic management recommendations

- In case of cytokine storm events, we recommend to discontinue fluid restriction strategies, but to return to them once the event is controlled

- The use of norepinephrine and vasopressin before high doses of norepinephrine should be evaluated in the management of hypotension associated with hypoxic pulmonary vasoconstriction crises
- Inotropic challenge if hemodynamic deterioration continues with $\text{SvCO}_2 < 60\%$ or vaCO_2 tension difference > 6 mmHg, as well as follow-up by of SvCO_2 and vaCO_2 tension difference parameters to evaluate the therapeutic response
- We recommend, in cases persisting with hemodynamic deterioration attributable to pulmonary hypertension, to evaluate pulmonary vasodilation therapies such as nitric oxide, and iloprost, and to consider the use of pulmonary artery pressure invasive advanced monitoring.

Mechanical ventilation ultrasonographic monitoring

Pulmonary ultrasound is a dynamic, low-cost, non-invasive, and patient-bedside tool that allows performed interventions to be evaluated, whether ventilatory or even pharmacological strategies, but it requires complementation with other monitoring modalities, among which right ventricular function assessment is necessarily included, intentionally seeking data consistent with over-distention.

Mechanical ventilation bedside monitoring with ultrasound confers several advantages:

- It is a non-invasive strategy
- It evaluates the state of the pulmonary parenchyma and the response to therapeutic interventions, both ventilatory strategies⁵⁸ and the evolutionary tendency with medication administration
- It allows to evaluate heart function⁵⁹
- It facilitates potentially complicable patients categorization in a timely manner⁶⁰.

Lung ultrasonography-guided PEEP titration

Mechanical ventilation with low tidal volumes and high PEEP is a standard strategy in patients with ARDS for improving oxygenation⁶¹. However, there are cases in which this objective is not accomplished, and alveolar recruitment maneuvers are required for appropriate opening, which should be closely monitored given that they can lead to hemodynamic instability⁶².

Table 3. Lung ultrasound ventilation index

Reaeration quantification			Reaeration loss quantification		
+ 1 point	+ 3 points	+ 5 points	– 5 points	– 3 points	– 1 point
B1 → N	B2 → N	C → N	N → C	N → B2	N → B1
B2 → B1	C → B1			B1 → C	B1 → B2
C → B2					B2 → C

Mechanical ventilation echocardiographic monitoring.

N: normal lung ultrasound pattern; B1: multiple B-lines with a 7-mm gap between them

(moderate aeration loss); B2: multiple coalescing B-lines (severe aeration loss);

C: pulmonary consolidation.

Within these strategies, the use of the ventilation index has been suggested in order to determine the best PEEP at different lung segments, with each hemithorax being divided into four segments and four patterns being identified:

Once lung patterns at the different segments have been identified, a numerical value can be assigned by means of the ventilation index by aeration loss rate (Table 3)⁶³.

In patients with ARDS on mechanical ventilation, PEEP increases above 10 cmH₂O have been observed to be associated with a progressive decrease in cardiac output and mean blood pressure, which has been associated with right ventricular overload and interventricular septum displacement. However, this analysis and other similar studies were carried out when clinical importance of tidal volume reduction and its effect on alveolar opening was not yet known, which favored ventilation with tidal volumes higher than 10 mL/kg of ideal weight, which in patients with ARDS with no doubt favors alveolar over-distension and ventilation-induced lung injury. Based on the acquired knowledge, elevated PEEP is known to generate right ventricle afterload increase, right ventricular dilation, interventricular septum displacement to the left and right ventricular ejection volume decrease. Right and left ventricle pressure invasive measurement shows that this effect is related to a reversed pressure gradient between both ventricles. Changes in right ventricular function related to different levels of PEEP could reflect the balance between recruitment and over-distension, and thus, if PEEP increase induces alveolar opening there is a decrease in transpulmonary pressure due to pulmonary compliance increase and there is no right ventricular involvement. However, if PEEP increase is excessive, there is alveolar over-distension and there is an increase in

trans-pulmonary pressure with an increase in right ventricular afterload⁶⁴.

Right ventricle assessment

The role of critical echocardiography is not only one of diagnostic surveillance, but also of therapeutic response evaluation.

Given these possibilities, monitoring of mechanical ventilation in patients with COVID-19 should be taken care of together with the cardiopulmonary unit, since 25% of patients with COVID-19-associated ARDS exhibit right ventricular acute failure, and more than 60% of patients with ARDS show hemodynamic failure on hemodynamic monitoring by echocardiography and acute right ventricular failure. Within the parameters of critical echocardiography, with regard to acute right ventricular failure occurrence, we considered the changes in basal right ventricle/left ventricle ratio, pulmonary vascular resistance, and ventricular interdependence to decide the type of right ventricular support with inotropic drugs, vasopressors or volume according to hemodynamic echocardiographic monitoring findings⁶⁵.

Pulmonary systolic pressure in ARDS and right ventricular acute failure

We can talk about the severity of pulmonary hypertension generated in ARDS in relation to pulmonary artery systolic pressure, as determined by inferior vena cava compliance. It is important to remember that heart-lung synchrony during positive pressure mechanical ventilation or other methods, such as airway pressure release ventilation, alters venous return, which is why sensitivity of right atrial pressure calculation through the vena cava is lost. In 92% of patients with ARDS, there is some degree of pulmonary hypertension⁶⁵. The value of pulmonary systolic pressure has no direct correlation with the development of the right ventricular acute failure.

When right ventricular acute failure is evaluated, the best prognostic and diagnostic marker of right ventricular systolic function, in terms of survival, is tricuspid annular plane systolic excursion. Other parameters, such as the shortening fraction, did not properly correlate. Patients with ARDS due to afterload increase start to develop right ventricular volumetric and vasopressor overload, which entails a systolic displacement from the interventricular septum to the left cavities, whereby interventricular contractile contribution to

right cardiac output is lost, with this displacement being one of the most important manifestations for driving the patient to acute right heart failure.

Septum displacement evaluation in two-dimensional mode can be difficult when it is not too marked, which is why the use of M-mode facilitates its diagnosis. In addition, this displacement causes right cavities' contraction dyssynchrony, since right ventricular lateral wall contraction is late with regard to the septum. It is through this mechanism that low right cardiac output occurs. Detection of systolic septal displacement to the left cavities causes ventricular interdependence; it is an echocardiographic finding in patients with ARDS that substantiates right ventricular acute failure diagnosis⁶⁶.

Right cardiac output in patients with ARDS and acute right heart failure

Anterograde volume through the pulmonary valve has a strict relationship with the mechanical ventilation cycle time it is found in. The anterograde volume that helps us calculate right cardiac output will be lower during the inspiratory phase in positive mechanical ventilation and will be higher during the expiratory cycle, which is why right cardiac output calculation determined by right ventricular outflow tract time/velocity index should preferably be measured at expiratory phase to avoid erroneous calculations⁵³.

Conclusions

During emerging crises, working without statistics is possible while they are being generated, but never without physiology and unity (protocols). The physiological explanation herein presented is as accurate as possible. The protocol is an induction derived from said physiology while awaiting to soon have statistical data that tell us if what we do is useful or not. Following well-structured protocols can help us quickly realize where we are wrong, as well as the direction and magnitude of our errors. In conclusion, what the reader has in his/her hands are conjectures in search of refutations. At the time, this article is being written, the only correct answer is "we don't know yet".

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Conflicts of interest

The authors declare that they have no conflicts of interest relevant to this manuscript.

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

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