COVID-19 associated spontaneous barotrauma: a literature review [version 1; peer review: awaiting peer review]

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Abstract

Reports of spontaneous pneumothorax and pneumomediastinum as a complication of coronavirus disease (COVID-19) have been increasing. COVID-19 causes inflammatory disease mainly affecting the respiratory system. Severity varies from asymptomatic pulmonary findings on imaging to acute respiratory distress syndrome along with pleural effusions, consolidations and spontaneous pneumomediastinum and pneumothorax.

The aim of this paper was to review the literature to explore the association between pneumomediastinum/pneumothorax and COVID-19 respiratory disease, both in patients on ventilators and without ventilators, on a spontaneous basis. To this end, we conducted a comprehensive online literature search using PubMed for articles published with the key words of ‘spontaneous pneumothorax’, ‘pneumomediastinum’ and ‘COVID-19’. Further references were obtained through cross-referencing the bibliographies cited in each publication.

We found that spontaneous barotrauma is one of the complications associated with COVID-19 infection and has been observed in patients with and without mechanical ventilation. The process of pneumomediastinum and pneumothorax development is not well understood, especially in patients without underlying lung disease or on mechanical ventilation. We identified various factors that predispose to barotrauma. First, the direct infection of the Type I and Type II pneumocytes by the virus. Second, the pressure gradient between the alveoli and the pulmonary interstitium. Finally, barotrauma can occur secondary to the severe inflammatory response from the COVID-19-related cytokine storm. These conditions are all associated with severe alveolar damage and rupture of the alveolar wall that can produce pneumomediastinum and pneumothorax, both in mechanically ventilated patients and non-ventilated patients.
COVID-19 is associated complications result in prolonged mechanical ventilation and length of stay, as well as overall increase in morbidity and mortality. Spontaneous pneumothorax and pneumomediastinum are two serious complications. Education regarding the adjustment of ventilation settings in the ventilator-dependent COVID-19 patient may perhaps offset the iatrogenic component of barotrauma seen in some such patients.

Keywords
COVID-19, Barotrauma, Pneumothorax, Pneumomediastinum

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Introduction
COVID-19 is a disease caused by a novel coronavirus (SARS-CoV-2), which was first identified in December 2019 in Wuhan China. The World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern at the end of January 2020 and a pandemic on March 11, 2020.1 The presentation of COVID-19 is quite variable, which can involve multiple organ systems, ranging from asymptomatic carriers to severe disease and death. However, over the course of the disease most patients present with fever, chills, cough, and shortness of breath, new loss of taste and/or smell, nausea, vomiting and diarrhea. However, it has been reported that this entity causes mainly respiratory disease. In some severe cases, patients will require endotracheal intubation and mechanical ventilation (MV). Pneumothorax and pneumomediastinum are known complications of MV. However, there have been reports of patients infected with SARS-CoV-2 that have developed pneumothorax, pneumomediastinum or both without any barotrauma. Here, we present a literature review of the potential mechanisms that cause spontaneous pneumothorax and/or pneumomediastinum in COVID-19 patients.

We conducted a comprehensive online literature search using PubMed for articles published with the key words of ‘spontaneous pneumothorax’, ‘pneumomediastinum’ and ‘COVID-19’. Further references were obtained through cross-referencing the bibliographies cited in each publication.

Background to COVID-19
The COVID-19 pandemic has changed our world. Scientists identified the novel coronavirus as COVID-19, which was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).1 The WHO had confirmed more than 80,000 cases by the beginning of March 2020 in China and approximately 70 countries around the world were also affected. At the present time, 218 countries and territories across the globe have been infected by the COVID-19 virus.1 As of May 2021, the United States leads the world with over 32 million confirmed cases worldwide and over 570,980 deaths currently reported according to the Centers for Disease Control and Prevention (CDC).2

The presentation of COVID-19 is variable and can involve multiple organ systems, with patients ranging from asymptomatic carriers to severe disease and death. However, over the course of the disease most patients present with fever, chills, cough, and shortness of breath, new loss of taste and/or smell, nausea, vomiting and diarrhea. The median incubation period time is 4-5 days from the exposure to the onset of symptoms.3

Radiologic characteristics of COVID-19
It has been reported that COVID-19 mainly causes respiratory disease, as observed in a large cohort study in China that included more than 44,000 patients diagnosed with the disease.4 As such, it is important to mention some important radiologic characteristics that may aid in the determination of disease severity. Chest radiography findings consist of isolated ground glass opacities, pleural effusion, pneumothorax, pneumomediastinum, and in more advanced disease findings are consistent with severe acute respiratory distress syndrome.4 In addition, computed tomography (CT) of the chest serves as an adjunct in diagnosing and assessing the severity of COVID-19, especially when chest x-rays have been reported as normal early in the course of the disease.5 CT chest imaging typically shows nonspecific bilateral peripheral ground glass opacities.5,6 This is quite non-specific and can be seen in many different pulmonary diseases for which a detailed clinical assessment is needed. Although CT imaging is of valid clinical utility, CT alone is not recommended nor for screening or diagnosis of COVID-19.5

Barotrauma and COVID-19
As respiratory disease is the most common presentation in patients with COVID-19, in some severe cases, patients require endotracheal intubation and MV. Pneumothorax and pneumomediastinum are known complications of MV.7 Figure 1 shows extensive barotrauma with pneumomediastinum and extensive subcutaneous emphysema in a COVID-19 patient on mechanical ventilation who has ground-glass peripheral infiltrates shown both on chest radiograph (CXR) and CT scan. There have been reports of patients infected with SARS-CoV-2 that have developed pneumothorax, pneumomediastinum or both, without any barotrauma.7-9

Pneumothorax can be classified into spontaneous, traumatic or iatrogenic. Iatrogenic pneumothorax is most related to MV.10 Pneumothorax is rare in intubated patients with normal lungs and most patients with MV associated pneumothorax are reported to have underlying lung diseases (obstructive, interstitial and acute respiratory distress syndrome [ARDS]).11 Tension pneumothorax accounts for approximately 30-97% of all pneumothoraxes in patients with MV. It is important to mention that the presence of pneumothorax has been identified as an independent predictor of mortality in MV with a rate of 46-77%. In addition, it has been associated with increased overall length of hospital stay.12
The classic risk factors for developing spontaneous pneumothorax regardless of COVID-19 status include tobacco smoking, age, short stature, male sex, low body mass index, prolong cough, strenuous exercise and some chronic pulmonary disease such as chronic obstructive pulmonary disease.

The etiology of pneumothorax in COVID-19 is not fully understood. It has been observed in patients with and without MV and, moreover, without significant pulmonary disease burden. The development of spontaneous pneumothorax and pneumomediastinum in COVID-19 patients who do not require MV is rare, and it has been reported in approximately 1-2% of patients with COVID-19 vs 5.9-8% in mechanically ventilated patients, and it can also occur during disease progression. However, if present, it may indicate a worse overall prognosis.

Causes of barotrauma in COVID-19 patients

The causes of pneumothorax in patients with MV may be related to increased peak airway pressure, high positive end expiratory pressures (PEEP), and high tidal volumes. Figure 2 demonstrates a COVID-19 patient on MV showing extensive pneumomediastinum and resolving pneumothorax post chest tube placement.

Spontaneous barotrauma in the absence of MV is a rare but serious complication in COVID-19 patients, however, the etiology of such barotrauma in the absence of ventilatory support is not completely understood. Some authors report that...
COVID-19 pneumonia may be associated with severe alveolar damage and rupture of the alveolar wall due to pressure gradient between the alveolus and the pulmonary interstitium.13

Another proposed mechanism for the cause of pneumothorax in patients with COVID-19 could be related to direct alveolar membrane damage by the virus infecting pneumocytes I and II, leading to alveolar rupture.15 Pathological characteristics of postmortem biopsies of patients who died from SARS-CoV-2 reported pronounced desquamation of pneumocytes and hyaline membrane formation, which are consistent with a diagnosis of ARDS, acute fibrinous pneumonia, and organizing pneumonia.16,17

Spontaneous pneumomediastinum has been observed in patients with mild or severe COVID-19 infection even without MV. Figure 3 demonstrates spontaneous pneumomediastinum in a non-mechanically ventilated COVID-19 positive patient, showing peripheral ground glass infiltrates. Chu et al reported cases of patients with confirmed SARS-1 and spontaneous development of pneumomediastinum with and without MV in 2004.18 It is important for clinicians to recognize the development of iatrogenic and spontaneous barotrauma in COVID-19 patients early because it may result in rapid clinical and respiratory deterioration leading to increased oxygen requirements and worsening barotrauma that can be lethal.

Cases of barotrauma in the literature
Several reports of the development of spontaneous pneumothorax in COVID-19 patients have been published in the literature. Aiolfi et al.19 described a case of a 60-year-old male patient with no previous pulmonary disease and COVID-19 infection that developed right side pneumothorax combined with pneumomediastinum and subcutaneous emphysema after approximately 20 days of the initial infection. He was started on oxygen therapy initially, but the patient failed to improve. A repeat CT demonstrated findings of barotrauma, and subsequently patient was placed on high flow nasal cannula (HFNC) along with steroids, broad spectrum antibiotics and antivirals, without MV. The patient recovered successfully approximately 3 weeks later. In another paper, Changyu et al.20 reported a 38-year-old male patient with no past medical history or smoking history admitted for COVID-19 who developed exertional angina with palpitations along with respiratory wheezing on day 11 of admission. CT of the chest revealed multiple ground-glass opacities with bilateral parenchymal consolidations, interlobular septal thickening as well as spontaneous pneumomediastinum and subcutaneous emphysema. The patient was not on MV and continued to receive treatment with supplemental oxygen, antitussives and bronchodilators. By day 25, the patient recovered, symptoms subsided and his breathing returned to normal. Chest CT revealed resolution of previous pneumomediastinum and a reduction of parenchymal consolidation with pulmonary fibrosis and pneumatocele in the inferior left lower lobe. The patient was discharged on day 30 with follow up in the outpatient setting.

Sun et al.21 described a young patient with COVID-19 pneumonia that developed mediastinal emphysema, a giant bulla in the left lung and multiple bullae in the sub pleural lung zones. This patient was not ventilated and placed on HFNC. Patient had no significant relevant medical or smoking history documented. Extensive barotrauma was also reported by Wang et al.22 in a young patient in whom a CT scan of the chest showed pneumatoasis extending from the mediastinal pericardium to the bilateral cervical soft tissue space. This patient clinically deteriorated despite immediate noninvasive ventilation and intensive care unit supportive care. In our institution, we also had a 37-year-old patient who was admitted for a second admission for respiratory distress related to COVID-19 infection who developed giant bullae over time in both his lung fields during his hospital stay. Figure 4 shows CXR and coronal chest CT scan of this patient demonstrating

Figure 3. Chest radiograph (A) and axial (B) and coronal (C) reformatted images of a non-contrast CT scan of the chest in a young patient who presented to the emergency room with shortness of breath, showing subtle spontaneous pneumomediastinum (straight arrows) and bilateral airspace opacities suggestive of lung infiltrates.
a large bullae involving the right middle lung zone, which eventually got smaller over the following days but a new bulla appeared in the left lingular region.

In a most recent retrospective study by McGuinness et al., the authors reviewed clinical and imaging data of patients seen between March 1, 2020, and April 6, 2020, who tested positive for COVID-19 and experienced barotrauma associated with invasive MV and were compared with patients without COVID-19 infection during the same period. A total of 601 patients with COVID-19 infection underwent invasive MV. They reported that 15% of patients had one or more barotrauma events with a total of 145 barotrauma events (95% confidence interval [CI]: 21%, 28%). During the same period, 196 patients without COVID-19 infection with invasive MV had one barotrauma event (0.5%; 95% CI: 0%, 3%; \( P < .001 \) vs the group with COVID-19 infection). Of 285 patients with ARDS on invasive MV during the previous four years, 10% of patients had 31 barotrauma events, with an overall barotrauma rate of 11% (95% CI: 8%, 15%; \( P < .001 \) vs the group with COVID-19 infection). The authors concluded that patients with COVID-19 infection and invasive MV had a higher rate of barotrauma than patients with ARDS and patients without COVID-19 infection. In addition, barotrauma is an independent risk factor for death in COVID-19 (odds ratio = 2.2; \( P = .03 \)) and is associated with a longer hospital stay (odds ratio = 0.92; \( P < .001 \)).

In contrast, Chung et al. in a retrospective study from China, reviewed CT chest scans of 21 symptomatic patients infected with COVID-19. Typical CT findings included bilateral ground glass opacities, consolidative pulmonary opacities with variable morphology, notably pneumothorax or pneumomediastinum lesions were not observed. This emphasizes the point that spontaneous barotrauma is not a common but a rare manifestation of COVID-19. The above study was done with only 21 COVID-19 patients and generally lacks the sample size required for a solid assessment of rare but dangerous barotrauma complication.

Pneumothorax is a medical emergency and a disease with a high mortality rate. It requires careful awareness, prompt recognition and immediate intervention to reduce morbidity and mortality. Most patients with pneumothorax related to mechanical ventilation have underlying pulmonary diseases, the most common of which are pneumonia, ARDS and obstructive lung disease. Pneumothorax/pneumomediastinum may have subtle or atypical features on plain radiography and may be missed early on. Most of the ventilated patients with a pneumothorax require immediate treatment with tube thoracostomy because of the high risk of progression to a tension pneumothorax. Small-bore catheters are now preferred in most ventilated patients. Management of non-ventilated barotrauma patient varies case by case but is generally conservative.

In a study by Housman et al. the authors hypothesized that COVID-19 patients requiring mechanical ventilation may develop significant pneumomediastinum and subcutaneous emphysema without associated pneumothorax. The study included 171 patients who tested positive for COVID-10 requiring endotracheal intubation. They identified 29 cases (17%) of mediastinal air without associated pneumothorax that were treated conservatively and 12 cases (41%) that showed improvement or resolution without intervention. In another study from Italy by Priti et al., the authors aimed to describe the incidence and risk factors of barotrauma in patients with COVID-19 on invasive mechanical ventilation. The study was performed via electronic survey and involved patients with COVID-19 who developed barotrauma while...
on invasive mechanical ventilation from 61 hospitals the COVID-19 Lombardy Intensive Care Unit network. Thirty-eight responses were submitted and out of 2041 patients included, about 7.1% developed barotrauma.

Furthermore, Udi et al.27 in their retrospective registry analysis that included 20 patients with severe COVID-19 pulmonary failure found that 40% of those patients developed severe barotrauma during mechanical ventilation that followed lung protective strategies. Their data suggested that barotrauma in COVID-19 patients may occur despite the use of recommended lung protective mechanical ventilation settings. In addition, data from a retrospective cohort study that included 343 COVID-19 positive patients suggested that these patients have a significant risk of developing barotrauma when receiving invasive mechanical ventilation with subsequent increased mortality rates. The study found that 15.4% of the patients developed barotrauma and 91% of these patients presented with pneumothorax, 3.7% with pneumomediastinum and pneumopericardium.28

Conclusion
Spontaneous pneumothorax and pneumomediastinum are rare, but serious, complications of COVID-19. The most common cause of iatrogenic barotrauma is related to mechanical ventilation in the setting of underlying lung disease, with variable proposed mechanisms ranging from high peak airway pressure, high PEEP and high tidal volume, although none have been proven. Spontaneous barotrauma in COVID-19 in the absence of ventilatory support is presumed to be due to pressure gradient between the alveolus and the pulmonary interstitium due to virus associated alveolar damage. The second mechanism is due to direct alveolar membrane damage leading to its rupture, which could be secondary to direct infection of COVID-19 of the pneumocytes type I and II. This can result in rapid respiratory deterioration with life-threatening consequences if not recognized in time. Pneumothorax associated with mechanical ventilation has more than two-fold increased mortality and this risk increases further in those with tension pneumothorax. Early diagnosis particularly in ventilated patients and immediate treatment with small tube thoracostomy is crucial for a positive outcome.

Data availability
No data is associated with this article.

Consent
The images published in this article were retrieved from patient records of patients treated at our institution. We gained IRB approval from our institution (St. Barnabas Hospital IRB; approval number, 2020.23) to use and publish the images in this article, which included a waiver of informed consent from patients. No patient identifiable data is included in the present article.

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