CURRENT OPINION

Advanced respiratory monitoring in mechanically ventilated patients with coronavirus disease 2019-associated acute respiratory distress syndrome

Peter Somhorst, Diederik Gommers, and Henrik Endeman

Purpose of review
To summarize the current knowledge about the application of advanced monitoring techniques in coronavirus disease 2019 (COVID-19).

Recent findings
Due to the heterogeneity between patients, management of COVID-19 requires daily monitoring of and/or aeration and inspiratory effort. Electrical impedance tomography can be used to optimize positive end-expiratory pressure, monitor the response to changes in treatment or body position and assess pulmonary perfusion and ventilation/perfusion matching. Lung ultrasound is more readily available and can be used to measure and monitor recruitment, provide an indication of diaphragm function and pulmonary perfusion disturbances. Esophageal pressure measurements enable the calculation of the transpulmonary pressure and inspiratory effort in order to prevent excessive stress on the lung. While esophageal pressure measurements are the golden standard in determining inspiratory effort, alternatives like $P_{O.1}$, negative pressure swing during a single airway occlusion and change in central venous pressure are more readily available and capable of diagnosing extreme inspiratory efforts.

Summary
Although there is little data on the effectiveness of advanced monitoring techniques in COVID-19, regular monitoring should be a central part of the management of COVID-19-related acute respiratory distress syndrome (C-ARDS).

Keywords
acute respiratory distress syndrome, coronavirus disease 2019, electrical impedance tomography, ICU, ultrasound

INTRODUCTION

Since coronavirus disease 2019 (COVID-19) was first described, 200 million confirmed cases have been reported worldwide [1] with an estimated 1.2 million people requiring invasive mechanical ventilation [2]. Infection with SARS-CoV-2 results in diffuse alveolar damage, pneumocyte hyperplasia and interstitial as well as alveolar edema, and has a high degree of involvement of the vascular system with endothelial injury and coagulopathy ultimately resulting in thrombotic complications of especially the pulmonary circulation [3▪]. The resulting bilateral lung infiltrates and impaired oxygenation fit the Berlin definition of acute respiratory distress syndrome (ARDS) [4].

An early large report on COVID-19 described patients with severe pneumonia similar to ARDS [5]. Gattinoni *et al.* [6] suggested COVID-19 leads to an atypical form of ARDS with distinguishable subtypes.

The 'H-type' was described as having high respiratory system compliance, high lung volumes and minimal recruitability. Hypoxemia is a result of ventilation/ perfusion mismatch caused by (micro-)thrombosis. Respiratory management should consist of oxygen therapy or mechanical ventilation with low positive end-expiratory pressure (PEEP) while preventing excessive inspiratory effort. The 'L-type' was described as having low respiratory system compliance, low lung volume and high recruitability akin to a 'typical' ARDS [7,8,9▪]. Ventilator-induced lung injury and patient

Department of Intensive Care, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence to Peter Somhorst, MSc, Erasmus Medical Center, Rotterdam, The Netherlands. Tel: +31 6 43990213; e-mail: p.somhorst@erasmusmc.nl

self-inflicted lung injury (P-SILI) are likely contributors to the extensive lung injury and edema. 'L-type' patients benefit from standard treatment for ARDS with low tidal volume, relatively high PEEP and prone positioning. However, the existence of two distinct phenotypes has been challenged by authors [10–12]. Instead, COVID-19-related ARDS (C-ARDS) is characterized by high heterogeneity between patients.

We now consider C-ARDS to have a continuous progression from the 'H-type' – characterized by local inflammation, (micro-)thrombosis, relatively normal lung mechanics and hypoxemia resulting from of ventilation/perfusion mismatch – to the 'L-type' –

characterized by hyperinflammation, severe lung injury, pulmonary edema and reduced lung compliance [13], as illustrated in Fig. 1.

In a recent review on mechanical ventilation in COVID-19 patients, Grasselli *et al.* [3▪] concluded that based in the similarities and due to lack of evidence supporting ventilation settings specific for C-ARDS, it should be managed using 'standard' lung protective ventilation – limitation of the tidal volume to 6 ml/kg and the plateau pressure to 30 cmH_2O. However, they emphasize the heterogeneity of respiratory mechanics, severity of hypoxemia and recruitability of the lung.

Treatment of 'H-type' patients has a major pitfall. PEEP/FiO_2 tables have been a central part of ventilation strategies for decades. When oxygenation is impaired, PEEP and FiO_2 are alternately increased to both improve oxygen tension in the alveoli and recruit collapsed lung tissue. When oxygenation is impaired this one-size-fits-all approach always results in high PEEP, increasing the risk of hemodynamic instability and lung injury [15]. With the high degree of involvement of the vascular anomalies, 'H-type' patients do not benefit from more PEEP but only from higher FiO_2.

Due to the heterogeneity of C-ARDS, monitoring the aeration and perfusion as well as the
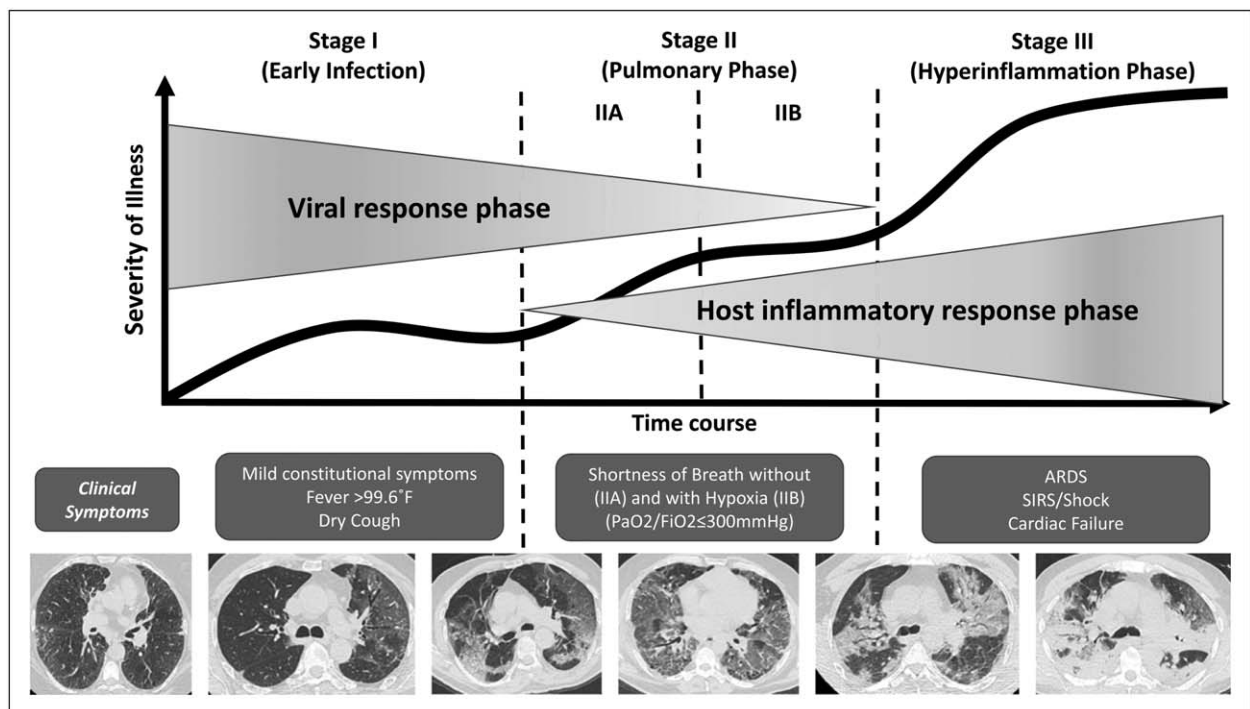
FIGURE 1. Classification of coronavirus disease 2019 and radiological imaging results. Three escalating phases are identified. Stage I is the prehospitalization phase. Stage IIB corresponds to the 'H-type' [6], evolving to stage III corresponding to the 'L-type' due to hyperinflammation. The computed tomography images show increasing disease severity showing minor local opacities on the left ('H-type'), and evolving into major morphological changes ('L-type'). Reproduced with permission [13,14].

involved pressures and strain plays a crucial role in the respiratory management. The aim of this pragmatic review is to describe the different modalities of advanced respiratory monitoring in C-ARDS and describe its usefulness at the bedside. We describe the use of electrical impedance tomography (EIT) and lung ultrasound (LUS) for monitoring both aeration and perfusion, the use of esophageal pressure measurements to measure the stress and the lung tissue and more accessible alternatives for assessing the inspiratory effort of patients.

VOLUMES AND AERATION

Diagnosing, monitoring and resolving atelectasis while preventing overdistention is one of the main challenges in the mechanical ventilation. Computed tomography (CT) is the golden standard for the assessment of aeration and potential for recruitment in ARDS [16,17], but lacks the practicality of bedside monitoring. Especially when resources are constrained due to an epidemic, bedside monitoring might serve as a viable or even essential alternative. In this review we therefore focus on bedside modalities.

Assessing aeration is especially important in the obese patient. The increased weight of the abdomen and chest wall puts pressure on the diaphragm and thoracic cage increasing the pleural pressure, decreasing the functional residual capacity and increasing the risk of atelectasis [18]. Obesity is a major risk factor for hospitalization, invasive mechanical ventilation, and death in COVID-19 patients [19]. We discuss two techniques for monitoring aeration of the lung.

Electrical impedance tomography

EIT is a noninvasive, radiation-free continuous monitoring technique that measures the distribution of air in the lungs during spontaneous breathing or controlled mechanical ventilation [20]. In patients with ARDS, EIT has been used to assess recruitability, monitor relative collapse and overdistention and set PEEP [21,22].

In sedated patients, a decremental PEEP trial is used to find the optimal PEEP level. First, PEEP is increased to a high level – generally 24 cmH$_2$O – for several minutes. Then PEEP is reduced in steps of 2–4 cmH$_2$O every 30–120 s until oxygen saturation falls below a preset value or a predetermined PEEP level has been reached. Optimal PEEP value is based on minimizing the relative collapse and overdistention. There is no consensus as to what the best approach is to set PEEP based on a decremental PEEP trial using EIT in patients with ARDS, let alone C-ARDS. We

hope the RECRUIT study will aid in reaching consensus [23]. Our own group [24] as well as Sella et al. [25] and Perier et al. [26], all in separate studies of 15–17 patients, showed a similar response to PEEP-trials in C-ARDS compared with patients with ARDS [22]. We found that optimal PEEP was correlated to the BMI of the patient [24]. This again underlines the importance of personalizing mechanical ventilation to the individual patient.

The ratio of recruitment to inflation (R/I ratio) is a measure of the potential for recruitment [27]. During a single large PEEP step, the recruited volume divided by the change in PEEP gives compliance of the recruited lung (C_{RECR}). The R/I ratio is defined as the ratio of C_{RECR} and the respiratory system compliance at low PEEP and indicates how much a patient might benefit from higher PEEP. In a prospective study in ten C-ARDS patients, Mauri et al. [28] estimated recruited volume with EIT and found that the potential for recruitment was highly variable, underlining the heterogeneous population of patients with C-ARDS. This simple method using two PEEP levels may give an indication of recruitability and changing lung mechanics over time, but does not provide a way to determine optimal PEEP.

Left/right asymmetry is not uncommon in patients with C-ARDS [29] and can require different positioning of the patient. A good lung down strategy may help increase oxygenation in the general population [30] but solid evidence of its effectiveness lacks. Mlček et al. [31▪] found left/right asymmetry in 15% of patients. They performed targeted lateral positioning based on EIT data in five patients, resulting in less overdistention and collapse compared with the supine position with similar levels of PEEP. In our own experience, targeted positioning in combination with a decremental PEEP trial increases ventilation homogeneity in C-ARDS with asymmetric lung injury.

The absence of regional tidal impedance changes, so-called silent spaces (different manufacturers use different cutoffs for nonventilated regions, and terminology differs between manufacturers), indicates lung regions with no or minimal ventilation, either due to collapse of lung tissue, or overdistention. Collapse of lung tissue is generally found in dependent lung regions – dorsal areas in supine position, ventral areas in prone position – while overdistended lung tissue is generally found in nondependent lung regions. Taenaka et al. [32] showed low PEEP increased silent spaces in the dependent areas (collapse) in two cases while high PEEP causes silent spaces in nondependent areas (overdistention) in one case. Prone positioning reduced the total silent space volume. Shono et al. [33] showed a typical case

where dependent lung tissue not ventilated at low PEEP is recruited using high PEEP.

EIT can also be used to monitor spontaneously breathing patients. Brunin *et al.* [34] described a spontaneously breathing obese patient with C-ARDS, low oxygenation and high respiratory rate with a high risk of intubation. In prone position EIT, showed a large increase in ventilation, mainly in the dorsal regions, compared with the supine position. Zhao *et al.* [35] reported a case of a patient with C-ARDS with a high flow nasal cannula at several flow rates, where they monitored change in end-expiratory lung impedance (ΔEELI). The highest ΔEELI corresponded to the lowest respiratory rate and the highest comfort level indicated by the patient. EIT has a clear role to play in optimizing the pre and postinvasive ventilation strategies, but studies into the best approach lack as of yet.

Summarizing, EIT can play a central role in the optimization of mechanical ventilation in the individual patients. In sedated patients PEEP should be set after a decremental PEEP trial such that relative collapse and overdistention are minimized. This is especially important in the acute phase, as early recruitment is more effective [36]. If EIT shows major ventilation impairment of dependent regions, prone positioning should be considered. In patients who have ventilation asymmetry, EIT can be used for targeted lateral positioning. EIT can be used in patients with intact respiratory drive to assess ventilation distribution at different levels of respiratory support or in different body positions.

Lung ultrasound

LUS is a relatively cheap and easy bedside technique to image pulmonary morphology. When using simple clear algorithms, for example the BLUE protocol [37], it is easy to learn and use. As so, it is available in many settings, including low-income environments. The images obtained by LUS are anatomical or are artifacts which correlate with findings by CT imaging of the thorax.

The use of LUS to adjust ventilatory settings is limited. To define optimal PEEP or guide recruitment by LUS there are different techniques: calculating the LUS score counting B-lines (an artifact), the change in lung sliding (anatomical) or looking for atelectasis at the posterior lateral lung point (anatomical). The first was tested in 24 invasively ventilated C-ARDS patients [38]. In high recruiters there was a significant decrease in LUS score especially in the lateral and posterior lung regions. These results were combined with the recruitment-to-inflation ratio and pulmonary compliance, so change in LUS alone can't define recruitability.

A more conventional way of using LUS is to identify the cause of respiratory deterioration. Loss of pleural sliding can indicate a pneumothorax, though it should be kept in mind that this can also be caused by hyperinflation or collapse. The latter is described by Lock and Nix [39] in which a sudden drop in oxygenation in combination of loss of pleural sliding was caused by partial collapse of the lung. Furthermore, there are some cases in which the indication of recruitment was made by finding dorso-basal atelectasis [40,41].

In conclusion, next to its use as diagnostic and prognostic tool, in our opinion LUS could be used to measure recruitability or monitor recruitment among other parameters and should be part of the diagnostic toolset in monitoring pulmonary function.

TRANSPULMONARY PRESSURE

A plateau pressure less than $30\,cmH_2O$ and a driving pressure less than $15\,cmH_2O$ are often used as upper bounds when setting the ventilator. While the plateau pressure and driving pressure indicate the total and dynamic stress put on the entire respiratory system, the stress that is put on the lung parenchyma depends on the relative compliance of the lung and chest wall [42]. Transpulmonary pressure measurements enables the distinction between the compliance of the lung and the chest wall and helps assess the total stress put on the lung parenchyma [43]. Maintaining a transpulmonary pressure between $0\,cmH_2O$ at end-expiration and $25\,cmH_2O$ at end-inspiration might prevent dorsal collapse of lung tissue [44] while preventing excessive strain [42,45] during mechanical ventilation. The same personalized approach should be used for C-ARDS as for ARDS: setting PEEP such that the end-expiratory transpulmonary pressure is positive, and limit tidal volume to keep the transpulmonary driving pressure as low as $10–12\,cmH_2O$ in injured lungs [46].

In a cohort of 15 C-ARDS patients, Mezidi *et al.* [47] showed that obese patients have a lower transpulmonary pressure at the same PEEP level compared with nonobese patients and require higher PEEP levels to maintain a positive end-expiratory transpulmonary pressure. Titrating PEEP based on a positive end-expiratory transpulmonary pressure or the best respiratory system compliance leads to a higher PEEP compared with PEEP/FiO_2 tables resulting in better oxygenation, improved lung mechanics and less collapse and overdistention [48].

If available, transpulmonary pressure measurements are an essential tool in the management of mechanical ventilation. It facilitates a careful approach of titrating PEEP to reach positive end-

expiratory transpulmonary pressure while maintaining a transpulmonary pressure below 25 cmH$_2$O. When treating obese patients, it is essential to consider the increased pleural pressure and change PEEP accordingly.

INSPIRATORY EFFORT

The respiratory muscles play a crucial role in the development and course of respiratory failure. Adequate inspiratory effort is essential in the recovery of patients when weaning from respiratory support, but can be harmful for the injured lung. Patients with acute hypoxemic respiratory failure are at risk of developing P-SILI caused by extreme inspiratory efforts resulting in excessive stress aggravating existing lung injury [49–51]. Gattinoni *et al.* [52▪] and Battaglini *et al.* [53] emphasize the importance of the respiratory drive and the risk of P-SILI in the development of C-ARDS. In a computational modeling study, Weaver *et al.* [54] showed injurious stress and strain can be present in patients spontaneously breathing COVID-19 patients with tidal volumes and respiratory rates often encountered in hospitalized patients. This corresponds with our experience that a relatively large proportion on COVID-19 patients on assist mechanical ventilation have high respiratory drive. Although no studies have demonstrated that P-SILI can be prevented with proper ventilation strategies, prevention of spontaneous breathing efforts in the acute phase of ARDS can lead to improved survival [55].

Identifying and preventing excessive stress due to spontaneous breathing efforts has been a major subject of research, resulting in many ways to quantify inspiratory effort. While some are easy to assess and featured in many mechanical ventilators, others require expertise and dedicated hardware.

Esophageal pressure

Esophageal pressure measurements are the golden standard when it comes to assessing inspiratory effort [43,56]. The pressure generated by the respiratory muscles is calculated as the sum of the esophageal pressure swing and the pressure required to expand the chest wall (measured during passive mechanical ventilation). We agree with Mauri *et al.* [46] that during assist mechanical ventilation peak transpulmonary pressure (P_L) should remain below 20–25 cmH$_2$O and the pressure generated by the respiratory muscles should be limited to 10 cmH$_2$O.

$P_{0.1}$

Pressure produced during the first 0.1 s of an inspiratory attempt against an occluded airway ($P_{0.1}$) is a widely used index of respiratory drive and effort. In ARDS patients $P_{0.1}$ more than 3.5 cmH$_2$O during assist mechanical ventilation is fairly accurate in detecting high inspiratory effort, while a $P_{0.1}$ of 1 cmH$_2$O is very accurate in predicting low inspiratory effort [57]. In a study of 28 ventilated C-ARDS patients, a high $P_{0.1}$ (≥ 4 cmH$_2$O) was associated with relapse during the weaning phase [58]. Due to the relative ease of use – if supported by the ventilator – $P_{0.1}$ is an ideal tool for detecting excessive respiratory drive if other methods are not available.

Negative pressure swing during a single airway occlusion

Negative pressure swing during a single airway occlusion (ΔP_{occ}) is a simple measurement that can be performed using different mechanical ventilators and can be used to estimate the pressure produced by the inspiratory muscles and transpulmonary pressure swing [59,60]. Roesthuis *et al.* [61] showed in a study with 13 COVID-19 patients that although agreement between the measured and estimated muscle pressure and transpulmonary pressure swing is poor, the estimated transpulmonary pressure swing has high accuracy in predicting excessive inspiratory effort. If featured on the mechanical ventilator ΔP_{occ} can accurately predict excessive inspiratory effort in an easy to perform maneuver.

Change in central venous pressure

Due to the low elastance of the vena cava, inspiratory efforts can be detected as change in central venous pressure (ΔCVP). Although this has been known for several decades [62], it seems ΔCVP has not been widely utilized. In a study in 14 COVID-19 patients on assist mechanical ventilation, Lassola *et al.* [63] showed that a ΔCVP at least 9 cmH$_2$O was fairly accurate in detecting high inspiratory effort. Because central venous catheters are widely used in ICU patients, the ΔCVP might give an easy indication of inspiratory effort if implemented in blood pressure monitors.

Ultrasound

Changes in the thickness of inspiratory muscles as measured using ultrasound reflect inspiratory effort. Lassola *et al.* [63], in a study of 14 patients with COVID-19, compared the diaphragm thickening ratio with esophageal pressures at different levels of support. There was a clear change in thickening ratio at the different levels of support, but correlation with esophageal pressure swing (ΔP_{es}) was modest

($R = 0.399$) and less than, for example, ΔCVP. The authors do not describe a correlation between inspiratory effort measured by ultrasound and outcome. Additional studies are needed to clarify the usefulness of ultrasound of the diaphragm as a measure of inspiratory effort in patients with C-ARDS.

Summarizing, monitoring inspiratory effort should be an integral part of daily care for COVID-19 patients on invasive mechanical ventilation, noninvasive support or oxygen therapy. While the golden standard – esophageal pressure measurement – requires dedicated hardware, several technologies that are more readily available and easy to implement can accurately detect excessive inspiratory effort. If available on the mechanical ventilator, daily monitoring of the $P_{0.1}$ or ΔP_{occ} should guide management of sedation and respiratory support. Large ΔCVP values should be used as a proxy if no other methods are available.

PULMONARY PERFUSION

Perfusion is a key factor in gas exchange in the lungs. The high involvement of vascular anomalies in patients with COVID-19 makes it essential to consider perfusion when choosing ventilation strategies, especially in the early phases of C-ARDS when ventilation/perfusion mismatch is the main contributor to oxygen impairment. CT angiography is the golden standard for diagnosing pulmonary embolisms and (micro-)thrombosis, but lacks the practicality of bedside monitoring and is of limited value for assessing ventilation/perfusion mismatch.

Electrical impedance tomography

The perfusion of the thorax can be assessed using EIT after injection of a bolus of saline fluid into a central venous catheter [64]. As the saline travels from the heart through the lungs, the increased electrical conductivity of blood is measured. As perfusion and ventilation are measured in the same manner, they can be overlaid to determine ventilation/perfusion matching and identify regions of the lung that are ventilated but not perfused (dead space) or perfused but not ventilated (shunt).

Mauri *et al.* [28] measured ventilation and perfusion in seven patients with C-ARDS. They showed a high degree of mismatch between ventilation and perfusion, with more pixels showing dead space ventilation than shunting. They were not able to distinguish between different causes of dead space ventilation, but repeated measurements at different PEEP levels or after treating thrombosis might reveal the underlying cause.

Morais *et al.* [65] presented three cases of patients with COVID-19 with similar levels of oxygenation, but very different pathophysiology. One case had a relatively normal respiratory system compliance, homogenous ventilation on EIT, only peripheral and basilar ground-glass opacities on CT imaging, but severe right-lung perfusion impairment ('H-type'). The other cases had a lower respiratory system compliance, less homogenous ventilation on EIT, diffuse bilateral ground-glass opacities on CT, but no major perfusion disturbances ('L-type'). In a single case, Zarantonello *et al.* [66] showed prone positioning can lead to an improvement in homogeneity of ventilation and perfusion and an increase in ventilation/perfusion matching. Safaee Fakhr *et al.* [67] showed the potential of EIT in monitoring perfusion defects over time.

The combination of information on the ventilation and perfusion of the lungs can help characterize and, maybe more importantly, monitor the pathophysiology leading to severe hypoxemia. There is currently no evidence on the merits of perfusion measurements using EIT in the COVID-19 population. However, the unique bedside insight into ventilation/perfusion mismatches makes it a promising technique for monitoring and potentially optimizing the complex interaction between the lungs, the heart and the vascular system in ventilated patients with C-ARDS.

Lung ultrasound

By combining LUS with cardiac ultrasound surrogate markers of perfusion of the lung can be found, especially in the case of sudden changes in right ventricular dimensions or flow over the tricuspid valve, which is suggestive for pulmonary embolism. One should keep in mind that these findings can also be due to mechanical ventilation (with high levels of PEEP) itself. Significantly, there are a few case reports in which microbubbles were added to pulmonary ultrasound (contrast-enhanced ultrasound; CEUS). CEUS revealed perfusion defects in consolidative regions which are not seen in non-COVID-19 pneumonia or atelectasis itself [68–70]. Similar findings are reported in case-series in which perfusion defects are more easily identified by CEUS compared with CT-angiography [68].

CONCLUSION

COVID-19 presented the world with a multitude of major challenges. While major improvements in the detection, prevention and treatment of COVID-19 have been made, it is expected many more patients will require ventilatory support due to infection

with SARS-CoV-2. In the management of C-ARDS we can make use of the extensive body of knowledge about ARDS. The high heterogeneity of respiratory mechanics, severity of hypoxemia and lung recruitability make bedside monitoring of the aeration, perfusion and pressures crucial in the personalization of the ventilatory treatment of C-ARDS.

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