Pathophysiology of coronavirus-19 disease acute lung injury

Luigi Camporota[a,b], *John N. Cronin*[a,c], *Mattia Busana*[d], *Luciano Gattinoni*[d], *and Federico Formenti*[a,e,f]

Purpose of review
More than 230 million people have tested positive for severe acute respiratory syndrome-coronavirus-2 infection globally by September 2021. The infection affects primarily the function of the respiratory system, where ~20% of infected individuals develop coronavirus-19 disease (COVID-19) pneumonia. This review provides an update on the pathophysiology of the COVID-19 acute lung injury.

Recent findings
In patients with COVID-19 pneumonia admitted to the intensive care unit, the PaO_2/FiO_2 ratio is typically <26.7 kPa (200 mmHg), whereas lung volume appears relatively unchanged. This hypoxaemia is likely determined by a heterogeneous mismatch of pulmonary ventilation and perfusion, mainly associated with immunothrombosis, endothelialitis and neovascularisation. During the disease, lung weight, elastance and dead space can increase, affecting respiratory drive, effort and dyspnoea. In some severe cases, COVID-19 pneumonia may lead to irreversible pulmonary fibrosis.

Summary
This review summarises the fundamental pathophysiological features of COVID-19 in the context of the respiratory system. It provides an overview of the key clinical manifestations of COVID-19 pneumonia, including gas exchange impairment, altered pulmonary mechanics and implications of abnormal chemical and mechanical stimuli. It also critically discusses the clinical implications for mechanical ventilation therapy.

Keywords
coronavirus-19 disease, critical care, physiology, respiratory, respiratory distress syndrome, SARS-CoV-2

INTRODUCTION

The coronavirus severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was first identified in late December 2019 and is the cause of a global pandemic affecting primarily – although not exclusively – the respiratory system. By September 2021, more than 7.4 million people tested positive for SARS-CoV-2 virus infection in the United Kingdom, leading to approximately 540,000 patients being admitted to hospital [1]. Of all infected individuals, around 20% develop coronavirus-19 disease (COVID-19) pneumonia with many clinical characteristics compatible with the definition of acute respiratory distress syndrome (ARDS) [2]. Specifically, they have bilateral lung infiltrates on chest radiology, an oxygenation defect with PaO_2/FiO_2 ratio < 300 mmHg and increased dead space ventilation [3]. Although all patients contract the same disease with a common aetiology, the clinical presentation at hospital admission and the response to oxygen supplementation is highly variable, largely depending on the time interval between symptom development and hospital admission. Indeed, background demographics and comorbidities, as well as the physiological severity at presentation, account

[a]Centre for Human and Applied Physiological Sciences, School of Basic and Medical Biosciences, King's College London, [b]Intensive Care Unit, Guy's and St Thomas' NHS Foundation Trust, [c]Department of Anaesthetics, Royal Brompton and Harefield, part of Guy's and St. Thomas' NHS Foundation Trust, London, UK, [d]Department of Anesthesiology, University Medical Center of Göttingen, Göttingen, Germany, [e]Nuffield Division of Anaesthetics, University of Oxford, Oxford, UK and [f]Department of Biomechanics, University of Nebraska Omaha, Omaha, Nebraska, USA

Correspondence to Dr Luigi Camporota, Centre for Human and Applied Physiological Sciences, School of Basic and Medical Biosciences, King's College London, London SE1 1UL, UK.
E-mail: luigi.camporota@gstt.nhs.uk

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KEY POINTS

- Hypoxaemia in COVID-19 is determined by a heterogeneous mismatch of pulmonary ventilation and perfusion, mainly associated with immunothrombosis, endothelialitis and neovascularisation.
- The progression to ARDS in COVID-19 is characterised by alteration in pulmonary perfusion, hyper-inflammation, hypercoagulability and pulmonary emboli with minimal radiological airspace involvement, followed by a stage with increasing inflammatory oedema and – over time – progressive parenchymal consolidation.
- A high respiratory drive can increase the risk of patient self-inflicted lung injury (P-SILI). The significance in terms of P-SILI of the oesophageal pressure swings (strain) during spontaneous ventilation need to be interpreted in the context of lung volume. At higher compliance (early in COVID-19), even lower stress may generate a strain (the ratio between the change in volume compared and the functional residual capacity) similar to the one seen in ARDS from other aetiologies with the higher level of stress (oesophageal swings).

for most of the mortality risk and the variations in hospital outcomes reported worldwide [4]. The progression to ARDS in COVID-19 goes through several stages and is characterised by alteration in pulmonary perfusion, hyper-inflammation, hypercoagulability and pulmonary emboli with minimal radiological airspace involvement, followed by a stage with increasing inflammatory oedema and – over time – progressive parenchymal consolidation: a phase more similar to the typical ARDS in terms of lung mechanics and responsiveness to respiratory support [5].

This review focuses on the pathophysiology of COVID-19 in the context of the respiratory system. It summarises the fundamental clinical manifestations of COVID-19 pneumonia, the associated gas exchange impairment, the altered pulmonary mechanics, and implications of abnormal chemical and mechanical stimuli, and contrasts these features with those of the ARDS from other aetiologies.

GAS EXCHANGE ABNORMALITIES

The majority of patients admitted to critical care have a PaO_2/FiO_2 ratio <26.7 kPa (200 mmHg) consistent with moderate or severe ARDS [2,6]. Despite the low PaO_2/FiO_2 ratio, most patients have preserved lung volumes at presentation, and the lung radiology shows bilateral multifocal ground-glass appearance mainly with peripheral distribution and minimal parenchymal consolidation [7▪]. This apparent paradox, which is only recorded in 10–12% of patients with ARDS from mixed aetiologies [8], is much more prevalent in COVID-19 ARDS and can affect up to 40–50% of the patients [9]. The relative paucity of alveolar consolidation contrasts with the severity of gas exchange. In ARDS from bacterial pneumonia, the hypoxaemia is generally proportional to the quantity of anatomical shunt – which is estimated as the fraction of nonaerated lung tissue mass in relation to the total tissue mass [10]. This compartment is assumed to have a ventilation/perfusion ratio of zero (right-left shunt), with a perfusion assumed to be constant throughout the lung tissue regardless of the aeration status [11,12]. On the contrary, in patients with COVID-19 pneumonia – particularly in the initial phases – the severity of hypoxaemia is more severe compared to what can be expected from the estimated anatomical shunt [12,13▪]. This discrepancy can be explained by the fact that a primary alteration of pulmonary perfusion leads to profound ventilation/perfusion inequalities [12] with higher prevalence of compartments with very low ventilation/perfusion ratio, which seems to be determined by the interaction between the higher cardiac output due to possible intrapulmonary [14] and splanchnic shunts [15], and the hyperperfusion of poorly ventilated compartments. These abnormalities can worsen further if inappropriate mechanical ventilation leads to hypoventilation (very low tidal volumes in normal size lung volumes) and, together with an absolute increase in cardiac output [16], this combination lowers the overall ventilation/perfusion ratio and worsens the hypoxaemia that can be explained even assuming limited hypoxic vasoconstriction [11,12,17]. The relationship between increased cardiac output and increase in venous admixture is well described [18–20] and seems to be amplified in COVID-19 [12,16,21,22]. These alterations in pulmonary perfusion have been described early in the course of the pandemic and of the natural history of the disease. Some of these changes are 'functional' leading to hyper-perfusion of poorly ventilated lung tissue (increase in venous admixture) and is consequent to a loss in hypoxic vasoconstriction [23,24], vasoplegia and inflammatory hyperaemia [25,26]; or to more 'structural' anatomical changes caused by vascular enlargement [27] or new-vessel formation (intussusceptive neovascularisation) [28▪] in the poorly ventilated and hypoxic lung tissue. The combination of functional and anatomical changes leading to hyperperfusion of poorly and nonaerated tissue ultimately explains some of the findings of severe hypoxaemia despite the relatively normal lung gas volumes [13▪,29▪]. Vascular malformation and vascular dilatation with 'tree-in-bud' appearance were associated with different

patterns of perfusion defects (i.e., mottled, wedge-shaped and mixed) in patients with more severe disease [30▪]. These vascular malformation and new vessel formation seem to increase over time with the duration of hospitalisation, in contrast with similar vascular malformation found in patients with influenza pneumonia [28▪,30▪].

As discussed above, ventilation/perfusion inequalities also include areas of the lungs with low perfusion – due to vasoconstriction and vascular occlusion by micro-thrombi [21,22] – despite normal or increased ventilation. These areas with high ventilation/perfusion ratio – which can explain the high deadspace reported in patients with COVID-19 ARDS – result from the interaction between structural phenomena (e.g., immunothrombosis), and functional phenomena (inflammatory and hydrostatic oedema) and excessive positive-pressure ventilation. These latter functional mechanisms can force pulmonary blood flow from normally ventilated areas of the lung – with high alveolar pressure (static strain) – to less ventilated areas. The combined result is an increased ventilation/perfusion inequality with increased venous admixture (contributing to hypoxaemia) and deadspace (with hypercapnia) [31] (Fig. 1).

COAGULOPATHY, INFLAMMATION AND ENDOTHELIALITIS

Three of the typical features of COVID-19 pneumonia are the derangement of haemostasis resulting in excessive clotting, inflammation, and damage to endothelial cells, contributing to respiratory failure in severe cases. In the early stages, COVID-19 pneumonia affects the periphery of the lungs [7▪,32]. Here, initial evidence of lymphocytic infiltrate at the alveolar level indicated progression to intra-alveolar fibrin deposition and injury of the microvasculature [33]. Lung biopsies from patients in these early stages of the disease identified coagulopathy and abnormalities at the level of the pulmonary microcirculation, with alveolar type II cell hyperplasia, a denser network of enlarged interstitial capillaries, pulmonary venules with thickened walls, and no evidence of hyaline membranes [34].

Similarly to the early disease phase, alveolar capillary microthrombi and new blood vessel growth were greatly increased in patients who died from COVID-19 pneumonia (i.e. at a late stage of the disease); the changes in the pulmonary microcirculation in this late stage of the disease appear mostly associated with intussusceptive angiogenesis [28▪]. This microangiopathy was associated with severe

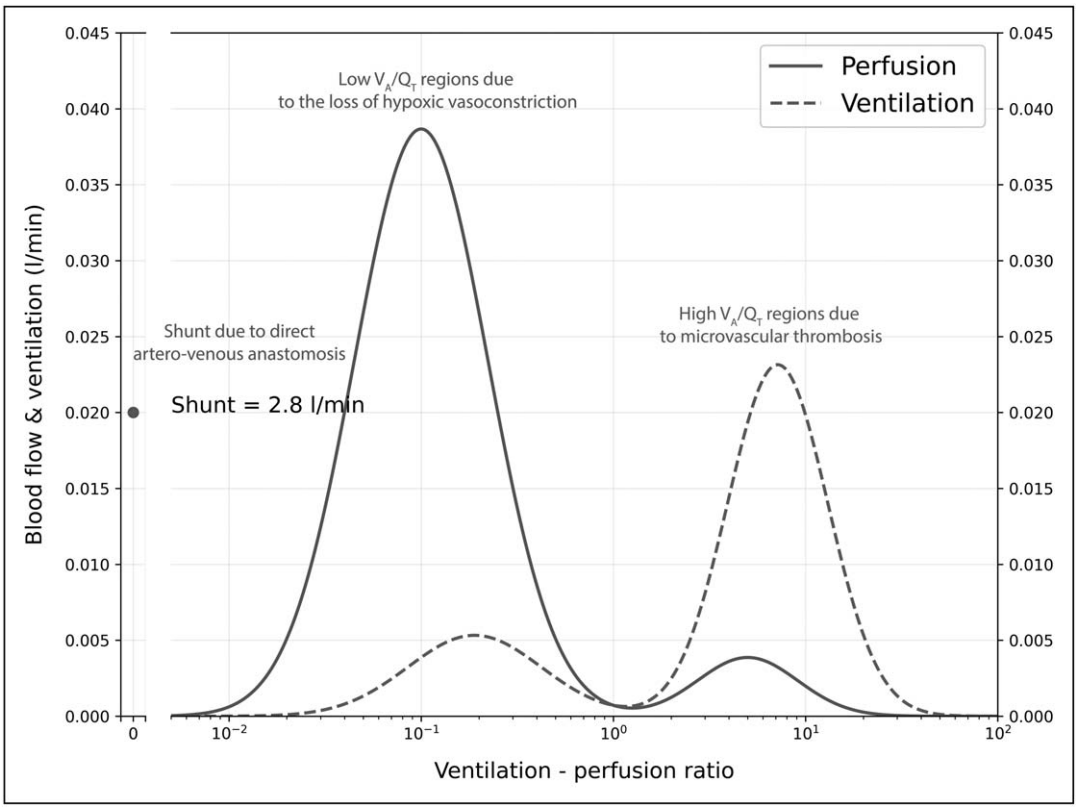

FIGURE 1. Graphical representation of the ventilation-perfusion (VA/Q) distribution inequalities described in COVID-19. COVID-19, coronavirus-19 disease.

endothelial injury, and hyaline membranes causing exudative diffuse alveolar damage, even in patients who had not been ventilated [32,35], in contrast with evidence from lung biopsies obtained earlier in the disease.

Thrombosis appears predominantly associated with pulmonary hypoperfusion observed with different imaging approaches (computed tomography (CT), positron emission tomography and single-photon emission computerized tomography, subtraction CT angiography) [30▪,36,37]. However, thrombi were not always detected in association with pulmonary hypoperfusion: it is plausible that the reduced levels of angiotensin-converting enzyme 2 (ACE2) lead to accumulation of angiotensin II and greater inflammation, causing vasoconstriction in the well-ventilated lung regions, and/or that vascular tone abnormalities such as the loss of the physiological hypoxic pulmonary vasoconstriction may determine a relative hyper-perfusion of nonaerated regions [12,22,24,38].

The coagulopathy, inflammation and alveolar damage later in the disease are likely downstream effects of what has been termed *cytokine storm* [39], a systemic dysregulated response of the immune system observed in response to SARS-CoV-2 infection. In parallel, D-dimer levels, serum ferritin, fibrinogen and C-reactive protein are all elevated in severe COVID-19 pneumonia [40]. The fundamental mechanism driving the response appears to be mediated by the interaction between the SARS-CoV-2 spike proteins and the ACE2 receptor [41,42] present in large quantities on type 2 cells lining the alveoli and on endothelial cells [43]. A positive-feedback loop may characterise the excessive immune response, likely determining an accumulation of pro-inflammatory cytokines in the lung initially, followed by a systemic, sustained inflammatory response that can lead to multiorgan failure [44,45].

Overall, the observed coagulopathy, inflammation and pulmonary perfusion abnormalities determine the mismatch between pulmonary ventilation and perfusion, with increased dead space and associated hypoxaemia [46,47].

RESPIRATORY SYSTEM MECHANICS

Case series from China, Europe and North America have explored the hypoxaemia and associated changes in lung mechanics in mechanically ventilated patients with COVID-19 pneumonia. The majority reports median PaO_2/FiO_2 ratio consistent with moderate ARDS [2,6]. However, there is variability in respiratory system compliance between various series with averaged values ranging from below 30 mL/cmH_2O [48–50] to over 45 mL/cmH_2O [9,13▪,51,52]. A large multicentre observational series in Spain suggested that patients with PaO_2/FiO_2 ratio consistent with moderate ARDS had compliance reduced to 35 [IQR 27–45] mL/cmH_2O [53] similar to that seen in classical ARDS [54]. In this series, patients received mechanical ventilation relatively late in their illness (approximately five days after hospital admission) and such a delay has been associated with a reduced compliance immediately the following intubation in a separate series [55]. Of note, however, in this series and others, is the wide spread of respiratory system compliance measurements, with 25% demonstrating a compliance greater than 45 cmH_2O, suggesting the underlying lung pathophysiology is significantly different between patients within the same series.

When ventilated COVID-19 patients are compared with historical controls from the same centre, matched upon PaO_2/FiO_2 ratio, the COVID-19 patients demonstrate a greater compliance [13▪,56]. This finding was not demonstrated in a separate study matching COVID-19 patients with historical ARDS patients [57], but the groups were not as well matched upon PaO_2/FiO_2 ratio in this study. There is a smaller volume of nonaerated tissue on CT imaging in COVID-19 pneumonia compared with classical ARDS [13▪], as well as a lack of association between this CT measure and PaO_2/FiO_2 ratio [13▪,30▪,58]. It is however difficult to interpret these results in the absence of a clear standardization of the measurement acquisition. Indeed, even with moderately low positive end-expiratory pressure (PEEP) levels (8–10 cmH_2O), COVID-19 lungs appear to be exposed to overdistension [59], a compliance measurement at a so-called 'clinical PEEP' can obviously vary widely from study to study, from centre to centre, especially considering the NIH suggestion to opt for the high-PEEP tables.

These findings, combined with the temporal progression of CT changes seen with COVID-19 [7▪] led to the proposal that early COVID-19 is characterised by low elastance, recruitability and lung weight, with perfusion deficits and increased dead space determining hypoxaemia [29▪,60,61]. In contrast, if patients worsen later in the disease, the phenotype typically becomes characterised by greater elastance, lung weight and recruitability more comparable with classical ARDS. Of note, however, there exists a significant overlap between these phenotypes [52] and due to significant heterogeneity between the time courses from initial symptoms to hospital presentation to initiation of mechanical ventilation amongst studies the temporal changes, whilst predicted from CT imaging, cannot be confirmed.

In some severe cases and at a later stage of the disease, COVID-19 pneumonia may be associated with irreversible pulmonary fibrosis [62–65]. At this

stage, the mechanical energy that can be delivered to the lung may provide insufficient ventilation, and the potential for lung recruitment caused by the restrictive lung pathology is minimal. This condition likely limits the chances of successful weaning and is associated with poor prognosis, when lung transplantation has been proposed as a life-saving treatment [63]. The milder forms of fibrosis developed following SARS-CoV-2 infection may not require admission to the hospital or intensive care unit but, given the high rates of infection globally, their burden is expected to increase dramatically, where antifibrotic therapies may mitigate profibrotic pathways [62].

COMPENSATIONS TO CHEMICAL AND MECHANICAL STIMULI: RESPIRATORY DRIVE, EFFORT AND DYSPNOEA

The interactions between the severe hypoxaemia, the variable reduction in lung volume (minimal early in the disease and progressively more marked during hospitalisation) and the metabolic alterations caused by inflammation are responsible for the increase in respiratory drive and effort. The aim for these feedback mechanisms is to increase minute ventilation to compensate for the hypoxia. In the early phases of the disease the compensatory mechanism for the hypoxia-induced respiratory drive is the generation of larger negative pleural and transpulmonary pressures and therefore increase tidal volumes. Only later, when additional increases in tidal volumes are energetically disadvantageous (the energy cost of breathing is excessive to sustain), compensation occurs via an increase in respiratory rate [66▪]. Therefore, it is important to stress three points: (1) high tidal volumes and respiratory efforts in patients with relatively normal lung compliance can co-exist with the absence of dyspnoea and air hunger [66▪,67–69] (the so-called 'silent hypoxaemia') [20]; (2) that tachypnoea is generally a late sign of increased respiratory effort; (3) a high inspiratory effort leads to an excessive global lung stress and strain (Fig. 2). In COVID-19 further amplification of mechanical forces caused by lung inhomogeneities [70] and inflammation may precipitate patient self-inflicted lung injury (P-SILI), further exacerbating the respiratory failure [71,72].

As the underlying pulmonary oedema increases, there is a reduction in the lung volume available for gas exchange, likely contributing to a positive-feedback loop where hypoxaemia stimulates respiratory drive [66▪], leading to the development of greater transpulmonary pressure and tidal volumes (greater strain and stress), which can increase the degree of

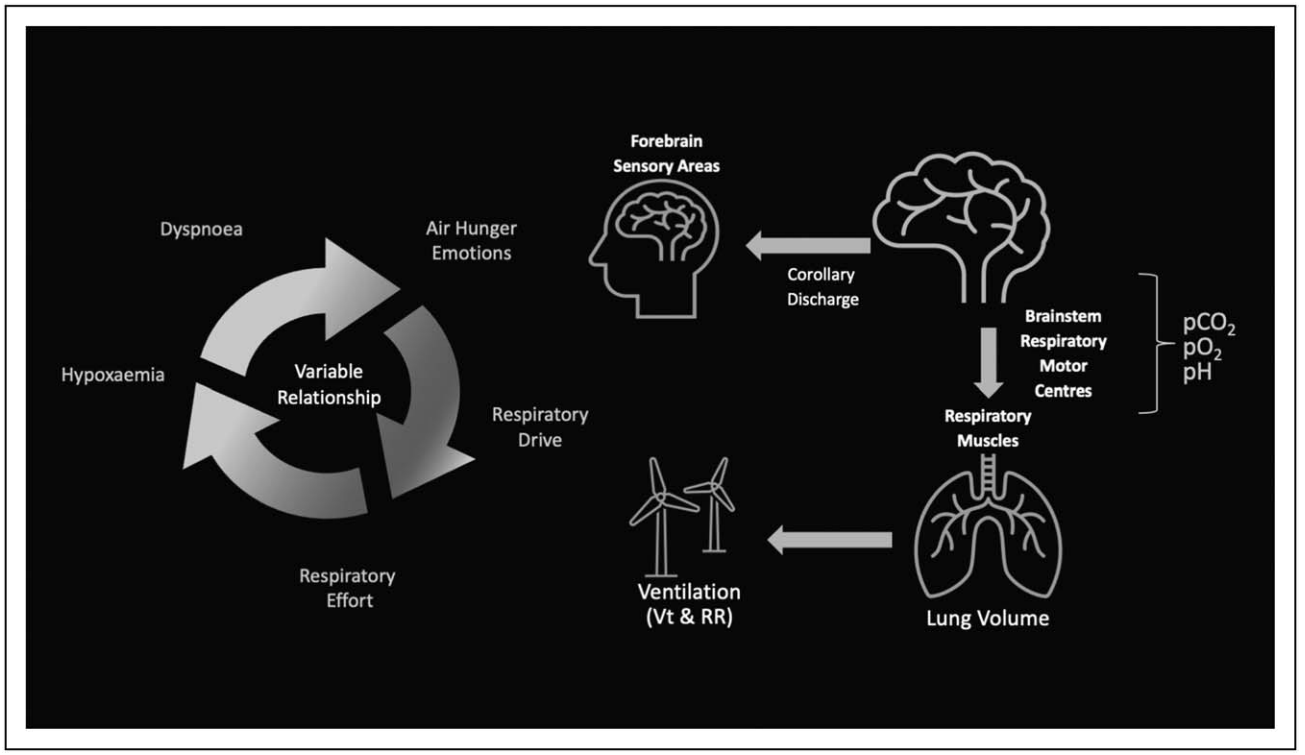

FIGURE 2. Schematic representation of the compensatory mechanisms to hypoxia or hypercapnia and the potential dissociation between increase in inspiratory effort, minute ventilation and perception of dyspnoea.

P-SILI [73], worsen pulmonary oedema and inflammation. P-SILI can manifest itself as progressive lung oedema and worsening respiratory failure or as more overt barotrauma or airleaks. However, the lung parenchyma is stiffer at this stage when breathing is perceived more effortful and therefore patients will report dyspnoea.

A recently published study demonstrated that the median oesophageal pressure swing in non-COVID-19 patients with moderate or severe respiratory failure undergoing noninvasive ventilation trial was 34 cmH_2O [72]. Although these phenomena have been identified in respiratory failure from any aetiology [74,75], including experimental lung oedema [76], modelling of data clearly shows that the forces generated by increased inspiratory effort are seen in COVID-19 are significant and compatible with the development of P-SILI [77]. Large inspiratory efforts – particularly when persisting despite noninvasive ventilation - are harbinger of physiological deterioration, failure of noninvasive support and need for invasive mechanical ventilation [72]. Studies in adults [72,78] and in paediatric populations [79] have shown that large tidal volumes and transpulmonary pressures increase lung oedema and can affect the length of stay [79].

More recent studies in COVID-19 patients have shown that oesophageal pressure swings during spontaneous ventilation are lower compared with those seen in ARDS patients from mixed aetiology [58,80]. However, given the higher lung volumes and compliance in COVID-19 [13▪], a lower stress in COVID-19 lung, may translate into a level of strain (the ratio between the change in volume compared and the functional residual capacity) similar to ARDS from other aetiologies.

Monitoring of inspiratory effort is therefore an essential component of the assessment and therapeutic decision-making [81].

CONCLUSION

The identification of the main mechanisms responsible for the abnormality in gas exchange, respiratory mechanics – and their changes overtime – should guide the optimal setting of respiratory support. In spontaneously breathing patients – whether on noninvasive or invasive ventilation – monitoring of inspiratory effort is an essential additional tool to inform of the choice of mechanical support and identify therapeutic failure.

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Conflicts of interest

There are no conflicts of interest.

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- ▪▪ of outstanding interest

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