Pneumomediastinum in COVID-19: Merely a Matter of Lung Frailty?

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Dear Editor,

Pneumomediastinum describes the presence of free air in the mediastinum. It is an uncommon diagnosis [1]. The natural history is of resolution with conservative management. However, albeit rarely, propagation and accumulation of air within the enclosed mediastinum, can progress to tension pneumomediastinum, with cardiorespiratory compromise [2].

Reports of pneumomediastinum in patients hospitalized due to infection by the beta coronavirus severe acute respiratory syndrome (SARS-CoV-2), (COVID-19) are regenerating awareness of this hitherto infrequent occurrence [3, 4]. They describe subsets of patients developing spontaneous pneumomediastinum, having had no exposure to positive pressure ventilatory support [5–7]. Moreover, the description of spontaneous pneumomediastinum during the smaller outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV-1) outbreak in 2003 was independently associated with increased intubation rates and risk of mortality [8, 9]. And so, in the absence of a definitive description concluding the development of pneumomediastinum in COVID-19 due to positive pressure ventilation thus far, natural questions arise regarding the aetiology of pneumomediastinum.

Fig. 1. Alveolar rupture with movement of air into the bronchovascular sheath.

What anatomico-mechanical risk factors predispose to pneumomediastinum? And is there a unifying mechanism of injury directly due to COVID-19 pneumonitis that underlies the pathophysiology of this complication? Further, why do those with predisposing factors and apparently conducive circumstances not necessarily develop pneumomediastinum?

Air in the mediastinum can arise from varied causes at a number of contiguous anatomical regions (Table 1). In the setting of COVID-19 pneumonitis, pneumomediasti-

Fig. 2. The visceral mediastinal compartment demonstrates extension of the mediastinal pleural beyond the pulmonary hilum, continuous with the distal bronchovascular sheath. The sequel of the propagation of air in the mediastinum leads to its accumulation in contiguous anatomical locations.

Table 1. Causes of pneumomediastinum by origin

Upper respiratory tract	Intrathoracic airways	Lung parenchyma	Gastrointestinal tract	Trauma	Infection with gas-producing organisms
Head and neck infection (odontogenic, tonsillitis, facial osteomyelitis)	Blunt or penetrating chest trauma	Direct alveolar disruption (surgery, penetrating trauma)	Intrathoracic oesophageal perforation	Penetrating neck or chest trauma	Acute bacterial mediastinitis
Facial fracture	Iatrogenic (bronchoscopy, transbronchial biopsy, needle aspiration)	Spontaneous alveolar rupture			
Oropharyngeal mucosal disruption					

num is thought to be precipitated by sub-pleural alveolar rupture [5]. Free air dissects the peribronchovascular sheath and leaks proximally to reach the mediastinum; the so-called Macklin effect [10] (Fig. 1–3). Lung units in COVID-19 may be more susceptible to alveolar rupture due to increased transalveolar pressures beyond the local stress-strain threshold for epithelial-interstitial integrity. The similarly applied concept in material properties describes fatigue as structural degradation with cyclical

loading [11]. In otherwise healthy lungs, spontaneous pneumomediastinum derives from a provoking mechanical mechanism that generates a transient massive rise in transpulmonary pressures that breaches the alveolar strain threshold. In the setting of COVID-19, a combination of factors interacts to reach this endpoint. These include clinical features such as cough and increased work of breathing, with its implication of increased stress applied to the respiratory system. Further, the SARS-CoV-2

Fig. 3. Pneumomediastinum and left pneumothorax in a non-intubated patient with COVID-19-related pneumonia (a – coronal, b – axial, and c – sagittal).

pneumonitis-related epithelial disruption, demonstrated at post-mortem [12], iatrogenic positive pressure respiratory support, and/or indeed patient inflicted self-induced lung injury [13] can all affect structurally frail alveoli that are vulnerable to injury [14].

Cough requires a Valsalva-like effort after the initial inspiratory effort, so as to generate extremely high airway pressures for the subsequent expiratory flow. In the spontaneously breathing patient, the inspiratory phase of the cough requires a rapid forceful activation of the diaphragm and inspiratory musculoskeletal apparatus, to generate a fall in intrathoracic pressure below atmospheric pressure. In doing so, the initial inhalation volume may range between 50% of the tidal volume, to 50% of vital capacity [15]. This is followed by a compressive phase, in which the glottis is transiently closed against expiratory effort. Isometric contraction of respiratory muscles (diaphragm, intercostal, and accessory muscles), which limits the rise in transpulmonary airway pressure by increasing pleural pressure, thereby preventing the barotrauma that would ensue through the generation of intrathoracic pressures up to ~400 cm H₂O [15]. Cough creates a traumatic mechanical stress upon the airway wall, with neutrophilic airway inflammation and increased cough hypersensitivity that is self-propagating in animal models [16]. Microscopic injury to the respiratory epithelial mucosa by such a self-perpetuating cycle has been demonstrated clinically in chronic obstructive pulmonary diseases and lower respiratory tract infections [17–19].

“Effort-induced lung injury” caused by increased spontaneous respiratory effort results from the generation of large negative intra-pleural pressures (P_{pl}) with already elevated airway pressures (P_{aw}), directly resulting in an increased transalveolar pressure. This translates

into an equivalent transpulmonary pressure (P_L) at the end of inspiration and expiration.

$$P_L = P_{aw} - P_{pl}$$

In healthy lungs, transmitted airway pressures rely on interdependence to ensure that forces acting on one segment of the lung are equally distributed along the visceral pleura, with all alveoli subjected to similar transalveolar pressures so dissipating the tensile forces [20, 21]. In inflamed lungs with de-recruited alveoli and airway oedema, the oscillations of negative pleural pressures created by vigorous diaphragmatic contractions during respiratory distress causes heterogeneous deformation stress in different pulmonary segments. In patients with moderate to severe SARS-CoV-2, lungs are ventilated in an inhomogeneous fashion with variations in parenchymal aeration [20]. A solid-like behaviour develops in response to inflation forces, with poorer equilibration of airway pressures. This leads to a focal concentration of stress at the interface between collapsed and ventilated alveolar segments. At this point of transition, these partially open alveoli experience elevated traction forces to recruit them with supra-physiological transalveolar pressures from adjacent better-expanded lung units. Studies have calculated that at a transpulmonary pressure of 30 cm H₂O, inflation pressures can reach as high as 140 cm H₂O in injured lungs [21, 22].

SARS-CoV-2 results in severe diffuse alveolar damage with autopsy series in patients who died directly due to SARS-CoV-2 infection, consistently identifying distal pulmonary epithelial involvement as diffuse alveolar injury, and in other areas, concurrent exuberant fibrosis [23, 24] (Fig. 4). In addition, the proximal airway is an

Fig. 4. Pneumomediastinum in an intubated patient with COVID-19-related pneumonitis (**a** – coronal, **b** – axial, and **c** – sagittal).

established site of disease manifestation with notable tracheobronchitis [12, 24–26]. Inflammatory involvement has also been demonstrated by scintigraphy imaging [27]. Importantly, these findings to varying degrees have been re-producible in nonsmokers, and in patients who did not receive mechanical ventilation [12, 24–26].

The inflammatory pulmonary pathology imposed by SARS-CoV-2 infection is now well documented. Moreover, there is notable heterogeneity in intrinsic respiratory mechanics that probably reflects unmeasurable variations in anatomical and physiological lung strain, both in spontaneously breathing and mechanically ventilated patients [28]. Thus, while the aforementioned contributory mechanical, inflammatory, and perpetuating factors to create pneumomediastinum exist, the majority of patients with COVID pneumonitis do not develop it. There would therefore appear to be a missing factor or individual critical threshold for the interaction of these components.

No clear answers related to pressure effects emerge from the available clinical studies, in those with low or higher risk of barotrauma. In case series of those with early COVID-19 and high lung compliance, pneumomediastinum is not widely reported. In a cohort of 169 mechanically ventilated patients with COVID-19 and poorly compliant lungs, Lemmers et al. [5] reported 13% who developed pneumomediastinum. None had a known history of COPD. Pneumomediastinum was detected mean 3.5 days (SD 0.25–7.5) following intubation. Respiratory system compliance at admission was not significantly different between those who did (not) develop pneumomediastinum (median 28; IQR 22–36 vs. 27; 22–33 $p = 0.55$) [5]. “Protective” low volume ventilatory strategy was reported [29]. Interestingly, the authors report that airway pressures were lower on the day pneumomediastinum was detected, compared to when mechanical ventilation was initiated. Lemmers et al. [5] suggest therefore that

given pneumomediastinum was found to develop when airway pressures were not elevated, it would be more accurate to attribute such findings to the “lung frailty” caused by the underlying disease process of COVID-19 as opposed to barotrauma [5].

Despite the plausibility of the aforementioned mechanisms which may involve a combination of bronchioloalveolar inflammation associated epithelial-interstitial rupture, transalveolar stress, differential strain (with or without purely distributed (self) imposed mechanical thoracic energy for the development of pneumomediastinum), visual demonstration of the Macklin effect has not been shown. Furthermore, the absence of pneumothorax in high-resolution CT scans in certain cases of pneumomediastinum, sustains the further question of whether and how air can reach the mediastinum without causing a visible breach in the alveolar lung parenchyma [30, 31].

The re-emergence of clinical interest in pneumomediastinum as a result of its proportion of the sheer number of cases of respiratory failure due to COVID-19 provides an opportunity for further detailed mechanistic study into its origins and whether the “Macklin” effect can be demonstrated. A proposed strategy could be to perform real-time MRI with fluorine-19 to interrogate the ventilated airspaces, which may reveal the route by which contained air leaks out of the tracheobronchial tree with mediastinal extension [32]. An intriguing question as to the cause of spontaneous cause of pneumomediastinum in de novo COVID pneumonitis in previously healthy individuals remains open for now.

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