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Valuable Lung Injury Lessons from a Little Known Disease.

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Our understanding of ventilator induced lung injury (VILI) has come a long way since the introduction of the “Respirator Lung Syndrome” in the 1960s. (1) We witnessed the discovery of diffuse alveolar infiltrates and hyaline membranes in those initial postmortem examinations and along the way, we learned the deleterious contributions of atelectrauma, barotrauma, biotrauma, and volutrauma. (2) We continue to unravel the causes of VILI and in the process, we better comprehend the ways in which mechanical ventilation worsens pre-existing lung injury. Lung strain, i.e. tidal lung deformation, and local tissue stress are likely the chief determinants of VILI. (3) We have recently become aware that spontaneous breathing can also damage the lungs under certain conditions: the concept of patient self-inflicted lung injury (P-SILI). (4)

In this issue of *Critical Care Medicine*, Liu et al. explore these newer concepts (5). In 100 spontaneously breathing patients with lung injury due to paraquat poisoning, they tested functional and imaging predictors of 90 day mortality. Patients were studied five days after paraquat ingestion. Distribution of lung aeration on quantitative computed tomography (CT), pulmonary function tests (PTFs), and plasma paraquat levels were obtained. In addition, the authors measured pulmonary strain (measured as tidal volume indexed by functional residual capacity) and respiratory system reactance (an estimate of ventilation heterogeneity). The fraction of poorly aerated lung tissue (after exponential transform) was a strong predictor of outcome, together with the ratio between residual volume and total lung capacity (an index of small airway obstruction). When adjusting for these factors, larger values of lung strain and of ventilation heterogeneity were associated with mortality, while plasma paraquat levels and arterial oxygenation were not.

The unique study population is worth discussing. Paraquat is a highly toxic pesticide that has become a major public health problem in the Asia-Pacific region due its high occurrence in suicide deaths. (6) Paraquat self-poisoning leads to an approximately 50% mortality due to lack of antidote and to the sequelae of fulminant multiorgan failure. Notably, patients

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develop lung injury resulting from a course of acute alveolitis over 1–3 days, followed by secondary fibrosis. Mechanical ventilation and supplemental oxygen are avoided, if possible, to avoid exacerbation of toxicity and oxidative stress. Therefore, paraquat poisoning provides a precious opportunity to study the natural history of lung injury in the absence of mechanical ventilation.

The results of the study suggest that patients whose lungs are poorly and heterogeneously ventilated are at higher risk of a bad outcome, which was compounded by higher lung strain. It is tempting to interpret these correlations as evidence that lung deformation and mechanical stress during spontaneous breathing drive the progression of lung inflammation. However, the study provides no mechanistic determination: poorly aerated tissue (the ground glass opacity) is a marker of worse alveolitis and disease severity. Similarly, higher strain was consequence of lower functional residual capacity rather than of larger tidal volumes, likely another severity indicator. Nevertheless, there is fair evidence that both suboptimal aeration and spontaneous breathing may injure the lungs. First, recent studies showed high metabolic activity (due to inflammation) in suboptimally inflated lung, (7, 8) and a propensity to injury evolution originating from those regions. (9) This may be related to large heterogeneity of inflation at the microscopic scale (below CT resolution), which locally increases tissue stress. Second, spontaneous breathing may be harmful when inflammation and aeration are heterogeneously distributed, leading to regional differences in pleural pressure, pendelluft (intra-pulmonary gas shift) and disproportionate levels of lung strain. (10, 11)

One of the limitations of this study is the questionable applicability of the results to the lung pathologies that are more common in the intensive care unit. Diffuse alveolar damage (DAD) seen after paraquat (and in ARDS) has similarities with acute interstitial pneumonia (AIP) and with acute exacerbations of interstitial lung disease (AE-ILD). All groups have clinical features of an acute onset, rapid development of respiratory failure, radiographic findings of bilateral ground glass opacities and high mortality rate. Conversely, only AE-ILD and paraquat poisoning share management commonalities, such as avoidance of mechanical ventilation and high oxygen concentrations. (12) An extrapolation of Liu's findings to AE-ILD is a stretch but not completely farfetched.

The key question is whether or not it is possible to protect the lungs of these patients and control the progression of disease. If diffuse ground glass opacities seen on CT correspond to sparse edema or micro atelectasis, there could be clinical benefit to the application of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP). As Liu et al. points out in their discussion, sufficient or higher PEEP can potentially reduce the injurious breathing pattern by attenuating the amplitude of negative pleural pressure swings, pendelluft, regional rapid inflation-deflation, or cyclic interruption and exaggeration of pulmonary blood flow. (11, 13, 14)

Yet, invasive or non-mechanical ventilation should not be viewed as the only or even best option. New forms of non-invasive respiratory support enable the application of mild to moderate levels of airway pressure that are well tolerated for an extended amount of time. These include high flow nasal cannula (HFNC), and CPAP or ventilation applied through

helmet. (15, 16) In addition to delivering mild positive pressure, HFNC reduces anatomical dead space, tidal volumes, and lung strain. Recently, the combination of HFNC and helmet support to augment applied pressure has been described. (17) All these other approaches merit a closer look. If supported by the results of a clinical trial, a form of protective respiratory support applied early after paraquat poisoning may generate a new paradigm of containment of acute inflammatory lung disease.

The authors present an interesting investigation and statistical analyses into a distinctive patient population with a lung pathology that mimics DAD such as AE-ILD. Their work continues to build upon our understanding of P-SILI and the progression of lung injury. Moving forward, an ‘exotic’ lung pathology may help us develop more effective and individualized therapies for traditionally difficult to treat groups, through widely accessible lung assessment tools. We continue to make valuable progress but further investigations are needed to bridge this gap.

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