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Noninvasive respiratory support and patient self-inflicted lung injury in COVID-19: a narrative review

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Summary

COVID-19 pneumonia is associated with hypoxaemic respiratory failure, ranging from mild to severe. Because of the worldwide shortage of ICU beds, a relatively high number of patients with respiratory failure are receiving prolonged noninvasive respiratory support, even when their clinical status would have required invasive mechanical ventilation. There are few experimental and clinical data reporting that vigorous breathing effort during spontaneous ventilation can worsen lung injury and cause a phenomenon that has been termed patient self-inflicted lung injury (P-SILI). The aim of this narrative review is to provide an overview of P-SILI pathophysiology and the role of noninvasive respiratory support in COVID-19 pneumonia. Respiratory mechanics, vascular compromise, viscoelastic properties, lung inhomogeneity, work of breathing, and oesophageal pressure swings are discussed. The concept of P-SILI has been widely investigated in recent years, but controversies persist regarding its mechanisms. To minimise the risk of P-SILI, intensivists should better understand its underlying pathophysiology to optimise the type of noninvasive respiratory support provided to patients with COVID-19 pneumonia, and decide on the optimal timing of intubation for these patients.

Keywords: ARDS; COVID-19; high-flow nasal oxygen therapy; lung injury; noninvasive ventilation; P-SILI; SARS-CoV-2; spontaneous breathing

Editor’s key points

- Experimental and clinical evidence on non-COVID-19 acute hypoxaemic respiratory failure and acute respiratory distress syndrome (ARDS) suggest that vigorous spontaneous breathing efforts during noninvasive respiratory support can worsen lung injury, inducing ‘patient self-inflicted lung injury’ (P-SILI).
- No clinical study has demonstrated that a ventilatory strategy to limit the risk of P-SILI can improve patient outcomes, particularly in patients with COVID-19.
- This review article highlights the controversy as to whether the pathophysiology of COVID-19 differs from that of conventional acute hypoxaemic respiratory failure and ARDS, and how it can be associated with P-SILI and its clinical management.

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COVID-19 may present with mild to severe symptoms, the latter often associated with acute respiratory distress syndrome (ARDS), possibly complicated by multiple organ dysfunction.\textsuperscript{1,2} Experimental and clinical evidence on non-COVID-19 acute hypoxaemic respiratory failure (AHRF) and ARDS supports the existence of ventilator-induced lung injury.\textsuperscript{3} Despite a clear rationale, comparatively few data report that vigorous spontaneous breathing efforts during noninvasive respiratory support can worsen lung injury, inducing what has been termed ‘patient self-inflicted lung injury’ (P-SILI).\textsuperscript{4,5}

To date, no clinical study has demonstrated that a ventilatory strategy to limit the risk of P-SILI can improve patient outcomes.\textsuperscript{6–8} During the early phase of the COVID-19 pandemic, P-SILI was highlighted as a rationale to justify early intubation over noninvasive respiratory support.\textsuperscript{9} Although evidence has been limited, it seems that regional strain and heterogeneity do not result in P-SILI in healthy lungs, thus raising questions regarding the mechanisms underlying P-SILI in already-damaged lungs, such as in COVID-19. It is likely that the loss of normally aerated lung volume for the same tidal volume increases global and regional strain, and leads to pivotal effects on diaphragm curvature and contraction. If respiratory neuromuscular function is intact, the increased respiratory drive is translated into stronger muscle contraction and more negative pleural swings, which could result in pendelluft phenomena, tidal recruitment, pulmonary oedema, and increased regional strain.\textsuperscript{10} However, in COVID-19, P-SILI may be only part of a complex multitude of events that can contribute as determinants of failure of noninvasive respiratory support. Attention should also be paid to the degree of hypoxaemia and its effects on peripheral organs, as COVID-19 is characterised by multiple organ involvement.\textsuperscript{1,11}

Thus, invasive mechanical ventilation (MV) should be considered, but bearing in mind its possible systemic complications.\textsuperscript{8,12} Controversy remains whether the pathophysiology of COVID-19 differs from that of conventional ARDS.\textsuperscript{13–16}

Therefore, the straightforward application of concepts derived from ARDS to COVID-19 pneumonia might have drawbacks.\textsuperscript{13–16} The aim of this narrative review is to provide an overview of the pathophysiology and the role of noninvasive respiratory support in COVID-19 pneumonia. Respiratory mechanics, vascular compromise, viscoelastic properties, lung inhomogeneity, work of breathing, and oesophageal pressure swings are discussed. Different approaches are described to help the intensivist minimise the risk of P-SILI.

COVID-19-induced pneumonia

Once SARS-CoV-2 enters the alveolar type II epithelial cells,\textsuperscript{17} it begins to replicate, compromising alveolar–capillary barrier integrity and infecting other cell types, ultimately resulting in multiple organ involvement.\textsuperscript{1} The exact pathophysiology of pulmonary involvement in COVID-19 is still under investigation, but there is evidence showing initial alveolar collapse, lung inhomogeneity, and changes in viscoelastic properties of the lungs,\textsuperscript{18} and macro- and microvascular involvement, including endothelial inflammation, oedema, and extracellular matrix injury,\textsuperscript{19} which result in an altered ventilation/perfusion ratio ($V_A/Q$) and impairment of hypoxic vasoconstriction.\textsuperscript{19,20} Some of these pathophysiological features are shared with other lung diseases, making the differential diagnosis quite challenging.\textsuperscript{17,21,22} In COVID-19, low arterial partial pressure of oxygen/fraction of inspired oxygen ratio ($P_{aO_2}/FiO_2$) is not only associated with true shunting, but also with extensive areas of low $V_A/Q$,\textsuperscript{23} which correspond to ground-glass areas on chest CT. Lung biopsies obtained from patients who died from COVID-19 demonstrated a distinctive vascular feature of endothelial injury, disrupted cell membranes, and widespread thrombosis with microangiopathy.\textsuperscript{24} The $V_A/Q$ mismatch can also be promoted by a hyperactivation of the coagulation cascade, which fosters thrombotic and embolic mechanisms, leading to higher $V_A/Q$ and physiological dead space.\textsuperscript{25} The natural history of COVID-19 pneumonia also involved diffuse alveolar damage after secretion of proteases and reactive oxygen species, and formation of antibody–virus immune complexes.\textsuperscript{26} Finally, endothelial cell damage and dysregulated angiogenesis may promote pathological fibroproliferation.\textsuperscript{27} The fibrotic pattern seems to be preponderant in late phases of the disease.\textsuperscript{28} Postmortem trans-bronchial lung cryo-biopsies of patients with COVID-19 admitted to the ICU showed intra-alveolar hyaline membranes, alveolar oedema, and proteinaceous exudate formation, and a proliferative profile characterised by derangement and obliteration of the alveolar structures and fibrosis.\textsuperscript{29–31} These anatomical and structural alterations result in significant changes in respiratory mechanics.\textsuperscript{27} The mechanical stretch of lung epithelia results in increased release of tissue growth factor and lung remodeling.\textsuperscript{28} All these mechanisms might be associated with different degrees of hypoxaemia, respiratory system compliance, and potential for lung recruitment.\textsuperscript{13–16} Different phenotypes of COVID-19 have been described and modelled since the beginning of the pandemic, alternately described as different presentations of COVID-19 or distinct stages of the same disease.\textsuperscript{9,29} In this context, a milder, earlier phenotype (I or 1) includes multiple, focal ground-glass opacities and is associated with low elastance, low $V_A/Q$ ratio, and low recruitability. An intermediate phenotype (2) represents the progression of phenotype I (or 1) to H (or 3).\textsuperscript{29} Finally, phenotype H (or 3) is more similar to a typical ARDS pattern.\textsuperscript{9,29} Different characteristics on chest CT have been identified in survivors vs non-survivors,\textsuperscript{30,31} and post-mortem studies reported a highly variable degree of lung damage corresponding to these distinct phenotypes.\textsuperscript{18} Nonetheless, patients that were actually intubated and subjected to invasive MV typically had high respiratory system elastance, similar to that seen in conventional ARDS.\textsuperscript{13} Despite distinct respiratory system elastance, recruitability patterns, and clinical presentations,\textsuperscript{15,16,20} the current literature seems to agree that COVID-19 phenotypes are the extremes of a single disease entity as it progresses, characterised by distinct host responses to SARS-CoV-2 and different levels of lung damage. Moreover, it remains difficult to determine whether the increase in lung damage is associated with the severity of COVID-19 pneumonia per se or the type of noninvasive respiratory support strategy, which may result in P-SILI.

Therefore, an individualised approach to the management of respiratory support in COVID-19 pneumonia is required.\textsuperscript{32–34}

Mechanisms of P-SILI

Patients with COVID-19 can present with dyspnoea and hypoxaemia, which may require noninvasive or invasive respiratory support. Because of the shortage of ICU beds during the pandemic,\textsuperscript{35} a relatively high number of patients were treated with noninvasive respiratory support for many days even when their clinical status would have required
intubation and invasive MV, which may have led to P-SILI in COVID-19, four potential mechanisms of P-SILI may be suggested: (i) increased lung stress/strain, (ii) inhomogeneous distribution of ventilation, (iii) changes in lung perfusion, and (iv) patient–ventilator asynchronies during noninvasive positive-pressure ventilation (NPPV).

**Increased lung stress/strain**

Stress is defined as the distribution of forces applied per unit of lung area, represented by the transpulmonary pressure $\Delta P_{\text{alv}}$, i.e. the difference between alveolar pressure and pleural pressure, estimated by oesophageal pressure $P_{\text{oes}}$. Strain is defined as the change in volume divided by the initial lung volume (functional residual capacity). Lung stress depends on the difference between airway and pleural pressures, whereas strain assesses overstretch and is directly proportional to stress.

During spontaneous breathing, airway pressure is reduced when compared with invasive MV, but this does not reduce the risk of high transpulmonary pressures. In fact, $P_t$ is the distending pressure of the lung and during spontaneous breathing reflects the inspiratory effort. Under normal spontaneous breathing conditions, during the inspiratory phase, pleural pressure is uniformly decreased, while $P_t$ is uniformly increased. Importantly, at a given lung elastance, swings in $P_t$ are similar whether generated by spontaneous breathing or controlled MV. Under pathological conditions, greater inspiratory efforts are needed to obtain a similar tidal volume, and early spontaneous breathing effort yields higher negative pleural pressure and $P_t$, in the dependent and more caudal regions of the lung, resulting in inhomogeneous distribution of pressures and volume across the vertical gradient. When positive airway pressure is added to spontaneous breathing, as occurs during CPAP and NPPV, the resulting $P_t$ is higher, depending on positive-pressure and negative-oesophageal-pressure swings. In patients with COVID-19, increased efforts have been associated with higher inspiratory pressures and volumes and increased $P_t$, which may progress to barotrauma (pneumothorax and pneumomediastinum). Recent studies emphasised that inspiratory efforts may also cause P-SILI. During excessive expiratory muscle activity, the pleural pressure increases, leading to markedly reduced $P_t$ and collapse of most dependent lung regions and of peripheral airways. Thus, both high inspiratory and expiratory efforts may promote P-SILI, especially in lung diseases, which feature inhomogeneous distribution, such as COVID-19.

**Inhomogeneous distribution of gas**

Inspiratory pendelluft has been defined as intraparenchymal gas redistribution when the inspiratory effort has not yet induced an
inspiratory flow at the airway opening. It is caused by different regional time constants or dynamic pleural pressure variations in spontaneously breathing patients, yielding significant tidal recruitment and regional over-distension of dependent regions, independent of inspired tidal volume $V_t$. \cite{50} Experimental studies suggest that pendelluft may further worsen lung damage. \cite{4,5,50} However, limited evidence is available from the clinical setting. \cite{50,51} A recent observational study of patients without COVID-19 reported pendelluft in 40% of those ventilated with pressure support. \cite{50} Upon reduction of pressure support, gases were redistributed from the ventral to dorsal regions, doubling the baseline pendelluft volume and increasing the carbon dioxide concentration at the lowest pressure support. The higher the pendelluft volume is, the higher are the respiratory distress and work of breathing, increasing the risk of P-SILI.

### Changes in lung perfusion

In COVID-19 pneumonia, there are perfusion inhomogeneities (areas hyper- and hypo-perfused). \cite{52,53} During spontaneous breathing with increased inspiratory effort, pulmonary capillary vessels may be compressed, thus increasing the pulmonary resistance. The increase in trans-alveolar and trans-capillary pressures recruits previously collapsed capillary vessels and over-distends those located in healthy and ground-glass areas, which may lead to increased blood flow in damaged regions and alveolar-capillary membrane injury (Fig. 3). At end-inspiration, the right atrium pressure may decrease to a lower level (below 0.27 kPa), not allowing a compensatory increase in the cardiac output (Frank–Starling law). In normal physiological conditions, a net balance between fluids from pulmonary capillaries and the interstitium occurs, with a negative interstitial pressure, which becomes more negative at increased inspiratory stress. \cite{54,55,56,57}

Higher negative interstitial pressure yields greater trans-capillary and trans-alveolar pressure gradient, facilitating injury of lung endothelial and epithelial cells and increased capillary perfusion and blood volume, thus leading to lung damage and oedema. \cite{58,59,60}

Furthermore, the pressure measured in the oesophagus underestimates interstitial pressure of around 0.78–0.98 kPa at lower stress and 1.47–1.67 kPa at higher stress. \cite{55} Thus, during spontaneous breathing and noninvasive respiratory support, the interstitial pressure becomes progressively more negative at higher inspiratory stress and lower at lower inspiratory stress. \cite{60} In COVID-19, the presence of micro-thrombi with abnormal pulmonary circulation alters the $V/Q$ distribution; this is compounded by hyper-perfusion of poorly ventilated lung regions, which is likely the cause of hypoxaemia, and by hypoperfusion of normally and poorly aerated lung regions, leading to higher $V/Q$ and dead spacing. \cite{53} Noninvasive ventilatory support increases intrathoracic pressure, reduces venous return and end-diastolic volume both in the right and left cardiac cavities, improves cardiac contractility, and decreases both trans-alveolar and trans-capillary pressure, thus resulting in less pulmonary damage. \cite{53}

### Increased patient–ventilator asynchronies

Patient–ventilator asynchronies are associated with worse outcomes in mechanically ventilated patients. \cite{61,62} The most common asynchronies are ineffective effort and double triggering, which can be seen during NPPV. \cite{41} Under-assistance carries a risk of excessive load on the respiratory muscles while increasing the tidal volume. \cite{61} Stronger inspiratory efforts increase the $P_{pl}$ trans-vascular pressure gradient, and tidal recruitment, with pendelluft and regional over-distension, possibly worsening injury of dependent lung regions. \cite{5,42} Over-assistance is more difficult to detect, but may result in excessive inspiratory flow (exceeding the patient’s demand), thus resulting in ineffective effort, delayed or prolonged cycling, and reverse triggering. \cite{61} However, the threshold at which the combination of asynchronies and increased $P_{pl}$ may lead to P-SILI is not clearly defined.

### How can P-SILI be prevented?

In recent years, the concept of P-SILI in spontaneously breathing patients has evolved, engendering many efforts for detection of the underlying mechanisms and development of therapeutic strategies to minimise P-SILI. Noninvasive respiratory support strategies may fail because of a variety of reasons, including P-SILI itself, high work of breathing, inadequate sedation, decreased level of consciousness, deterioration of gas exchange, interface intolerance, or underlying conditions. \cite{55} A recent consensus of 39 experts concerning the management of COVID-19-related acute respiratory failure using a Delphi method suggested that high-flow nasal oxygen therapy (HFNOT) should be used in patients who are unable to maintain peripheral oxygen saturation ($SpO_2$) > 90% despite oxygen delivery through a Venturi mask, to avoid the need for tracheal intubation and invasive MV. NPPV (with PEEP) should be considered when the patient’s work of breathing increases progressively or in case of mixed (hypoaxemic and hypercapnic) respiratory failure. In case of altered mental status or haemodynamic instability, or failure of noninvasive respiratory support to maintain $SpO_2$ > 90%, tracheal intubation should be considered, with a lung-protective ventilation strategy: $V_T$ of 4–6 mL kg$^{-1}$ of predicted body weight, plateau pressure $P_{plat}$ < 2.94 kPa, driving pressure < 1.47 kPa, and individualised PEEP. Recruitment manoeuvres should be adopted in selected cases, whereas prone positioning can be safely and widely adopted. Following these recommendations, three approaches have been suggested to minimise P-SILI: (i) the limitation of tidal volume, (ii) the application of PEEP, and (iii) the reduction of spontaneous effort. All three of these strategies should be combined with appropriate sedation and metabolic control.

### Limitation of tidal volume

High tidal volume during noninvasive respiratory support has been associated with potential risk of lung damage and worse prognosis in patients without COVID-19. \cite{65} Therefore, $V_T$ should be limited during spontaneous breathing, although this is very difficult to monitor at the bedside, especially when using HFNOT or CPAP via helmet interfaces. \cite{65,66}

### Application of PEEP

In patients without COVID-19, the efficacy of PEEP in reducing P-SILI is explained by less atelectatic areas and peripheral airway collapse, more homogeneous distribution of inspiratory stress, reduced regional over-distension in dependent regions, and decreased pressures generated by spontaneous efforts. \cite{57} In a recent small RCT, PEEP did not affect pendelluft despite decreased ventilation heterogeneity. \cite{58} That is in contrast with a previous study, where PEEP reduced the amplitude of pendelluft. \cite{60} Higher PEEP levels increase end-expiratory lung volume, acting also on the curvature of the
diaphragm, possibly leading to less pulmonary and muscular injury. PEEP frequently improves gas exchange, which can potentially reduce respiratory drive. Given the existence of different degrees of lung damage in patients with COVID-19, those with lower elastance of the respiratory system and poor recruitability may present alveolar over-distension and increased PL, driving pressure, and plateau pressure with high PEEP levels. In contrast, using low PEEP levels, Pplat and PL remain within safe range, while driving pressure decreases. In patients with severe COVID-19 with increased respiratory system elastance (patchy-like ARDS), higher PEEP levels may be required. The common approach of applying high levels of PEEP may worsen the underlying microvascular injury.

Figure 2 summarises the effects on the lung during spontaneous breathing at ZEEP or CPAP, with the addition of pressure support in a representative patient with COVID-19. Patient self-inflicted lung injury in COVID-19 -

Reduction of spontaneous effort
Spontaneous breathing during AHRF and ARDS is not always encouraged because of the possible inhomogeneous distribution of pressures and regional volumes, which cannot be monitored with standard methods. Thus, patients at risk of P-SILI should be promptly recognised and managed through a two-pronged strategy: (i) adequate sedation, preferably assessed by a validated instrument, such as the Richmond Agitation Sedation Scale, to minimise respiratory drive; and (ii) appropriate use of neuromuscular blocking agents (NMBAs). COVID-19 pneumonia may present with a rapid onset of respiratory failure with initially preserved respiratory system elastance, reversible with few days of positive-pressure ventilation, and a slow moderate-to-severe form of ARDS, which may require longer duration of MV and rescue therapies, such as NMBAs. An observational study concluded that longer use of NMBA may protect patients with COVID-19 ARDS from barotrauma. NMBAs decrease chest wall elastance, reduce ventilator asynchronies, and improve lung recruitment and inflammation. However, as mentioned previously, COVID-19 may present at different stages of illness, which calls into question the propriety of using a one-size-fits-all strategy for all patients. Thus, more conservative
approaches should be recommended, but patients cannot be kept on passive MV for a long time and other approaches need to be pursued.

Figure 3 shows the differences in airway pressure; transpulmonary pressure; and oesophageal pressure of possible active, passive, and active plus support strategies in a representative patient with COVID-19.

Noninvasive respiratory supports and P-SILI

In most cases, noninvasive respiratory supports represent the first steps in the complex management of COVID-19 pneumonia. Gattinoni and colleagues claimed that early intubation and MV should be prioritised in severe COVID-19 pneumonia to prevent progression to more severe lung injury. However, this assertion was not based on strong scientific evidence and should be interpreted cautiously. Spontaneous breathing is known to be beneficial in mild-to-moderate cases of ARDS (non-COVID-19). Indeed, recent evidence raised concern on the need for early intubation of patients with COVID-19 because neither the time from ICU admission to intubation nor the use of high-flow oxygen support was associated with increased survival in patients with COVID-19. Additionally, in a cohort of 4643 patients with COVID-19, those who received NPPV or invasive MV on ICU admission had a higher severity of ARDS and higher 90 day mortality. A recent meta-analysis in a cohort of 8944 patients with COVID-19 reported no differences on all-cause mortality between patients who undergo early vs late intubation. Moreover, early intubation may be unavailable in some locations or unnecessary (if patient severity is low, the patient is well adapted to noninvasive respiratory support despite hypoxaemia, or because of clinical misjudgement). Large-scale provision of respiratory support is the main problem of the COVID-19 pandemic, as the number of available ICU beds is often lower than the number of patients requiring assistance. Noninvasive respiratory support, when possible, requires lower doses of sedatives, causes less delirium, facilitates mobilisation, and prevents secondary infections and ICU-acquired weakness. Interestingly, when compared with patients without COVID-19, patients with COVID-19 receiving noninvasive respiratory support were burdened by a two-fold higher risk of failure. The following paragraphs discuss the main noninvasive respiratory supports used in COVID-19 pneumonia: (i) conventional oxygen therapy (COT), (ii) HFNOT, (iii) CPAP, and (iv) NPPV.

Conventional oxygen therapy

Non-intubated patients with COVID-19 who receive various levels of oxygen support are still susceptible to sudden increases in $P_T$ with possible lung damage, favouring the development of pneumothorax or pneumomediastinum. COT is a readily available low-complexity first-line respiratory support modality, which requires less monitoring and
specialized staff. However, it may not be considered for patients with increased inspiratory effort.102

**High-flow nasal oxygen therapy**

Early in the COVID-19 pandemic, international scientific societies suggested that HFNOT should be avoided because of the potential risk of airborne exposure to SARS-CoV-2 when compared with COT.91–93 However, the rationale for this recommendation came from weak evidence. The correct use of face masks and other personal protective equipment (PPE) reduces exposure to droplets and aerosol amongst front-line healthcare workers,104 enough to make these strategies a viable first-step therapy before NPPV and invasive MV are considered. More recent guidelines suggested HFNOT as first-line oxygen therapy as long as staff are wearing adequate PPE.95 The WHO96 recommended strict monitoring (for 1 h) of patients at high risk of intubation by experienced personnel in case of respiratory deterioration. HFNOT, compared with COT, has not been associated with increased survival, even though it reduced the rate of invasive MV and ventilator-free days.96,97 Patients with COVID-19 who present reduced PaO2/FiO2 are at higher risk of noninvasive ventilation (NIV) failure, and the availability of devices that can provide HFNOT may be limited during this global health crisis. HFNOT may create a low level of PEEP, but it is unable to prevent P-SILI.91 Additionally, the use of HFNOT during prone positioning did not result in further improvement.95 Compared with CPAP, it has been associated with varying and controversial impacts on mortality (69% vs 36%100 and 16% vs 30%95). When compared with NPPV, HFNOT resulted in no significant difference in days free of respiratory support within 28 days.101 In patients with COVID-19 pneumonia with poorly recruitable lungs, oxygenation improvement with HFNOT may be associated with a higher and more stable inspired oxygen fraction.102 HFNOT is promising in patients with low severity98,102 but not in those who need more aggressive treatments, which may increase the risk of P-SILI.

**Continuous positive airway pressure**

Different interfaces have been proposed to deliver CPAP to patients with COVID-19 pneumonia. In a retrospective COVID-19 cohort, the use of face-mask CPAP resulted in improvement in one-third of patients, whereas half were ultimately intubated.103 CPAP has been associated with lower risk of death if applied within 7 days from hospital admission.104 In a small retrospective study, CPAP administered through a face-mask interface, compared with COT, avoided intubation from Day 7–14.105 In Europe, helmet CPAP has been considered the first choice for respiratory failure to minimise aerosol generation,106 although the importance of this concern is controversial, as noted previously. Both face-mask and helmet CPAP have been used in patients with COVID-19 to improve oxygenation. However, CPAP failure was frequently observed and associated with the severity of pneumonia on admission and higher inflammation.107 Helmet CPAP treatment presents a success rate greater than 60%108 and has been considered as a rescue therapy to improve survival.109 One RCT is ongoing to evaluate the impact of helmet CPAP in patients with COVID-19 pneumonia.110

**Noninvasive positive-pressure ventilation**

Compared with HFNOT, helmet NPPV did not reduce the number of days free of respiratory support within 28 days, but did reduce the rate of intubation.101 Large RCTs are required to better evaluate the advantages of using helmet NPPV in patients with COVID-19 pneumonia.

**Prompt recognition of patients at risk of noninvasive respiratory support failure**

The recognition of patients at risk for noninvasive respiratory support failure and tracheal intubation is of particular relevance in COVID-19.9 Noninvasive or invasive respiratory supports may temporarily improve clinical status and oxygenation without changing the natural course of the disease.54,101 This makes rapid recognition of patients who are at higher risk of disease progression—and thus of the optimal timing for intubation—quite challenging9; however, the literature seems to agree that patients who are at high risk of noninvasive respiratory support failure should be promptly identified and tracheally intubated.72 Several scores have been proposed for AHRF, but none has been validated yet in COVID-19. A useful method to apply at bedside for identifying patients with AHRF at risk of noninvasive support failure is the heart rate, acidosis, consciousness, oxygenation, and respiratory rate (HACOR) score, currently under investigation in the specific setting of COVID-19.112 This score includes heart rate, pHa, Glasgow Coma Scale (GCS), PaO2/FiO2, and ventilatory frequency, and should be calculated after 1 h of noninvasive support. In case of a HACOR score >5, intubation and MV should be provided (specificity 90% and sensitivity 72%).113 Other scores have been proposed in the specific setting of COVID-19 (e.g. the ‘COVID-19 score’, which includes evaluation of consciousness, oxygenation, vital capacity, ionotropic support, and lung damage on plain chest radiograph or CT scan),114 but again, none has been validated. In one study, lung ultrasound was able to detect patients with COVID-19 who would benefit from tracheal intubation.115 Another score to predict failure of noninvasive respiratory strategies has been developed116 and externally validated. The score includes age, number of comorbidities, respiratory rate oxygenation index (ROX), GCS, and use of vasopressors on the first day of noninvasive respiratory support as independent predictors of failure. A retrospective observational study suggested chest radiograph findings as possible predictors of intubation. The COVID-19 Opacification Rating Score (CORS) was developed by assigning 1 point to each of the 12 lung zones of interest, in which an opacity was observed. This score was predictive of intubation at 24 h, <48 h, and during admission (all P<0.001).117 The Pneumonia Severity Score has also been recognised as an independent predictor of intubation in COVID-19 (P<0.001).118 Higher VT alone is also a good predictor of need for intubation and noninvasive support failure. However, it is very hard to control and monitor VT during noninvasive support, and the main driver of larger VT is the respiratory drive.56,119 As theorised two decades ago, the higher the dead space and minute ventilation, the greater the severity of ARDS.120 The use of heated and humidified oxygen at high-flow rates, as in HFNOT, can reduce the dead space and yield survival benefits.15 For patients treated with HFNOT, a ROX index (SpO2/FiO2/ventilatory frequency) <2.85, <3.47, and <3.85 indicates need for intubation after 2, 6, and 12 h, respectively.121 A single multicentre observational study identified the Sequential Organ Failure Assessment (SOFA) score and the ROX index as predictive tools for respiratory failure and tracheal intubation during HFNOT in COVID-19.122 Moreover, in the early stage, when elastance is relatively preserved, ventilatory
Conclusions

The concept of P-SILI has been widely investigated in recent years, even though controversies persist regarding its mechanisms. To minimise the risk of P-SILI, intensivists should better understand the pathophysiology of this condition to optimise the modality of noninvasive respiratory support provided to patients with COVID-19, and determine the optimal timing of intubation for those in whom noninvasive support fails.

Authors’ contributions

Conception: DB, PP, PRMR

Literature review: DB, PP, PRMR

Drafting of paper: DB, PP, PRMR
Review and approval of paper: all authors

**Declarations of interest**
The authors declare that they have no conflicts of interest.

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