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MINI-REVIEW

The role of Macklin effect in management of ARDS: beyond spontaneous pneumomediastinum

Alessandro Belletti[1,*], Diego Palumbo[2,3], Michele De Bonis[3,4], Giovanni Landoni[1,3], Alberto Zangrillo[1,3]

[1]Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy
[2]Department of Radiology, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy
[3]School of Medicine, Vita-Salute San Raffaele University, 20132 Milan, Italy
[4]Department of Cardiac Surgery, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy

***Correspondence**
belletti.alessandro@hsr.it
(Alessandro Belletti)

Abstract

Barotrauma (including pneumomediastinum, pneumothorax or subcutaneous emphysema) is a frequent complication of patients with acute respiratory distress syndrome (ARDS) and is associated with worse outcome. Furthermore, some Authors hypothesize that pneumomediastinum could be a sign of ongoing patient self-inflicted lung injury (P-SILI) in patients with respiratory failure receiving non-invasive respiratory support. It has been recently found that a well-known radiological sign, the Macklin effect (or pulmonary interstitial emphysema), could be a powerful predictor of subsequent development of barotrauma in patients with ARDS (sensitivity = 89.2% (95% confidence interval (CI): 74.6 to 96.9); specificity = 95.6% (95% CI: 90.6 to 98.4)). Of note, Macklin effect is visible on chest computed tomography (CT) scan 8–12 days before overt barotrauma. Furthermore, patients with Macklin effect not currently receiving invasive ventilation have a high risk of subsequent intubation. Accordingly, it could be hypothesized that Macklin effect could be a marker of lung fragility, disease severity, and P-SILI in patients with ARDS. Therefore, detection of Macklin effect on chest CT scan could be used to stratify baseline risk of patients with ARDS, select which patients should be evaluated for alternative management algorithms, including advanced respiratory monitoring, ultraprotective ventilation, or institution of extracorporeal support without invasive ventilation.

Keywords

Acute respiratory distress syndrome; Mechanical ventilation; Pneumothorax; Pneumomediastinum; Extracorporeal membrane oxygenation; Ventilator-induced lung injury; Barotrauma; Macklin effect

1. Background

Barotrauma, spanning from asymptomatic small pneumomediastinum to life-threatening massive pneumothorax, occurs relatively frequently in patients with acute respiratory distress syndrome (ARDS). The occurrence rate of barotrauma may be particularly high in patients requiring invasive ventilation due to coronavirus disease 2019 (COVID-19) ARDS, with a reported rate of about 15% [1]. Unfortunately, development of barotrauma is associated with high mortality rates (greater than 60% in COVID-19 ARDS patients, around 46% in non-COVID-19 ARDS patients) [1]. Fragility of lung parenchyma represents a major issue in ARDS. In addition, it is well established that in high-risk patients, mechanical ventilation may cause pulmonary damage (ventilator-induced lung injury (VILI)) and potentially induce barotrauma even when optimal, "protective" mechanical ventilation [2, 3] is applied. Furthermore, abnormal breathing patterns and altered respiratory mechanics in spontaneously breathing patients with respiratory failure may worsen lung injury (patient self-inflicted lung injury (P-SILI)) [4]. Indeed, barotrauma occurs also in patients with COVID-19 ARDS not receiving respiratory support [5]. Interestingly, several studies suggest that development of air leak may be a marker of P-SILI in patients with respiratory failure in spontaneous breathing [6, 7]. Early assessment of lung frailty could therefore allow to early stratify the risk of barotrauma susceptibility and potentially P-SILI amongst ARDS patients, providing a rationale for the deployment of protective management strategies in those at high-risk for barotrauma. However, there is no established prediction method in terms of timing, accuracy and easiness.

2. Macklin effect and barotrauma

Macklin effect (also described as pulmonary interstitial emphysema or Macklin-like radiological sign) is a subtle and well-known radiological sign consisting of an air tracking along pulmonary bronchovascular sheaths, interlobular septa and/or visceral pleura [8, 9], easily recognizable on chest computed tomography (CT) scan, irrespective of contrast medium administration (Fig. 1). Historically, Macklin-like radiological sign has been used to differentiate between pneumomediastinum due to "central" causes (*e.g.*, lesion to large airways or esophagus) and pneumomediastinum due to "peripheral" causes (*e.g.*, lesion to the alveoli), especially in the context of blunt chest trauma or spontaneous pneumomediastinum [8, 10].

Some Authors recently demonstrated that Macklin effect has a high accuracy in predicting barotrauma in patients with COVID-19 ARDS requiring invasive ventilation, with a specificity of 95.6% (95% confidence interval (CI) = 90.6 to 98.4), and a sensitivity of 89.2% (95% CI = 74.6 to 96.9) [11, 12]. Importantly, the Authors found that Macklin effect is usually already evident on chest CT scan 8 to 12 days before clinically overt barotrauma [11, 12]. They also found that there is a relationship between the time to the first radiological evidence of barotrauma and the topographical distribution of Macklin effect within the lung parenchyma: the larger (and more "central") the bronchovascular sheath involved, the shorter the temporal advance [11]. These results have been confirmed in a study enrolling 698 COVID-19 patients (specificity: 99.85% (95% CI = 99.2 to 100); sensitivity: 100% (95% CI = 89.1 to 100); accuracy: 99.8% (95% CI = 99.2 to 100) [13], as well as from studies from other research groups [14, 15]. The same Author group also published a proof of concept study suggesting that Macklin effect may be used as an early marker to candidate patients for ultraprotective mechanical ventilation or early extracorporeal membrane oxygenation [16].

From a pathophysiological point of view, it is possible that the high respiratory effort (typical of patients with respiratory failure) leads to excessive transpulmonary pressure and hence to rupture of distal airways [4]. Indeed, several studies and Authors now suggest that increased transpulmonary pressure, increase burden of lung disease, and inappropriate management of non-invasive respiratory support may trigger barotrauma in patients with respiratory failure [6, 7, 17–19]. Furthermore, some conditions such as COVID-19 ARDS could increase the risk of alveolar rupture, due to possible formations of microthrombi in the pulmonary vessels, with the potential risk of ischemic damage to alveolar cells superimposed to P-SILI/VILI, and therefore increased lung fragility [7, 20]. However, whether *primum movens* of alveolar rupture is the excessive respiratory effort, fragility of lung parenchyma, or a combination of both, remains at present to be determined.

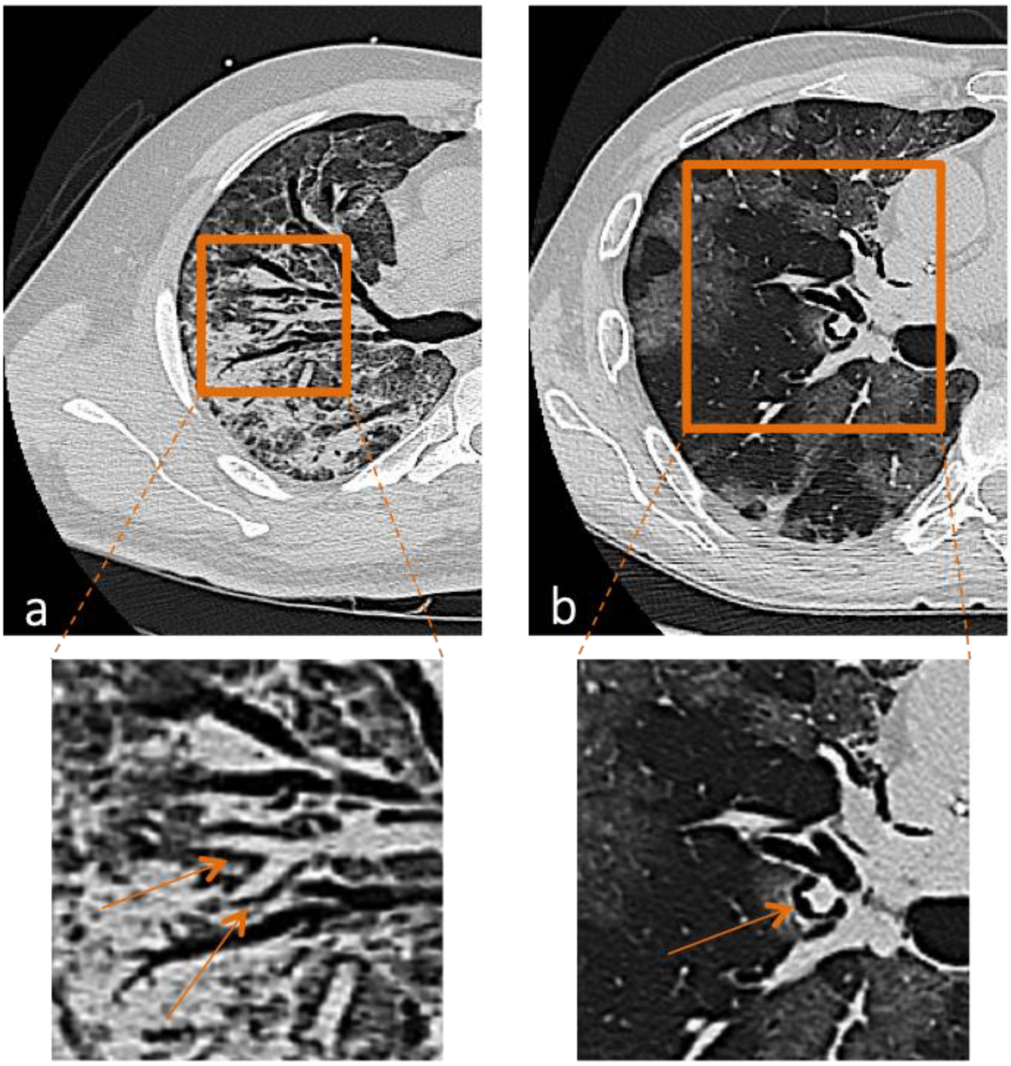

FIGURE 1. Chest CT scan of a patient with Macklin sign. (a) Macklin sign in mid-distal bronchovascular tree. (b) Macklin sign in proximal bronchovascular tree.

3. Clinical applications of Macklin effect in ARDS

Accordingly, it could be hypothesized that detection of Macklin effect might be used to characterize a specific ARDS subphenotype characterized by higher lung fragility and, potentially, greater disease severity. In addition, some Authors hypothesized that occurrence of pneumomediastinum may be a marker of P-SILI in patients undergoing non-invasive respiratory support [6, 18, 19]. As Macklin effect precede clinical and/or radiologically evident pneumomediastinum by several days, it can be speculated that detection of Macklin effect may help in detecting P-SILI.

Management of barotrauma in patients with respiratory failure is difficult, non-standardized and generally involve institution of very low-pressure ventilation or avoidance of invasive ventilation [21]. Detection of Macklin effect might accordingly be used to select high-risk patients for specific management algorithms and/or advanced monitoring (Fig. 2). For example, clinicians might decide to initiate advanced monitoring of respiratory mechanics using esophageal pressure [22–24] in patients receiving non-invasive respiratory support. In addition, patients receiving non-invasive respiratory support may be selected for strategies including awake pronation [25–28] or, alternatively, decision to proceed immediately with invasive, protective mechanical ventilation. An interesting, alternative option for the most severe cases could be the institution of early extracorporeal support without invasive ventilation [16, 29–31]. Patients who are already invasively ventilated could be considered for ultraprotective ventilation combined with early extracorporeal support before meeting suggested criteria for extracorporeal membrane oxygenation [2, 31, 32].

4. Conclusions

The integration of clinical signs, symptoms, respiratory mechanics and radiological findings may ultimately help to develop personalized medicine in ARDS. Clinicians may better identify which patients may be more likely to benefit from implementation (or avoidance) of various management strategies. Furthermore, such integration might contribute to further understand why several promising strategies for ARDS management (*i.e.*, recruitment maneuvers, use of ultraprotective ventilation together with extracorporeal support) did not show improved outcome, or were even associated with harm when assessed in randomized controlled trials [33, 34].

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

AB, DP and GL—designed the research study. AB and DP—drafted the manuscript. MDB, AZ and GL—critically reviewed the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

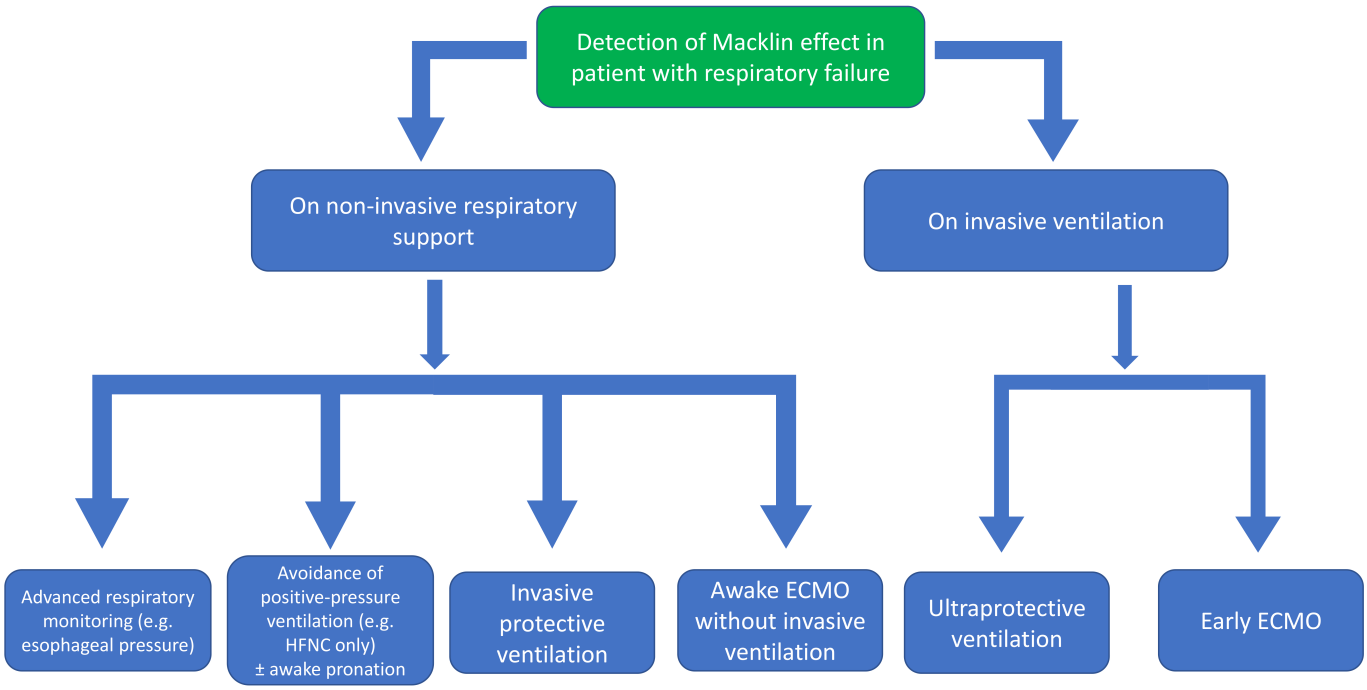

FIGURE 2. Hypothetical management algorithm for patients with respiratory failure and evidence of Macklin effect on chest computed tomography scan. HFNC: high-flow nasal cannula; ECMO: extracorporeal membrane oxygenation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Giovanni Landoni is serving as the Editor-in-Chief, Alessandro Belletti is serving as one of the Editorial Board members of this journal. We declare that Giovanni Landoni and Alessandro Belletti had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to OK.

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