REVIEW ARTICLE

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Mechanical ventilation in COVID-19: A physiological perspective

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Abstract

Severe respiratory failure from coronavirus disease 2019 (COVID-19) pneumonia not responding to non-invasive respiratory support requires mechanical ventilation. Although ventilation can be a life-saving therapy, it can cause further lung injury if airway pressure and flow and their timing are not tailored to the respiratory system mechanics of the individual patient. The pathophysiology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to a pattern of lung injury in patients with severe COVID-19 pneumonia typically associated with two distinct phenotypes, along a temporal and pathophysiological continuum, characterized by different levels of elastance, ventilation-to-perfusion ratio, right-to-left shunt, lung weight and recruitability. Understanding the underlying pathophysiology, duration of symptoms, radiological characteristics and lung mechanics at the individual patient level is crucial for the appropriate choice of mechanical ventilation settings to optimize gas exchange and prevent further lung injury. By critical analysis of the literature, we propose fundamental physiological and mechanical criteria for the selection of ventilation settings for COVID-19 patients in intensive care units. In particular, the choice of tidal volume should be based on obtaining a driving pressure $< 14\,cmH_2O$, ensuring the avoidance of hypoventilation in patients with preserved compliance and of excessive strain in patients with smaller lung volumes and lower lung compliance. The level of positive end-expiratory pressure (PEEP) should be informed by the measurement of the potential for lung recruitability, where patients with greater recruitability potential may benefit from higher PEEP levels. Prone positioning is often beneficial and should be considered early. The rationale for the proposed mechanical ventilation settings criteria is presented and discussed.

KEYWORDS

artificial, COVID-19, critical care, physiology, respiration, respiratory, respiratory distress syndrome, SARS-CoV-2

1 | INTRODUCTION

At the time of writing, > 4 million people in the UK have tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection (Dong et al., 2020), but < 25,000 have developed illness severe enough to warrant critical care admission (ICNARC, 2021). This severe respiratory illness, termed coronavirus disease 2019 (COVID-19) pneumonia, typically develops 8 days after symptom onset (Hu et al., 2021) and, when it does not respond to non-invasive respiratory support, it requires advanced respiratory support, including high concentrations of inspired oxygen and mechanical ventilation. Such therapies are also required for the acute respiratory distress syndrome (ARDS) (Ranieri et al., 2012), which has been widely studied over several decades. This review highlights the pathophysiology of SARS-CoV-2 infection and subsequent COVID-19 pneumonia, its similarities with and differences from classical ARDS, and the implications for mechanical ventilation strategies to support COVID-19 patients in the intensive care unit.

During inspiration, the lung expands owing to a positive trans-pulmonary pressure. In spontaneous ventilation, this gradient is produced by a negative pleural pressure created by the inspiratory muscles, mainly the diaphragm. In contrast, controlled mechanical ventilation relies upon a positive airway pressure driving gas into the lungs, with the positive transpulmonary gradient dependent upon an increased alveolar pressure, and passive movement of the chest wall. The fundamental ventilator parameters that can be set are airway pressure and flow and their timing, which need to match the patient's respiratory system resistance and elastance (inverse of compliance). At each time point during inspiration, airway pressure is determined by the equation of motion and equals the sum of end-expiratory alveolar pressure, the product of flow and resistance to flow, and the product of tidal volume and elastance of the respiratory system. Mechanical ventilation can be delivered in mandatory mode or in assisted mode to support spontaneous breathing. In the latter modality, the patient's inspiratory effort triggers the delivery of breaths (Pham et al., 2017), the work of breathing is shared in various proportions between the respiratory muscles and the mechanical ventilator, and the trans-pulmonary pressure is generated by a combination of a negative pleural pressure and a positive alveolar pressure.

This ventilatory support can be necessary to sustain life in the acute phase of the disease while the immune system fights the viral infection, yet can cause harm to the patient if the levels of positive pressure are not tailored to the associated lung mechanics (ventilator-induced lung injury). Ventilator-induced lung injury is well studied in classical ARDS, a syndrome associated with a distinct histopathological entity termed diffuse alveolar damage (DAD). Diffuse alveolar damage is a widespread, heterogeneous inflammatory reaction comprising alveolar infiltrates with leuco-cytes and proteinaceous deposits, damage to alveolar pneumocytes, the basement membrane and endothelium, and patchy areas of haemorrhage (Nash et al., 1967; Ware & Matthay, 2000). Under-standing the microstructural changes in disease processes is a requisite for effective ventilatory management, with large-scale clinical trials

New Findings

- **What is the topic of this review?**
  This review presents the fundamental concepts of respiratory physiology and pathophysiology, with particular reference to lung mechanics and the pulmonary phenotype associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and subsequent coronavirus disease 2019 (COVID-19) pneumonia.

- **What advances does it highlight?**
  The review provides a critical summary of the main physiological aspects to be considered for safe and effective mechanical ventilation in patients with severe COVID-19 in the intensive care unit.

supporting the use of low tidal volumes (ARDSnet, 2000) and driving pressures (Amato et al., 2015) to reduce the risk of stretch or over-pressure damage to the already injured, fragile lung parenchyma (Slutsky & Ranieri, 2013). It is not clear whether and how these guidelines for ventilation of patients with ARDS are applicable for the management of patients with COVID-19 pneumonia, which appears to demonstrate a distinct pattern of injury.

2 | PATHOPHYSIOLOGY OF HYPOXAEMIA IN COVID-19 PNEUMONIA

Early COVID-19 pneumonia is a process predominantly affecting the peripheries of both lungs (Fox et al., 2020; Shi et al., 2020). The lack of a significant burden of atelectatic, consolidated lung in early COVID-19 pneumonia explains the lack of response to increases in positive end-expiratory pressure (PEEP) in this cohort (Ball et al., 2021; Chiumello et al., 2020), who nevertheless demonstrate a significant reduction in oxygenation (Gattinoni, Chiumello, Caironi et al., 2020; Figure 1). The disease progresses with development of patchy bilateral ground-glass opacification and, finally, dense consolidation in keeping with ARDS (Shi et al., 2020), and post-mortem studies of patients who died with COVID-19 pneumonia have identified alveolar injury similar or identical to DAD, even in those patients who did not receive invasive mechanical ventilation (Fox et al., 2020; Konopka et al., 2020; Menter et al., 2020).

All post-mortem studies by their definition include patients who did not survive their disease, probably determining a disproportion of evidence available with greater weight to the late-/end-stage disease and associated bias. Biopsies from living patients earlier in the disease process, however, demonstrate a number of important differences from classical ARDS histology, including a marked absence of DAD features, hyperplasia of type 2 pneumocytes and an increased number
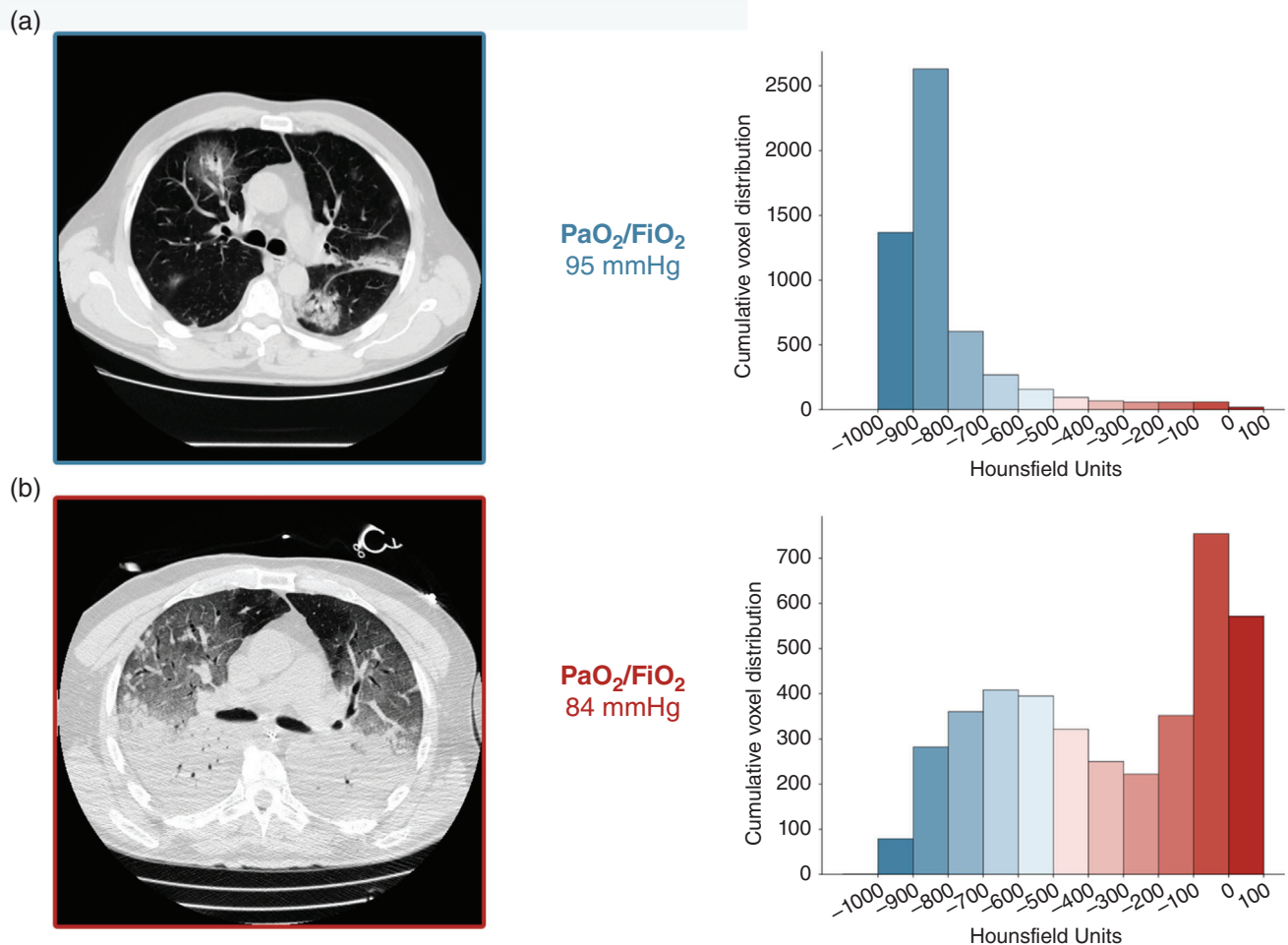
(a)

PaO_2/FiO_2
95 mmHg

(b)

PaO_2/FiO_2
84 mmHg

FIGURE 1 Computed tomography (CT) scans showing different degrees of lung consolidation associated with similar levels of arterial oxygenation in patients with coronavirus disease 2019 (COVID-19). (a) The CT scan was acquired during spontaneous breathing and associated with low Hounsfield unit values, indicating well-aerated compartments. (b) The CT scan was acquired during controlled mechanical ventilation, with positive end-expiratory pressure at 5 cmH$_2$O, and associated with a marked proportion of high Hounsfield unit values, indicating non-aerated compartments. Abbreviations: F_{I,O_2}, fraction of inspired oxygen; P_{aO_2}, arterial partial pressure of oxygen. Reproduced with permission from Gattinoni, Chiumello, Caironi, et al. (2020)

and size of both interstitial capillaries and postcapillary venules (Doglioni et al., 2021).

A small autopsy series, looking at patients who died earlier in the disease process, also demonstrated some differences from classical DAD, with a lymphocytic alveolar infiltrate in the early stages followed by a progression to intra-alveolar fibrin deposition and microvascular injury (Copin et al., 2020). This latter finding of severe microvascular injury associated with pulmonary capillary microthrombi was also present in other series (Fox et al., 2020; Menter et al., 2020).

The pathogenesis of these microthrombi is likely to be related to direct pulmonary endothelial cell damage attributable to SARS-CoV-2 infection, in addition to widespread immunothrombosis triggered by a widespread dysregulated immune response ('cytokine storm') (Gupta et al., 2020). SARS-CoV-2 spike proteins, similar to those on the original SARS-CoV-1, interact with the angiotensin-converting enzyme 2 (ACE2) receptor (Hoffmann et al., 2020; Li et al., 2003). The ACE2 receptor is abundantly expressed on type 2 pneumocytes

and on endothelial cells (Hamming et al., 2004), and it is postulated that viral particles interacting with this receptor lead to endocytosis of the SARS-CoV-2/ACE2 complex and the subsequent pneumonia and local pro-inflammatory, pro-thrombotic response. This endothelial injury is similar to the endotheliitis associated with T-cell-mediated rejection of solid organ transplants (Ackermann, Mentzer, et al., 2020; Varga et al., 2020) and is associated with alveolar capillary and post-capillary venule thrombosis to an extent up to nine times greater than is seen in other viral pneumonias, such as H1N1 pneumonia (Ackermann, Verleden, et al., 2020; Figure 2). Brisk neovascularization, particularly intussusceptive, is also seen early in the disease process in COVID-19 pneumonia (Ackermann, Verleden, et al., 2020).

Using a variety of imaging methodologies including iodine maps from dual-energy computed tomography (CT) imaging and positron emission tomography/single photon emission computed tomography (PET/SPECT) imaging, different groups have confirmed the co-existence of widespread pulmonary perfusion deficits both with and
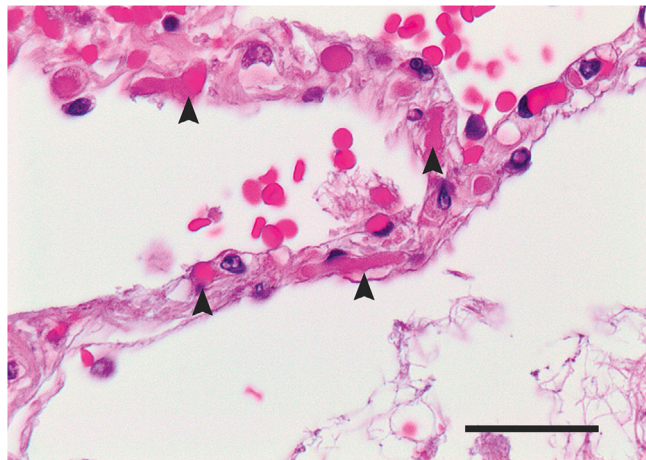
FIGURE 2 The interalveolar septa of a 78-year-old male patient who died from coronavirus disease 2019 (COVID-19), showing slightly expanded alveolar walls and multiple fibrinous microthrombi (arrowheads) in the alveolar capillaries. Scale bar: 50 μm. Reproduced with permission from Ackermann, Verleden, et al. (2020), Copyright Massachusetts Medical Society

without radiologically visible thrombi (Grillet et al., 2020; Patel et al., 2020; Ramos et al., 2021; Ridge et al., 2020; Santamarina, Boisier, et al., 2020; Santamarina, Boisier Riscal, et al., 2020), the latter hypothesized to reflect vascular inflammation or alteration of the vascular tone (Busana et al., 2021). Regions of reduced perfusion demonstrated otherwise near-normal lung parenchyma and air spaces. There is additionally evidence that pulmonary blood volume is redistributed towards regions of ground glass opacification, with the potential to exacerbate shunt (Si-Mohamed et al., 2020). These findings fit with clinical evidence of increased dead space, as measured by ventilatory ratio (Chiumello et al., 2020; Patel et al., 2020), in addition to venous admixture (Chiumello et al., 2020) in COVID-19 pneumonia.

Based upon these imaging studies and the known endothelial dysfunction induced by SARS-CoV-2 infection, one of the causes of ventilation–perfusion ($\dot{V}/\dot{Q}$) mismatching and therefore hypoxaemia in COVID-19 pneumonia is hypothesized to be loss of the normal hypoxic pulmonary vasoconstriction (HPV) response (Gattinoni, Chiumello, Caironi et al., 2020; Ramos et al., 2021), in addition to the physical redistribution of blood owing to occlusive thrombi.

Macrovascular complications, including pulmonary emboli, are also common in severe SARS-CoV-2 infection (Helms et al., 2020) and can arise either from lower limb sources consistent with widespread immunothrombosis or from in situ pulmonary thrombosis (Loo et al., 2021).

3 | COMPARISONS WITH CLASSICAL ARDS

In ARDS with other aetiology, the severity of disease, evaluated using the arterial partial pressure of oxygen/fraction of inspired oxygen ($P_{aO_2}/F_{I,O_2}$) ratio according to the Berlin definition (Ranieri et al., 2012), is directly proportional to the quantity of lung oedema and to the amount of non-aerated lung tissue (Caironi et al., 2015). This inverse relationship between the $P_{aO_2}/F_{I,O_2}$ ratio and the quantity of non-aerated lung tissue is a hallmark of ARDS, and because of the strong relationship, it is possible to estimate the shunt fraction and therefore the $P_{aO_2}/F_{I,O_2}$ ratio from the amount of collapsed tissue obtained from the lung CT (Reske et al., 2013).

The implication of this relationship is that a progressively more severe disease is associated with progressively smaller lung volumes available for ventilation ('baby lung') and a progressively larger amount of collapsed but potentially recruitable lung (Gattinoni et al., 2006). These two characteristics underpin the widely accepted recommendations on the use of ventilation with a lower tidal volume (to protect the baby lung) and a progressively higher amount of PEEP (according to PEEP/F_{I,O_2} tables), to keep open the atelectatic but potentially recruitable lung.

Although some uncertainty remains with regard to the underlying mechanisms, the hypoxaemia observed early in COVID-19 results from a more complex interaction between a dysregulation in pulmonary perfusion through alteration of angiotensin II metabolism, vascular inflammation, loss of hypoxic pulmonary vasoconstriction, neo-angiogenesis and immunothrombosis (Ackermann, Verleden, et al., 2020; Busana et al., 2021; Habashi et al., 2021; Sherren et al., 2020). As the disease progresses, as evidenced by serial CT and post-mortem examinations, changes consistent with classical ARDS are seen. As such, two differing phenotypes of COVID-19 pneumonia have been proposed: 'type L', associated with low elastance, $\dot{V}/\dot{Q}$ ratio, lung weight and recruitability, and 'type H', associated with high elastance, right-to-left shunt, lung weight and recruitability (Gattinoni, Chiumello, Caironi et al., 2020). In terms of the underlying pathophysiology, type L relates to the early peripheral disease process, where the hypoxia is mediated by perfusion deficits and an increased dead space, whereas type H refers to a pathophysiology consistent with classical ARDS. Such a distinction must be made with caution, because it is clear that some patients will exhibit features of both types, some will transition between types, and some will remain in one or the other for the entirety of their disease process. Understanding the particular underlying pathophysiology in any particular patient is crucial for the appropriate choice of mechanical ventilation settings, both in order to optimize gas exchange and to prevent further damage to the already injured lung.

Owing to the primarily vascular phenomena in type L disease, the alteration in gas exchange (venous admixture and dead space ventilation resulting in hypoxaemia and hypercapnia) can occur in the presence of near-normal lung volumes (Gattinoni, Chiumello, Rossi, et al., 2020; Gattinoni, Coppola, et al., 2020; Gattinoni, Meissner, et al., 2020; Gattinoni et al., 2021). In this case, there is a complete dissociation between the severity of alterations in gas exchange (mainly hypoxaemia) and the relatively preserved lung volumes and therefore compliance of the respiratory system (Chiumello et al., 2020).

Ultimately, some patients with COVID-19 pneumonia develop irreversible pulmonary fibrosis (George et al., 2020; Mo et al., 2020), which is also seen late in ARDS (Masclans et al., 2011). This phenotype

manifests as a restrictive lung pathology with minimal potential for lung recruitment (PLR) and is associated with difficulties in weaning from mechanical ventilation and a poor prognosis, in some cases warranting lung transplantation (Bharat et al., 2020).

The above considerations are essential for the appropriate management of patients with hypoxaemic respiratory failure secondary to COVID-19 (Habashi et al., 2021; Robba et al., 2020). This management requires a shift between the concepts of selecting low tidal volumes based on the severity of hypoxaemia and the selection of PEEP based on the $P_{aO_2}/F_{I,O_2}$ ratio (Marini & Gattinoni, 2020) and will require a more global assessment of the patient, which starts with an understanding of the duration of the symptoms, the radiological characteristics (particularly CT) and an assessment of lung mechanics, preferably at PEEP 5 cmH$_2$O (Caironi et al., 2015; Chiumello et al., 2020).

4 | SELECTION OF TIDAL VOLUME

Typically, a tidal volume of 6 ml/kg predicted body weight (PBW) is used in patients with the ARDS because, compared with the delivery of larger tidal volumes, it increases both survival and the number of days spent without ventilation (ARDSnet, 2000). Given the above-mentioned dissociation between the severity of oxygenation and lung volumes, a tidal volume of 6 ml/kg PBW may not be appropriate for every patient at every stage of the disease process. Recent studies make it clear that selecting total volumes based on a value of driving pressure (DP; measured as plateau pressure minus PEEP or as tidal volume divided by compliance) is a better way of personalizing the total volume to the lung compliance, and therefore the lung volume, hence adapting tidal volumes to the different phenotypes of the disease, with the aim of maintaining lung strain within a narrow range (Amato et al., 2015; Costa et al., 2021; Goligher et al., 2021).

Practically, the first approach in a patient receiving controlled mechanical ventilation should be to select a tidal volume that reflects a threshold of driving pressure rather than being based on PBW, or to set the lowest driving pressure (in pressure control) to achieve any initial tidal volume of 8 ml/kg PBW. If the driving pressure is < 14 cmH$_2$O (Tsolaki et al., 2021), the associated tidal volume can be maintained. However, the driving pressure might be well above 14 cmH$_2$O in patients with reduced compliance, and in this case the tidal volume needs to be lowered until the target driving pressure has been achieved (Marini & Gattinoni, 2020). This approach of selecting total volume based on obtaining a driving pressure < 14 cmH$_2$O ensures the avoidance of both hypoventilation in patients with preserved compliance and the excessive strain in patients with smaller lung volumes and lower lung compliance.

The total energy delivered by the mechanical ventilator to the respiratory system every minute can be calculated by combining tidal volume, PEEP, plateau and peak inspiratory pressures and respiratory rate, all used to determine mechanical power. The trade-off between a decrease in tidal volume and an increase in respiratory rate to achieve a given minute ventilation necessary to remove a sufficient quantity of carbon dioxide can be calculated using either the formula of mechanical power (Giosa et al., 2019) or an abbreviated practical formula of 4DPRR (4 × driving pressure + respiratory rate) (Costa et al., 2021). Using this formula, it is possible to select the most appropriate total volume (based on driving pressure) and respiratory rate that will give the lowest possible total value of 4DPRR (Costa et al., 2021).

5 | SELECTION OF POSITIVE END-EXPIRATORY PRESSURE

The selection of PEEP in COVID-19 is complex, given the dissociation between hypoxaemia and anatomical shunt fraction, which normally reflects the amount of non-aerated lung tissue (Chiumello et al., 2020). Choosing high PEEP based solely on the severity of hypoxaemia in patients with preserved lung compliance will add static stress and strain, alter lung perfusion and haemodynamics, and ultimately, increase the static component of mechanical power and contribute to volutrauma (Güldner et al., 2016).

The best approach to evaluate the effects of different levels of PEEP is by measuring the PLR either through the CT scan or, more simply, at the bedside using a single-breath recruitment-to-inflation ratio (R/I ratio). This ratio is calculated as the compliance of the lung volume recruited with an abrupt release of PEEP from 15 to 5 cmH$_2$O (or to airway opening pressure) divided by the compliance at a PEEP of 5 cmH$_2$O (or airway opening pressure). An R/I ratio > 0.5 indicates higher lung recruitability, and these patients may benefit from higher levels of PEEP (Chen et al., 2020). In COVID-19, recruitability is highly variable (Beloncle et al., 2020) and seems to be dependent crucially on the delay from symptoms to intensive care unit admission or to intubation, in addition to the treatment received in hospital before the institution of mechanical ventilation.

It is important to stress that an improvement in oxygenation after an increase in PEEP does not necessarily indicate recruitability. Positive intrathoracic pressure has a complex relationship with oxygenation. By decreasing alveolar capillary transmural pressure, it can impair pulmonary perfusion (Versprille, 1987) and even redistribute it to non-ventilated areas (Cronin et al., 2020), but by increasing lung volume it can also increase the flow through extra-alveolar vessels and, additionally, reduce the shunt fraction by a depressive effect upon cardiac output (Dantzker et al., 1980). Therefore, many patients can respond to an increase in PEEP with an improvement in oxygenation but a deterioration in dead space ventilation, a reduction in respiratory system compliance and an increase in driving pressure (Grieco et al., 2020). Only when all these changes are taken into consideration is it possible to determine whether a higher or lower PEEP setting is required for individual patients.

6 | RESCUE INTERVENTIONS

When deciding on the use of recruitment manoeuvres (RMs), determining PLR is again crucial. Recruitment manoeuvres and

high PEEP in patients with low PLR can cause overdistension of areas of the lung already opened, increasing dynamic strain, volutrauma and barotrauma owing to the effects of stress risers (areas of the lung where amplification of mechanical forces takes place), which can represent 14–23% of the lung parenchyma (Cressoni et al., 2014). In these patients, the most effective strategy is to use PEEP of 5−8 cmH$_2$O, avoid RMs and adopt the prone position early, ideally within the first 24 h of intubation (Guerin et al., 2013; Langer et al., 2021; Mathews et al., 2021; Shelhamer et al., 2021; Weiss et al., 2021; Zarantonello et al., 2020).

On the contrary, in patients with high PLR, PEEP > 10 cmH$_2$O (but possibly ≤ 15–18 cmH$_2$O) can lead to opening of new alveolar units, reducing dynamic strain and increasing the recruited volume. In these patients, higher PEEP may improve lung homogeneity.

In both circumstances, the most effective way to achieve lung homogeneity and protective ventilation and to optimize $\dot{V}/\dot{Q}$ matching is the use of prone positioning (Beitler et al., 2014; Gattinoni et al., 2003; Munshi et al., 2017; Weiss et al., 2021). Prone positioning has been effective at improving gas exchange in patients with ARDS and in those with COVID-19 (Guérin et al., 2020; Scaramuzzo et al., 2021), and other studies are in progress to determine its capacity to reduce mortality. During the COVID-19 pandemic, the use of prone positioning has been extended to patients who were not intubated but were receiving non-invasive mechanical support or simply high-flow nasal oxygenation. Awake proning has improved gas exchange, but the ultimate effects on preventing intubation, improving outcome or altering the course of the trajectory of the disease are unclear (Coppo et al., 2020; Ferrando et al., 2020).

7 | SPONTANEOUS BREATHING AND RISK OF PATIENT SELF-INFLICTED LUNG INJURY

Severe hypoxaemia is associated with an increase in ventilation (Weil et al., 1970), but its correlation with the symptom of dyspnoea is moderate at best, with other factors, such as hypercapnia and mechanical limitation of ventilation, exhibiting stronger relationships based on accepted physiological principles (Manning & Schwartzstein, 1995). In severe SARS-CoV-2 infection, a subgroup of patients tolerate life-threatening degrees of hypoxaemia without obvious distress or air hunger (Tobin et al., 2020). Several mechanisms are proposed to account for this phenomenon. The relative lack of changes in lung parenchyma and respiratory system compliance seen with early infection might override the dyspnoeic response that would be expected owing to hypoxaemia from severe $\dot{V}/\dot{Q}$ mismatch (Couzin-Frankel, 2020). Neurological manifestations of SARS-CoV-2 infection are common, particularly anosmia, and direct impairment of the respiratory control centre might represent a further effect of the brainstem inflammation caused by the virus (Matschke et al., 2020).

During the COVID-19 pandemic, it has become clear that other groups of patients with severe hypoxaemic respiratory failure presented with barotrauma, mediastinal emphysema and subcutaneous emphysema generated during spontaneous breathing, often in the absence of any additional positive airway pressure. This barotrauma caused during spontaneous breathing has been named patient self-inflicted lung injury (P-SILI) (Cruces et al., 2020; Yoshida et al., 2017), to reflect the fact that often excessive inspiratory effort (e.g., > 15 cmH$_2$O) (Esnault et al., 2020; Roesthuis et al., 2021), even in the absence of high-pressure ventilation, can contribute to severe lung injury and progression of lung disease. Given the high risk of P-SILI in these COVID-19 patients, it is important to monitor the inspiratory efforts during both non-invasive and invasive ventilation.

Monitoring of inspiratory effort during non-invasive ventilation is more challenging and relies on recording of total volumes, the diaphragmatic excursions measured with ultrasound, or signs of activation of inspiratory muscles. However, the most accurate measurement of inspiratory effort is obtained by the insertion of an oesophageal balloon catheter that, although carrying some practical difficulties, can record the swings in oesophageal pressure (Tonelli et al., 2020). The swings in (or delta) oesophageal pressure reflect the changes in plural pressure and can therefore give an indication of whether a given inspiratory effort is excessive and can lead to P-SILI. This strategy was effective in monitoring respiratory effort and predicting failure of non-invasive mechanical ventilation (Tonelli et al., 2020).

In patients who are ventilated invasively, it is possible to measure the P0.1 (the airway pressure developed during the first 100 ms of inspiration), which reflects the inspiratory drive, and to calculate the occlusion pressure (DP$_{occ}$, which is the difference between the most negative airway pressure obtained during an expiratory occlusion manoeuvre and the value of PEEP). The importance of these measurements has been shown recently in a study where 62.5% patients with high P0.1 (> 4 cmH$_2$O) and DP$_{occ}$ (< −15 cmH$_2$O) had a relapse in respiratory failure compared with none of the patients with low P0.1 and DP$_{occ}$ (Esnault et al., 2020).

Multiplying the DP$_{occ}$ by 0.75 enables estimation of the respiratory muscle pressure ($P_{musc} = -0.75 \times DP_{occ}$) and the dynamic transpulmonary pressure (DPL = DP − ⅔DP$_{occ}$). As a general guide, it has been suggested that if the estimated P_{musc} is > 13–15 cmH$_2$O or DP$_L$ ≥ 16 cmH$_2$O, more careful monitoring of transpulmonary pressure with oesophageal pressure should be used, or alterations in the sedation and ventilatory strategy should take place to reduce lung stress and strain (Bertoni et al., 2020).

8 | CONCLUSIONS

COVID-19 pneumonia is a pathophysiological entity distinct from classical ARDS and requires different ventilatory management (Figure 3). In early, type L disease, the hypoxaemia is predominantly underpinned by an increased dead space and $\dot{V}/\dot{Q}$ mismatch and is not correlated with the healthy lung volume. As such, tidal volumes should not be limited stringently, but should be more liberal as long as the driving pressure is limited. Likewise, PEEP levels should not be titrated in relationship to hypoxaemia but on the potential for recruitability of the lung, which is not necessarily high if there is minimal air-space

FIGURE 3 Diagram summarizing pathophysiological features associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the proposed management of mechanical ventilation for patients with severe coronavirus disease 2019 (COVID-19) in the intensive care unit. The figure shows the main known pathophysiological mechanisms that can lead to hypoxaemia, with paired CT images (top row) and iodine perfusion maps (bottom row) indicative of the main phases. Initially, hypoxaemia is related to increased shunt (arrows) and dead space ventilation (asterisks), with minimal lung parenchymal pathology at risk of ventilator-induced lung injury. Lung gas volume can decrease over time because of oedema and atelectasis, which may be reversible with prone positioning or higher PEEP. Eventually, dense consolidation and/or fibrosis can make the condition less responsive to both proning and PEEP (low PLR). Macrothrombosis is also present, with pulmonary emboli causing large areas of reduced or absent perfusion. Abbreviations: CT, computed tomography; DP, driving pressure (plateau pressure minus PEEP); PEEP, positive end-expiratory pressure; PLR, potential for lung recruitment or recruitability (ability to open previously gasless lung regions with an increase in transpulmonary pressure); VT, tidal volume. Left-hand images are from Santamarina, Boisier Riscal, et al. (2020) and right-hand images from Ridge et al. (2020), with permission
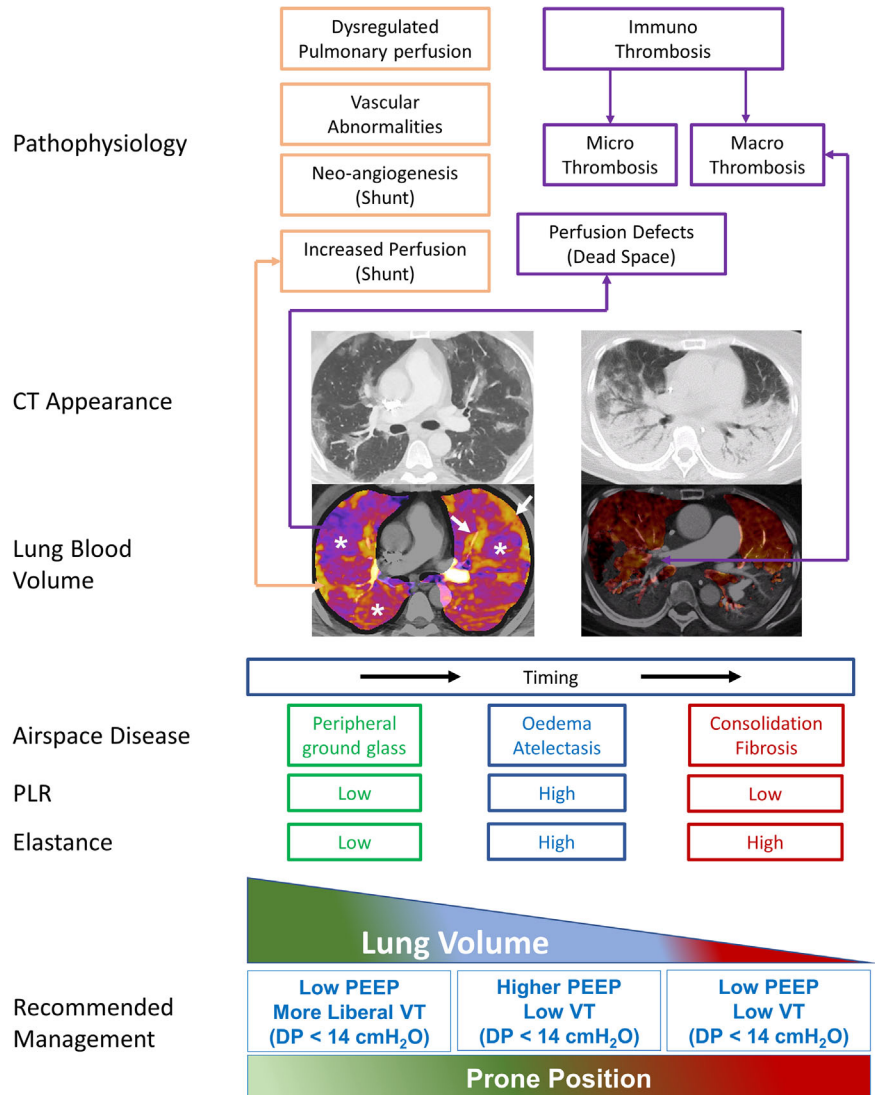
disease. Prone positioning in both spontaneously breathing and ventilated patients is often beneficial and should be considered early.

COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

All authors participated in the writing and revision of the manuscript, approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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