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REVIEW

Barotrauma during non-invasive ventilation for acute respiratory distress syndrome caused by COVID-19: a balance between risks and benefits

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on behalf of Gemelli Against COVID 2019*

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Abstract

Ventilatory support is vital for the management of severe forms of COVID-19. Non-invasive ventilation is often used in patients who do not meet criteria for intubation or when invasive ventilation is not available, especially in a pandemic when resources are limited. Despite non-invasive ventilation providing effective respiratory support for some forms of acute respiratory failure, data about its effectiveness in patients with viral-related pneumonia are inconclusive. Acute respiratory distress syndrome caused by severe acute respiratory syndrome-coronavirus 2 infection causes life-threatening respiratory failure, weakening the lung parenchyma and increasing the risk of barotrauma. Pulmonary barotrauma results from positive pressure ventilation leading to elevated transalveolar pressure, and in turn to alveolar rupture and leakage of air into the extra-alveolar tissue.

This article reviews the literature regarding the use of non-invasive ventilation in patients with acute respiratory failure associated with COVID-19 and other epidemic or pandemic viral infections and the related risk of barotrauma.

Key words: Acute respiratory distress syndrome; Barotrauma; COVID-19; Non-invasive ventilation; Severe acute respiratory syndrome-coronavirus 2

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Introduction

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with a wide spectrum of clinical severity.

The significant limitations in resources caused by the pandemic forced physicians across the world to deal with some unique challenges, not least the shortage of places in intensive care units. It is not clear whether non-invasive ventilation is effective or not in patients with viral-related acute respiratory distress syndrome (Ñamendys-Silva, 2020), but with the worsening of the pandemic, all available options for ventilatory support needed to be considered. As a result, clinicians started to use non-invasive ventilation as a second-line therapy for patients who did not match criteria for intubation. This review uses the term non-invasive ventilation to encompass both pressure support ventilation and continuous positive airway pressure. The latter remains the main modality of treatment for COVID-19 patients. It provides positive end-expiratory pressure that increases alveolar recruitment, and consequently improves oxygenation. In turn, it may induce pulmonary barotrauma, especially when adding a pressure of support (Nava et al, 2011). Indeed, inappropriately elevated transalveolar pressure may lead to intra-alveolar rupture, with air leaking from the lungs and dissecting towards tissues. Even though barotrauma is less common during non-invasive ventilation, patients with COVID-19 often develop acute respiratory distress syndrome, which is a major risk factor for hyperinflation and alveolar rupture because of a significant reduction in lung compliance.

Any patient with acute respiratory distress syndrome requires personalised management, along with a multidisciplinary approach taking into account the risks and benefits of ventilation, to prevent the therapy from becoming a potential threat.

During previous pandemics and epidemics that caused hypoxaemic respiratory failure – such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and H1N1 – clinicians tried non-invasive ventilation as an alternative to invasive mechanical ventilation for ventilatory support, but the evidence for its efficacy and safety is not uniform, and data are still very variable.

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Use and side effects of non-invasive ventilation in previous viral pandemics

During previous viral pandemics and epidemics that caused similar patterns of hypoxaemic respiratory failure and acute respiratory distress syndrome, non-invasive ventilation was used to provide ventilatory support for mild-to-moderate cases, with uneven results in terms of efficacy. Table 1 summarises the results of studies assessing the role of non-invasive ventilation in acute respiratory failure associated with viral pneumonia.

Table 1. Studies assessing the role of non-invasive ventilation in acute respiratory failure associated with viral pneumonia

Reference	Disease	Type of study	No. of subjects	Results and conclusions
Yam et al (2005)	Severe acute respiratory syndrome	Review	-	Non-invasive ventilation with continuous positive airway pressure of 4–10 cmH_2O or pressure of support <15 cmH_2O and expiratory positive airway pressure 4–6 cmH_2O reduced the intubation rate
Chen et al (2003)	Severe acute respiratory syndrome	Observational retrospective	25	Non-invasive ventilation should be used as an alternative to endotracheal intubation in the early phase of acute respiratory failure related to severe acute respiratory syndrome, and it should be started as soon as possible
Li et al (2003)	Severe acute respiratory syndrome	Observational retrospective	105	Non-invasive ventilation was safe and effective for the treatment of severe acute respiratory syndrome and decreased the chances of invasive mechanical ventilation being needed
Cheung et al (2004)	Severe acute respiratory syndrome	Observational retrospective	20	Non-invasive ventilation was effective in the treatment of acute respiratory failure caused by severe acute respiratory syndrome, and did not expose healthcare workers to a significant risk of contracting severe acute respiratory syndrome
Yam et al (2003)	Severe acute respiratory syndrome	Observational retrospective	493	Compared to invasive mechanical ventilation, non-invasive ventilation was associated with reduced intubation rate and mortality if used as initial ventilatory support
Kumar et al (2009)	H1N1	Multicentre prospective observational	168	Non-invasive ventilation failed in up to 85% of patients with acute respiratory failure caused by H1N1 influenza
Arabi et al (2020)	Severe viral pneumonia	Review	-	Non-invasive ventilation in hypoxaemic patients with acute respiratory failure caused by severe viral pneumonia was associated with a high likelihood of transition to invasive mechanical ventilation
Rodriguez et al (2017)	Influenza	Observational retrospective	806	Non-invasive ventilation failed in 56.8% of patients with acute respiratory failure caused by influenza
Alraddadi et al (2019)	Middle East respiratory syndrome	Multicentre observational retrospective	105	92.4% of patients with acute respiratory failure caused by Middle East respiratory syndrome who initially underwent non-invasive ventilation subsequently required intubation
Duca et al (2020)	COVID-19	Retrospective observational	99	Non-invasive ventilation helped to reduce the mortality rate among patients who cannot undergo intubation
Schünemann et al (2020)	COVID-19	Review	-	Non-invasive ventilation may have similar effects to invasive mechanical ventilation and probably reduced mortality, but may increase the risk of transmission to healthcare workers
Winck et al (2020)	COVID-19	Review	-	Non-invasive ventilation may work in patients with moderate acute respiratory distress syndrome and a coupled strategy alternating non-invasive ventilation and high flow nasal cannula may be beneficial

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The most promising evidence came from the SARS epidemic, when several studies showed that early application of non-invasive ventilation was effective in improving clinical conditions and in reducing the intubation rate (Chen et al, 2003; Li et al, 2003; Yam et al, 2003, 2005; Zhong et al, 2003; Cheung et al, 2004; Benditt, 2009).

Different results arose during the MERS pandemic, when non-invasive ventilation did not seem to be significantly helpful in reducing the risk of intubation (Alraddadi et al, 2019), as well as in the H1N1 pandemic, when a study showed that non-invasive ventilation failed in up to 85% of 168 critically ill patients (Kumar et al, 2009).

More recently, a multicentre observational study of 1898 critically ill patients with acute respiratory failure caused by influenza aimed to identify the profile of patients with risk factors for non-invasive ventilation failure. Non-invasive ventilation failed in 56.8% of 806 patients who received it, and intensive care unit mortality was higher in those who failed non-invasive ventilation (38.4%) (Rodríguez et al, 2017).

As for side effects resulting from the use of non-invasive ventilation in such conditions, barotrauma does not seem to have had a huge impact, according to the literature. A review of ventilatory support used in intensive care units to treat SARS-induced acute respiratory failure reported the incidence of non-invasive ventilation-induced barotrauma as between 6.6% and 15% (Yam et al, 2003). A similar study, summarising the best management strategies for patients with SARS in intensive care units, found that the incidence of barotrauma caused by non-invasive ventilation or invasive mechanical ventilation ranged from 20–30%. This incidence is higher than that seen in patients with other forms of acute respiratory distress syndrome, although the exact underlying mechanism could not be clarified (Joynt and Yap, 2004). With a study conducted on 120 patients with SARS – 28 of whom were treated with non-invasive ventilation – barotrauma was detected in seven individuals (six under non-invasive ventilation and one under no ventilatory support). Among those receiving non-invasive ventilation, barotrauma presented with severe cough and acute, life-threatening hypoxaemia, even though the pressures used in these patients were the same as those used in patients who did not experience any complications (Han et al, 2004).

Use and side effects of non-invasive ventilation in patients with COVID-19

With the outbreak of the COVID-19 pandemic, the scientific community tried to assess the efficacy of every therapeutic drug and alternatives for ventilatory support.

Despite the high rate of failure considered as death or need for intubation, non-invasive ventilation seems to be useful in reducing the mortality rate among patients who cannot be treated invasively by orotracheal intubation (Duca et al, 2020). A systematic review commissioned by the World Health Organization shows that non-invasive ventilation is more effective than high flow nasal cannula oxygenation, it may have similar effects as invasive mechanical ventilation, and it reduces mortality compared with no invasive mechanical ventilation in patients with COVID-19 (Schünemann et al, 2020). In particular, non-invasive ventilation seems useful in patients with mild–moderate COVID-19-related acute respiratory distress syndrome (arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) 100–200) with a window of opportunity of 1–2 hours from the start of non-invasive ventilation. If PaO_2/FiO_2 significantly increases and the respiratory rate decreases with a relatively low exhaled tidal volume, the non-invasive strategy could be considered effective and intubation delayed (Winck et al, 2020). A multicentre trial by Grieco et al (2021), including 109 patients with COVID-19 and moderate to severe hypoxaemic respiratory failure ($PaO_2/FiO_2 \leq 200$), confirmed the superiority of non-invasive ventilation to high flow nasal cannula oxygenation, since it was associated with a significantly lower rate of endotracheal intubation and a significantly higher median number of days free of invasive mechanical ventilation within 28 days since non-invasive ventilation was started.

Interestingly, pneumothorax and pneumomediastinum may occur also as a primary spontaneous complication in patients with COVID-19 who are not undergoing non-invasive ventilation or invasive mechanical ventilation. This seems to represent a peculiarity of SARS-CoV-2 infection, since this was not reported during other viral epidemics.

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Quincho-Lopez et al (2020) presented two cases of patients with COVID-19 who developed primary pneumothorax and pneumomediastinum, and reviewed the available literature. They found 20 cases already published, 15 spontaneous and five occurring during invasive mechanical ventilation or non-invasive ventilation. The authors felt that the most plausible aetiopathogenetic hypothesis for these spontaneous cases is rupture of the alveolar wall caused by the increased pressure difference between the alveolus and the interstitium during COVID-19-related pneumonia. Mallick et al (2020) reported a case series of three patients with primary spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema as the first presentation of COVID-19, none having a history of previous lung disease. Interestingly, all patients had high levels of inflammatory markers, suggesting that the mechanism could be an inflammation-induced pulmonary injury associated with an air leak within the pleural cavity.

In a large case series from the UK, of 61 patients with COVID-19 who had pneumothorax and/or pneumomediastinum, 33% of these complications were spontaneous, while in 67% they occurred during continuous positive airway pressure (three patients) or invasive mechanical ventilation being used to treat severe COVID-19 (38 patients) (Martinelli et al, 2020).

In fact, mechanical ventilation can further facilitate pulmonary barotrauma since elevation of the transalveolar pressure leads to alveolar rupture and leakage of air into the extra-alveolar tissue (Kallet and Diaz, 2009; Carteaux et al, 2016). The risk of barotrauma is significantly higher in the presence of acute respiratory distress syndrome, since the involvement of alveoli units is not uniform. Normal alveoli receive a greater percentage of the tidal volume, which leads to preferential ventilation and ultimately overdistention to accommodate the larger tidal volume (Diaz and Heller, 2020). In addition, an autopsy series of 10 patients with SARS-CoV-2 showed substantial epithelial damage within the alveoli, which is consistent with the hypothesis that the excess release of cytokines characterising severe cases of COVID-19 may result in the release of air within the damaged alveoli, to cause the so-called 'Macklin effect'. This consists of the development of a linear collection of air along with the bronchovascular ramifications, which protracts towards the hilum and can provoke pneumomediastinum and pneumothorax (Vobruba et al, 2013; Murayama and Gibo, 2014; Ye et al, 2020; Kangas-Dick et al, 2021).

The majority of studies assessing the incidence of barotrauma during mechanical ventilation in patients with severe COVID-19 are retrospective, often single centre, cohort studies performed in intensive care units (**Table 2**).

Few data are available about patients treated with non-invasive ventilation in whom barotrauma occurred – this was seen in 4.7–8.1% of cases (Kahn et al, 2021; Kalpakam et al, 2021; Rajdev et al, 2021). Only Kahn et al (2021) assessed mortality, but their patients were also treated with invasive mechanical ventilation, and they did not find any association between mortality and barotrauma.

Much more literature is available on COVID-19 patients treated with invasive mechanical ventilation. The incidence of barotrauma was higher in this population (7.1–40%), despite following recommendations for lung protective ventilation (Lemmers et al, 2020; McGuinness et al, 2020; Belletti et al, 2021; Edwards et al, 2021; Elsaaran et al, 2021; Kahn et al, 2021; Kalpakam et al, 2021; Protti et al, 2021; Rajdev et al, 2021; Sami and Sereshti, 2021; Udi et al, 2021). Mortality was assessed in four studies: McGuinness et al (2020) and Belletti et al (2021) showed an association between barotrauma and mortality, while Lemmers et al (2020) and Kahn et al (2021) did not.

McGuinness et al (2020) retrospectively assessed the rate of barotrauma in three different cohorts of patients undergoing invasive mechanical ventilation: 601 patients with severe COVID-19, 196 with neither COVID-19 nor acute respiratory distress syndrome and an historical group of 285 with non-COVID-19 acute respiratory distress syndrome. Patients with COVID-19 showed a significantly higher rate of barotrauma (15% in the first group, 0.5% in the second and 10% in the third). A lower incidence of barotrauma in acute respiratory distress syndrome not associated with COVID-19 (1.9–6.5%) was reported from other authors (Anzueto et al, 2004; Lemmers et al, 2020). This could be related to distinct characteristics of acute respiratory distress syndrome caused by SARS-CoV-2 infection (Marini et al, 2020). COVID-19 is considered to cause a unique form of lung parenchymal injury, as also demonstrated by the unpredictable clinical course. Despite poor

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Table 2. Studies on barotrauma during mechanical ventilation in patients with COVID-19				
Reference	**Type of study**	**Incidence of barotrauma**	**Type of ventilation**	**Association with mortality**
McGuinness et al (2020)	Retrospective, single centre	89/601 (14.8%)	Invasive mechanical ventilation	*P*=0.03
Lemmers et al (2020)	Retrospective, multicentre	23/169 (13.6%)	Invasive mechanical ventilation	Not significant
Edwards et al (2021)	Retrospective, single centre	13/139 (9.4%)	Invasive mechanical ventilation	Not assessed
Protti et al (2021)	Retrospective, multicentre	145/2041 (7.1%)	Invasive mechanical ventilation	Not assessed
Elsaaran et al (2021)	Retrospective, single centre	54/343 (15.4%)	Invasive mechanical ventilation	Not assessed
Sami and Sereshti (2021)	Retrospective, single centre	13/103 (12.6%)	Invasive mechanical ventilation	Not assessed
Kalpakam et al (2021)	Retrospective, single centre	18/163 (11%) 20/247 (8.1%)	Invasive mechanical ventilation Non-invasive ventilation	Not assessed
Rajdev et al (2021)	Retrospective, single centre	21/121 (17.3%) 11/232 (4.7%)	Invasive mechanical ventilation Non-invasive ventilation	Not assessed
Belletti et al (2021)	Retrospective, single centre	28/116 (24.1%)	Invasive mechanical ventilation	*P*=0.04
Kahn et al (2021)	Retrospective, single centre	13/39 (33%) 3/36 (8%)	Invasive mechanical ventilation Non-invasive ventilation	Not significant
Udi et al (2021)	Retrospective, single centre	8/20 (40%)	Invasive mechanical ventilation	Not assessed

oxygenation and ground-glass opacities on computed tomography scans, in the first stage of the disease patients are not usually dyspnoeic and the lungs maintain good compliance with low elastance, low lung weight and poor response to positive end-expiratory pressure. Although many individuals stabilise in this phase, others suddenly progress to a more severe condition characterised by low compliance with high elastance, high lung weight and a good response to positive end-expiratory pressure. A possible reason for such a fast and unpredictable evolution could be endothelial damage causing the loss of normal pulmonary vasoconstriction, thus leading to ventilation/perfusion mismatch and severe hypoxaemia. At this stage, patients usually experience deep dyspnoea, the respiratory rate rises, and the strong inspiratory efforts increase tissue stress and pulmonary transvascular pressure, vascular flows, and fluid leakage (Marini and Gattinoni, 2020). All these changes increase the risk of barotrauma in patients with COVID-19.

Conclusions

Based on the available literature, it seems rational to perform a trial of non-invasive ventilation in COVID-19 patients with moderate acute respiratory distress syndrome (PaO_2/FiO_2 100–200) with a window of opportunity of 1–2 hours. If PaO_2/FiO_2 significantly increases and the respiratory rate decreases, the non-invasive strategy can be continued and intubation delayed. In case of failure, intubation should be performed as soon as possible, if resources are available and an invasive strategy is not contraindicated.

Patients with acute respiratory failure caused by SARS-CoV-2 infection are at high risk of either spontaneous or iatrogenic pneumothorax or pneumomediastinum. The high level of thoracopulmonary stress, along with the excess inflammation that weakens the lung parenchyma, the pressure generated by non-invasive ventilation and the non-homogeneous distribution of ventilation in acute respiratory distress syndrome, predisposes patients with COVID-19 pneumonia to a significant risk of barotrauma.

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Key points

- Non-invasive ventilation should be the first attempt of respiratory support in COVID-19 patients with moderate acute respiratory distress syndrome (arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) 100–200).
- If PaO_2/FiO_2 does not significantly increase within 1–2 hours of starting non-invasive ventilation, intubation and mechanical ventilation should not be delayed.
- Patients with acute respiratory distress syndrome caused by COVID-19 are at high risk of either spontaneous or iatrogenic barotrauma.
- Patients with acute respiratory distress syndrome caused by COVID-19 need strict monitoring and, in case of sudden deterioration of respiratory function, barotrauma should be considered.

The delicate balance between risk and benefits means that the non-invasive ventilation strategy in acute respiratory distress syndrome associated to SARS-CoV-2 infection needs to be carefully considered, and the patient should be constantly monitored.

In case of sudden deterioration of the respiratory function or occurrence of clinical symptoms or signs suggestive of barotrauma, a chest X-ray should be promptly performed. Chest tube drainage successfully treats such complications in most cases. Ventilatory support with non-invasive ventilation or invasive mechanical ventilation can provide a vital period for recovery in these patients, and the authors believe that the risk of barotrauma must not prevent clinicians from using these supports.

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Conflicts of interest
The authors declare that they have no conflict of interests.

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