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Air leaks in COVID-19 infection

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Abstract

COVID-19 infection continues to create havoc and may present with myriad complications involving many organ systems. However, the respiratory system bears the maximum brunt of the disease and continues to be most commonly affected. There is a high incidence of air leaks in patients with COVID-19 infection, leading to acute worsening of clinical condition. The air leaks may develop independently of the severity of disease or positive pressure ventilation and even in the absence of any traditional risk factors like smoking and underlying lung disease. The exact pathophysiology of air leak with COVID-19 remains unclear, but multiple factors may play a role in their development. A significant proportion of air leaks may be asymptomatic; hence, a high index of suspicion should be exercised for enabling early diagnosis to prevent further deterioration as it is associated with high morbidity and mortality. These air leaks may even develop weeks to months after the disease onset, leading to acute deterioration in the post-COVID period. Conservative management with close monitoring may suffice for many patients but most of the patients with pneumothorax may require intercostal drainage with only a few requiring surgical interventions for persistent air leaks.

INTRODUCTION

COVID-19 is a multisystem disorder that can lead to a myriad of complications. The pathogenesis of respiratory failure is complex and covers different clinical scenarios such as pneumonia, acute respiratory distress syndrome (ARDS) with normal to low lung compliance, pulmonary embolism, and heart failure. Air leak (AL) injury is a well-documented but rare complication of COVID-19, leading to increased morbidity and mortality, particularly in the intensive care unit (ICU) setting[1]. AL is a clinical phenomenon associated with the leakage of air from a cavity that contains air into spaces that usually, under normal circumstances, do not have air[2]. The air leak syndrome (ALS) is the presence of air leak with associated symptoms of respiratory distress[2]. The AL may be classified as pneumothorax (air within the pleural cavity), pneumomediastinum (air in the mediastinum), pneumopericardium (air within the pericardial sac), pneumoperitoneum (air within the peritoneal cavity), subcutaneous emphysema (air within the subcutaneous tissue), pneumorrhachis (air within the spinal canal) and retroperitoneal emphysema (air within the retroperitoneum area).

Because of the possible inherent component of COVID-19, the patients are more prone to develop AL than other ICU patients. It can be spontaneous, occurring without any precipitating event, or iatrogenic due to invasive or non-invasive mechanical ventilation[1]. Pneumothorax has been reported as the most common cause of AL, followed by pneumomediastinum, and subcutaneous emphysema, with a few case reports of pneumopericardium and pneumoperitoneum[1,3]. However, pneumomediastinum may be under-recognized and under-reported as most patients are asymptomatic, and pneumomediastinum may be easily missed in chest x-rays. Some case series have reported that pneumomediastinum may be the commonest form of AL and may also be a predictive factor for pneumothorax [4,5].

The literature on AL in COVID-19 patients is limited to case reports, case series, and meta-summaries. The data on the guidelines and management of AL does not explicitly address the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients. This review aimed to examine the breadth of the available literature on this challenging clinical entity concerning the ongoing pandemic, its clinical effects, and its management strategies.

EPIDEMIOLOGY

The exact incidence of AL remains uncertain in these patients, as most studies on the subject did not have a specific imaging protocol for the diagnosis. The reported incidence of AL in patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) is 12%-30% and 15%-30%, respectively[6-8]. However, the incidence is lower (0.6–1%) among COVID -19 patients, but a higher incidence (12.8-28.6%) has been reported in critically ill patients[1,9]. Compared with non-COVID-19 acute respiratory distress syndrome (ARDS), the patients of COVID-19 related ARDS (CARDS) requiring invasive mechanical ventilation (IMV) had a seven times higher incidence of AL, despite using lung-protective mechanical ventilation[10,11].

A retrospective analysis of the SARS-CoV database identified the mean presentation of AL at 19.6 ± 4.6 days from the onset of symptoms[10]. While most of the data shows variability in the onset of AL from 9 to 19.6 days from the time of COVID-19 admission[9], it has been seen up to 60 days in some case reports[13]. In patients requiring IMV, it is generally detected after 4-14 days of its initiation[9].

Risk Factors

ALs have been shown to occur more commonly in the older population with COVID-19, and there is a higher incidence in males (M:F = 4:1)[3,14,15]. Nevertheless, this age difference could result from the selection bias of elderly patients who tend to run a more severe course of COVID-19.

While pulmonary diseases like asthma, chronic obstructive airway disease (COPD), interstitial lung disease, lung bulla, and a history of smoking are known risk factors for pneumothorax in the general patient population, no such correlation has been observed in COVID-19 patients[3,9,13-15]. In fact, studies have shown that non-smoking COVID-19 patients have 5.5 times increased risk of developing pneumothorax[15]. Several other risk factors have been reported in different studies, as enumerated in table 1.

PATHOGENESIS

The pathogenesis of SARS-CoV-2 causing AL injuries is complex and not entirely comprehended. Whether CARDS represents a typical or atypical form of ARDS remains a matter of debate. The primary target site of SARS-CoV-2 is angiotensin-converting enzyme-2 (ACE-2) receptors. The high affinity of ACE-2 receptors for SARS-CoV-2 than that to the SARS coronavirus-1 (SARS-CoV1) may be responsible for the high infectivity of the former[16]. ACE-2 receptors are mainly expressed in type II pneumocytes, besides vascular endothelium, myocardium, proximal tubules of kidneys, and intestines[16]. Downregulation of ACE-2 receptors by SARS-CoV-2 Leads to the loss of ACE2 protective function in the local renin-angiotensin system of the lung on inflammation, fibrosis, and pulmonary arterial hypertension. Endothelial dysfunction plays a pivot role in the pathogenesis of SARS-CoV-2 by 1) Unopposed angiotensin II upregulation causes vasoconstriction, increasing the dead space and producing arterial hypoxemia; 2) coagulation and complement system activation, leading to a thrombotic macro- and microangiopathy; 3) maladaptive immune response and exaggerated inflammatory response[17]. Eventually, these elements cause a lung injury characterized by interstitial inflammatory infiltrates, interstitial alveolar edema, hyaline membrane formation, airway inflammation, and microvascular thrombosis[1,16,17,18]. These factors increase the frailty of airways and alveoli, with early cyst or bullae formation and extensive alveolar destruction, forming cavitary lesions over time, mainly in the non-dependent and caudal region. The peripherally located cysts can either rupture spontaneously or during positive pressure ventilation (PPV) due to increased alveolar pressures, especially in the advanced stages when the lung has undergone fibrotic changes. While PPV may be a contributing factor, data suggest that 30-40% of the patients with COVID-19 who developed air leaks were never on invasive ventilation, suggesting mechanisms apart from barotrauma may play a significant role in the development of AL[3,14].

AL in spontaneously breathing patients

Macklin phenomenon

The marginal alveoli have bases in the bronchi, bronchioles, blood vessels, and pleura separated by a connective tissue layer or interstitium. Increased intrathoracic pressure, by coughing, vomiting, sneezing, defecation, or in cases of asthma or COPD exacerbation, results in increased intra-alveolar pressure and overinflation of the alveoli creating a large pressure gradient between the damaged marginal alveoli and lung interstitium. A pressure gradient may also develop during the Valsalva manoeuvre by reducing the calibration of pulmonary vasculature without affecting alveolar pressure. This can rupture the marginal alveoli causing the air to leak with centripetal dissection along the bronchovesicular sheath towards the lung's hilum and follow to the low-pressure mediastinum causing spontaneous pneumomediastinum. Pressure in the mediastinum is relieved by the escape of the air into the subcutaneous tissue resulting in subcutaneous emphysema, mainly at the root of the neck, as the cervical fascia is continuous with the mediastinum. Air can then further tract to various cavities causing pneumothorax, pneumopericardium, and retroperitoneal emphysema (Figure 1)[19].

Patient self-inflicted lung injury

Patient self-inflicted lung injury (P-SILI) signifies the possibility of lung injury induced by or worsened by the patient's intense inspiratory effort. P-SILI is a vicious cycle as worsening lung injury increases the respiratory drive, resulting in further strong respiratory efforts. A strong inspiratory effort in a previously injured lung can lead to the following changes[20]:

(a) Swings in transpulmonary pressure causing the inflation of large volumes, i.e., excessive strain;

(b) Abnormal decrease in the alveolar pressure below the positive end-expiratory pressure (PEEP) during assisted ventilation increases the transvascular hydrostatic pressure, favoring the aggravation of negative-pressure pulmonary edema;

(c) Significant regional transpulmonary pressure differences in the dependent (posterior) regions than non-dependent (anterior) ones are accompanied by a pendelluft phenomenon, an intrapulmonary shift of gas from non-dependent to dependent lung regions at the very onset of inspiratory effort, even before the start of ventilator insufflation. These effects lead to regional volutrauma and increased cyclic inflation of the dependent regions that were collapsed during expiration (atelectrauma);

(d) Diaphragm injury caused by injurious eccentric contractions.

Early intubation was recommended earlier during the pandemic; however, with the increasing incidence of morbidity and mortality associated with IMV, a trial of high-frequency nasal cannula (HFNC) or non-invasive ventilation (NIV) is generally recommended for respiratory support at the outset. Although these strategies might delay IMV, they can still contribute to AL injury by increasing P-SILI. In addition, NIV and HFNC may be associated with a higher incidence of barotrauma than standard low-flow oxygen therapies[21]. Hence, delaying intubation and initiation of IMV may also increase the chances of AL. Therefore, the time from symptom onset to intubation is an independent predictor of AL development[11].

Secondary bacterial infections may enhance the inflammatory mechanism of lung injury triggered by SARS-CoV-2 infection, thus increasing the susceptibility of persistent air leaks (PALs). Necrotizing lung infections caused by *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Aspergillus spp*. may also increase the susceptibility for AL (Figure 2).

CLINICAL FEATURES

As already stated, ALs generally develop later in the disease course, but a minority of patients (less than 1%) have been shown to have AL at the initial presentation[15]. Clinical manifestations can vary from being asymptomatic to having life-threatening conditions. AL may be an incidental finding in 50% of the patients as they may be asymptomatic or have symptoms that might be attributed to disease progression rather than air leak[3].

In some studies, pneumothorax in COVID-19 is primarily unilateral and predominately on the right side [1,3]. The most common symptoms of pneumothorax include chest pain and dyspnoea, causing respiratory distress and requiring hospital admission, or worsening of pre-existing respiratory symptoms with increased oxygen requirement. Chest pain is of sudden onset, often sharp and stabbing type of pleuritic pain, which radiates to the ipsilateral shoulder or arm. The patient might be tachypnoeic, tachycardic, with reduced chest movements and absent breath sounds on examination.

Pneumomediastinum is generally benign; however, retroperitoneal chest pain, dyspnoea, coughing spells, neck pain, or dysphagia can be present[22]. Mediastinal crunching over the cardiac apex and the left sternal border, synchronous with the heartbeat, known as the Hamman's sign, can be heard on auscultation. Subcutaneous emphysema causes painless swelling over the neck and chest, which on palpation gives a feeling of tissue paper in the hands, known as crepitus. This may be the first sign suggestive of an air leak. On physical examination, pneumopericardium can be detected by water wheel sound ("bruit de Moulin").

Malignant pneumomediastinum, pneumopericardium, or tension pneumothorax can result in mechanical obstruction, causing a decrease in venous return, hemodynamic instability, and circulatory collapse. This compels a prompt diagnosis and intervention.

CLINICAL EVALUATION

Thorough clinical history and physical assessment remain the key to diagnosing ALs. Apart from pulmonary embolism and acute coronary syndrome, a high index of suspicion for ALS is advised in COVID-19 patients with acute onset of hemodynamic instability, worsening hypoxemia, and or hypercapnia.

Laboratory parameters

As such, there are no single laboratory parameters that assist in making the diagnosis or confirming AL. In patients with SARS-CoV AL, high lactate dehydrogenase (LDH) levels were associated; however, in COVID-19 patients, LDH levels are not significantly high, and mixed results are observed [21,23,24]. Other laboratory parameters associated with increased incidence of AL have increased serum bilirubin and C-reactive protein levels[11]. Arterial blood gases may be helpful to document hypoxemia and sometimes hypercapnia. The resultant respiratory distress or shock may lead to hyperlactatemia.

Imaging

Chest radiography

Chest radiography is the first investigation performed as it is simple, inexpensive, and rapid. Chest X-ray has a pooled sensitivity of 52-60% and a specificity of 88-95% for diagnosing pneumothorax and pneumomediastinum[25]. The best diagnostic film for pneumomediastinum or pneumothorax is a lateral chest X-ray, with the affected side up for the latter. However, the lateral view is challenging to achieve in the ICU setting. Pneumomediastinum can be differentiated from pneumopericardium on chest x-ray as the former shows air around the heart anteriorly (behind the sternum) and superiorly lifting the thymus but not below (diaphragmatic border). In contrast, air surrounds all the heart's borders in pneumopericardium.

Chest ultrasonography

Ultrasonography is a readily available bedside tool in evaluating critically ill patients and is the only imaging modality that allows scouring for reversible causes of nonarrhythmogenic cardiac arrest during ongoing resuscitation. The ultrasound has a pooled sensitivity of 88-95% and a specificity of 100% for diagnosing pneumothorax. However, the presence of subcutaneous emphysema can affect the accuracy of the ultrasound[26].

Features of the lung ultrasound for the diagnosis of pneumothorax include:

Absence of lung sliding (high sensitivity and specificity),

Absence of comet-tail artifact (high sensitivity, lower specificity), and

Presence of lung point (high specificity, lower sensitivity).

Pneumopericardium and pneumomediastinum are arduously diagnosed with ultrasound. In the case of a large pneumopericardium, an echocardiogram shows "no heart" or absent cardiac images, especially during systole as the heart is pushed further away from the transducer by the air and then returns with diastole. This finding is also known as an "air gap sign" found in pneumomediastinum and pneumopericardium seen using M-mode[27]. One distinguishing factor between the two is the inability to see the heart in the subxiphoid view in the case of pneumopericardium. In contrast, the heart is usually well visualized in pneumomediastinum due to its direct contact with the diaphragm without an obstructing air artifact[28]. However, similar findings are often seen with respiratory interference, which may develop if the patient is tachypnoeic. Spontaneous or swirling bubbles may be seen in the pericardial space in patients with pneumopericardium. Ultrasonography is heavily operator-dependent, and its sensitivity further drops in patients with ARDS. In addition, it cannot be used to discriminate between a COPD-associated bleb and pneumothorax.

Computed tomography scan

Computed tomography (CT) scan is the gold standard in diagnosing ALs and differentiating bullous disease from pneumothorax. Nevertheless, transporting a critically ill patient on mechanical ventilation and vasopressors to the imaging facility could be perilous. Also, the risk-benefit should be contemplated owing to radiation risk with CT. In addition, the risk of spread of infection should also be kept in mind in patients with active COVID-19 disease.

The Macklin effect on lung parenchyma in CT images is a linear collection of air contiguous to the broncho-vascular sheath. CT scan has a sensitivity of 89.2% (95% confidence interval [CI]: 74.6–96.9), a specificity of 95.6% (95%CI: 90.6–98.4), and an accuracy of 94.2% (95%CI: 89.6–97.2) to detect the Macklin effect. Macklin's effect on CT scan can accurately predict AL development in CARDS patients 8.5 days in advance[29].

CLASSIFICATION OF SEVERITY

The most straightforward and widely used technique to quantify AL is asking the patient to cough while observing the water column and the water seal column in the chest tube drainage system. During this manoeuvre, no air bubbles in the water seal suggest that pleural space is devoid of air. If the intensity of bubbles remains the same on repeated coughs, it is likely to be an active leak. The AL is deemed significant if bubbling is even present during normal breathing or while the patient is talking. However, this method lacks standardization and validation among observers.

The other most commonly used classification is the Cerfolio system[30], which is also based on observation but is less subjective and is a validated classification. It is based on the degree of the leak (measured by an air leak meter) and the phase of respiration in which it appears (Table 2). However, there is no specific classification for AL in COVID-19 patients.

PERSISTENT AIR LEAK

Persistent air leak (PAL) refers to the continued airflow from the endobronchial tree to the pleural space, which can occur due to an abnormal connection between the pleural space and airways (bronchopleural fistula, BPF) or alveolus. An AL is referred to as a

PAL when it persists longer than 5–7 days. This typically used 5-day cut-off to define PAL was initially derived from the expected length of stay following pulmonary resection, where an AL for several days was not uncommon[31,,32]. However, some authors suggest that an AL in the setting of secondary spontaneous pneumothorax should be considered persistent after 48 h[31]. Although the exact incidence of PAL is unknown, it may be prevalent in patients with COVID-19. Before diagnosing PAL, one must inspect the chest tube drainage circuit, as a leak in the circuit or malfunctioning three-way stop cock may masquerade as BPF.

MANAGEMENT

The treatment option for COVID-19 associated ALs depends on their type and severity. Currently, there are no guidelines for managing ALs in COVID-19 patients. Many patients with ALs may be managed conservatively, gradually absorbing the air in the following days. The patient should be closely monitored for any clinical deterioration. If possible, PPV should be avoided in such patients, and low-flow oxygen delivery devices for oxygen supplementation or, if required, a HFNC might be preferable over NIV. No independent lung ventilation strategies are consistently effective at expediting the resolution of ALs in a patient on PPV. Although reducing the tidal volume, PEEP, and inspiratory time, if feasible, can promote closure of the pleural defect[33].

Even though most of the COVID-19 patients with pneumomediastinum and around 30% of patients with pneumothorax may be managed conservatively, the remaining patients will require intercostal drainage (ICD), and a few will require further surgical intervention[34]. Tension pneumothorax, pneumomediastinum, or pneumopericardium can be fatal and require immediate decompression. For tension pneumothorax, needle drainage may be performed through the second intercostal space anteriorly in the midclavicular line, followed by chest tube drainage. For tension pneumomediastinum drains on the anterior thoracic wall, and for tension pneumopericardium pericardiocentesis may be performed for decompression.

As per British Thoracic Society guidelines, in bubbling chest drains in patients with COVID-19, viral filters should be installed onto the suction port of a chest drain bottle. An alternative approach to reducing the risk of spread of infection through droplets is the use of Digital drain circuits (for example, Thopaz+, Medela), though they do not contain a viral filter[35].

Management of PAL

The management of PAL can prove to be a challenging task, the first step being localization of AL. The lack of predictive models to identify patients in whom a resolution of AL is likely to occur conservatively leads to incertitude. As a result, management strategies have been highly variable among different centres. There are reports of 80% of cases having been treated conservatively for 14 days with success; however, a delay in surgery may detrimentally affect surgical outcomes and prolong hospital stay. Therefore, an individualized approach to PAL is suggested to improve patient outcomes[31]. As per the two guidelines on the management of PAL, based on the consensus of expert panels, one should consider early surgery in case the AL persists beyond 4 days, followed by pleurodesis to prevent recurrence[36,37]. However, surgical repair may not be feasible in critically ill patients with CARDS due to a further increase in morbidity or mortality. In the case of an expected conservative resolution, ICD for a prolonged duration may be preferred[3]. The other promising option is the bronchoscopic placement of a one-way endobronchial valve, which appears to be a reasonable minimally invasive therapeutic option with a high success rate. Again, the risk of spread of infection while performing bronchoscopy should be considered in patients with active COVID-19 infection. Autologous blood pleurodesis, Heimlich valve positioning, and albumin-glutaraldehyde tissue adhesives are additional less invasive options for recurrent and refractory cases[38].

Negative Pressure Suction

It is common to apply negative suction to chest tubes to enhance pleural apposition. There is no unanimity on whether or not applying suction to the chest tube is beneficial or hazardous. A water seal is usually not helpful or even contraindicated in patients with severe restrictive lung disease and a substantial risk of bleeding. An "alternate suction" protocol with suction pressure of –10 cm H2O during the night and water seal only during daytime appears to be a safe option in such patients. It may decrease AL or chest tube duration in patients without a relevant pneumothorax, progressive subcutaneous emphysema, or cardiorespiratory deterioration[39]. There is no data regarding the use of suction in COVID-19 patients. While managing COVID-19 patients, if no viral filter is attached to the suction port, the drainage system can be placed on suction with a suction canister, and the medical gas vacuum lines exhaust providing negative pressure.

PREVENTION OF AIR LEAK SYNDROME

As the development of AL is associated with substantial morbidity and mortality, every measure should be taken to prevent AL. If the CT scan demonstrates the Macklin effect, such patients should take extra care to avoid further damage, *e.g.*, avoiding PPV, avoiding high airway pressure, and favoring extracorporeal technologies instead.

Conceptually, HFNC could limit P-SILI risks compared to NIV, but the tidal volume in the former is difficult to monitor. Also, clinicians should be aware that HFNC may be associated with a higher incidence of barotrauma than the standard, low-flow oxygen therapies, which should be preferred if the patient's condition allows.

In patients on IMV, using a lung-protective ventilation strategy by reducing the alveolar pressure and distension reduces the risk of developing pneumothorax. Judicious use of neuromuscular blockers in patients with high airway pressures or those with patient-ventilator dyssynchrony may also reduce the chances of AL by reducing the negative pressure and shear stress in the pleural cavity.

An excessive and insufficient respiratory effort may result in deleterious anatomical and functional modifications of the diaphragm. Thus, if feasible, using lung and diaphragm protective ventilation simulates a normal inspiratory effort, which also benefits early weaning by reducing the sedation requirement. Transposing this notion into clinical practice needs assessment of the patient's inspiratory effort and potentially perilous patient-ventilator interactions, which may be significantly facilitated by oesophageal pressure (Pes) monitoring. If Pes is unavailable, meticulous clinical assessment and analysis of tidal volume, flow, and airway pressure waveforms from the ventilator can help detect situations at risk of P-SILI. Nonetheless, no clinical study has demonstrated improved patient outcomes by limiting P-SILI risk[20,40].

Lastly, timely application of extracorporeal carbon di-oxide removal and extracorporeal membrane oxygenation with lung-protective ventilation strategy may play a key role in preventing pneumothorax in critically ill patients with severe ARDS and refractory hypoxemia.

OUTCOME

The overall prognosis of patients with AL is guarded. The development of AL has been associated with a higher need for IMV, prolonged hospitalization, and higher in-hospital mortality[1,9,13]. High mortality rates ranging from 40 to 74% have been reported. Patients with pneumothorax have been reported to have higher mortality than patients with pneumomediastinum. Also, patients developing AL while on PPV may have higher mortality rates[1,3,9,33].

CONCLUSION

As our clinical knowledge of COVID-19 expands, we must recognize that AL is not an uncommon complication of COVID-19 infections. It is likely a sequela of COVID-19 disease progression resulting from an inflammatory insult and increase in respiratory effort that may foist changes within the lung parenchyma. A high level of clinical suspicion is merited for an early diagnosis as most patients are asymptomatic, and it should be suspected when there is sudden respiratory or hemodynamic deterioration. One should be vigilant when choosing to continue oxygen therapy *via* various oxygen delivery devices in patients with a high respiratory drive, as P-SILI can aggravate the disease progression, especially in patients who have evidence of Macklin effect on CT scan. Patients with AL may be managed conservatively but under strict observation. ALS is associated with increased morbidity and mortality, especially in the elderly and patients on IMV despite lung-protective ventilation.

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