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Conceptual Paper

Acute Respiratory Distress Syndrome: Update of Pathophysiology and Treatment

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Acute respiratory distress syndrome (ARDS) was first described by Ashbaugh., *et al*. in 1967 in patients with refractory cyanosis due to respiratory failure that needed mechanical ventilation. ARDS is an acute severe lung disease commonly occurred in intensive care units (ICU). ARDS has been acknowledged to be a major clinical problem in pulmonology worldwide. A recent multicentric prospective cohort study in 50 countries (The LUNG SAFE trial, 459 ICUs) across five continents, for assessing the clinical recognition of ARDS according to the latest definition with patient inclusion following the Berlin criteria revealed that ARDS is underdiagnosed. Potentially, there is improvement in ARDS management. ARDS can be triggered by several causes including trauma and pneumonia contributing to high morbidity and mortality burden. There is still a high variability in both epidemiology and clinical outcomes various healthcare settings although the recent Berlin definition is probably much better than the previous ones. ARDS is described by widespread injury of the alveolar-capillary membrane, leading to protein-rich noncardiogenic pulmonary edema and acute respiratory failure (ARF). Generally, the incidence of ARDS ranges from 1.5 cases per 100,000 to 79 cases per 100,000, depending on geographic location and on the reporting system used. The term "acute lung injury" (ALI) was previously used to describe a milder form of ARDS, but it is no longer recommended for use. ARDS results in severe hypoxemia, that is refractory to oxygen treatment and requires mechanical ventilation. In 1994, the American-European Consensus Conference (AECC) agreed the criteria for defining the ARDS that specified an acute onset, refractory hypoxemia, and radiological evidence of bilateral pulmonary shadowing due to increased permeability of the alveolar-capillary membrane, with the exclusion of left ventricular failure as the cause. Pulmonary artery catheterization that shows a pulmonary artery occlusion pressure (PAOP) of less than 18 mmHg or by clinical evidence of left atrial hypertension as a sign of left heart failure can exclude a cardiogenic cause of pulmonary edema. The ratio of the arterial oxygen tension (PaO_2 measured in mmHg) to the inspiratory oxygen fraction (FiO_2, where room air is 0.21 and pure oxygen is 1.0) can define the severity of ARDS. Nevertheless, the AECC' s ARDS criteria was refined by the Berlin definition of 2012. Presently, the onset of ARDS is fixed as being within 7 days of an insult or of new or worsening respiratory symptoms, while bilateral radiological shadowing are still necessary. Other causes, such as nodules, partial or complete collapse of a lobe or lung, and effusion should be excluded. Echocardiography presently can exclude cardiac failure or fluid overload. Grading of ARDS is defined as the following: mild (PaO_2/FiO_2 of 200 mmHg to 300 mmHg), moderate (PaO_2/FiO_2 of 100 mmHg to 200 mmHg), and severe (PaO_2/FiO_2 of 100 mmHg or less than 100 mmHg).

ARDS can be triggered by several distinct conditions that contribute to a common pathophysiological pathway. The initiating conditions are grouped into two classes: direct "pulmonary" and indirect "extrapulmonary" events. The direct conditions include several events that injure the pulmonary parenchyma, including pulmonary contusion, pneumonia, aspiration, inhalation, or ingestion of toxic substances, whereas the indirect causes are sepsis which is the most common indirect highly lethal cause, overdose of certain drugs (thiazides or opiates), multiple blood product transfusions (hypertransfusion), disseminated intravascular coagulation, and acute pancreatitis. Later stages of ARDS demonstrates a uniform pathological and clinical pattern despite the variety of triggers and even though the pathophysi-

ological mechanisms and routes of lung injuries. In acute phase of ARDS, there is injury to the alveolar-capillary barrier, with disruption contributing to increased permeability ("leakiness"). There is leukocyte accumulation in the pulmonary capillaries and invasion of the airspaces contributing to inflammatory vasoconstriction (in contrast to inflammation-induced vasodilation in the systemic circulation), and reduced lung compliance and atelectasis due to loss of surfactant that lines and normally stabilizes alveoli and reducing surface tension of the alveolar lining fluid. There is severe ventilation/perfusion mismatching with some perfused alveoli no longer receiving any ventilation ("shunt"), whereas others are ventilated but not perfused ("dead space"). These consequences aggravate respiratory failure.

Three histopathological phases are revealed during the evolution of ARDS: 1) early exudative phase which results from endothelial injury and diffuse alveolar damage; 2) proliferative phase which lasts around 7 - 14 days after the lung injury, incorporating re-establishment of the barrier function, repair of the damaged alveolar structure, together with fibroblast proliferation; 3) fibrotic phase with chronic inflammation and fibrosis of the alveoli in some patients. There is insufficient awareness about the individual and environmental risk factors although most ARDS predisposing factors are well known. Active or passive cigarette smoke and chronic alcohol abuse have been associated with an increased incidence of ARDS, while the impact of environmental pollution on the incidence of ARDS has not been established. In previous cohort studies, long-term ozone exposure (OR = 1.58, 95% CI = 1.27 - 1.96, $p < 0.001$) and vitamin D deficiency were found to be risk factors for ARDS. Some previous studies have demonstrated experimentally that the virulence capacity of *Pseudomonas aeruginosa* is a major determinant of the severity of the lung injury.

Management of ARDS includes mechanical ventilation, fluid management, inflammation management (corticosteroids), decreasing oxygen consumption, increasing oxygen delivery, and supportive care. A previous study by ARDSnet, a strategy of "protective ventilation" demonstrated that using a low tidal volume (6 ml/kg predicted bodyweight) compared with a traditional high tidal volume (12 ml/kg predicted bodyweight) was successful in significantly reducing mortality rates from 39.8% to 31%.

In conclusion, ARDS frequently remains an misdiagnosed syndrome, carrying high patient morbidity and mortality despite the well-established advances in its supportive treatment. Mechanisms of lung injury in humans and animals are poorly understood. Both high ozone exposure and vitamin D deficiency as risk factors for ARDS development have to be understood and confirmed.

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