EDITORIAL

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Pharmacotherapy for Acute Respiratory Distress Syndrome: Limited Success to Date

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Acute respiratory distress syndrome (ARDS) is characterized by diffuse inflammation of the lung in response to various pulmonary and extra-pulmonary insults[1]. Regardless of the inciting event, the pathogenesis of ARDS features damage to the alveolar-capillary membrane, with leakage of protein-rich edema fluid into alveoli[2]. This endothelial damage is associated with an inflammatory response that includes neutrophil activation, formation of free radicals, activation of the coagulation system, and release of pro-inflammatory mediators. The complex pathophysiology thus provides multiple potential targets for pharmacologic therapy for ARDS[3]. A number of pharmacologic therapies for ARDS were once regarded as promising based on the extensive, supportive, preclinical data and sound physiologic rationale; however, clinical trials of potential therapies apparently fail to improve outcomes in established ARDS.

Diabetes, a metabolic disorder causing hyperglycemia, has been found to be protective against the development of ARDS[4]. The pathways involved are complex and likely include effects of hyperglycemia on the inflammatory response, metabolic abnormalities in diabetes, and the interactions of therapeutic agents given to diabetic patients. The common therapies used in diabetes, like insulin, may also influence the development of ARDS[5]. In addition, other drugs commonly used in the management of diabetes may have protective effect on the progression of ARDS. Metformin, a widely used drug for treatment of diabetes, was recently shown to reduce severity of lipopolysaccharide-induced lung injury by modifying mitochondrially derived reactive oxygen species[6]. Therefore, the use of metformin as a potential therapy for ARDS has generated considerable interest and experimental animal studies have found that metformin has anti-inflammatory[6], antioxidant[7], and anti-thrombotic effects[8] that may influence the outcome of critical illness by attenuating the development and progression of acute organ dysfunction, including lung injury. However, there are limited data supporting that metformin could be a potential candidate for pharmacologic therapy for ARDS in patients.

In this issue of *Tuberculosis and Respiratory Disease*, Jo et al.[9] report the results of a retrospective cohort study of 128 patients with ARDS in which the effect of preadmission of metformin on clinical outcomes were examined. The hypothesis of this study was that the use of metformin at the time of the development of ARDS would prevent an excessive proinflammatory response and thereby reduce of the risk of organ failure and death. In a propensity-matched analysis, however, the authors could not demonstrate that preadmission metformins were associated with reduced 30-day mortality in patients with ARDS. Secondary outcomes included ventilator-free days and length of stays, which were not significantly different.

One of the primary weaknesses of the study, as identified by the authors, is that metformins were discontinued at the time of admission. Based on the previous animal studies, the pleiotropic properties of metformin might influence the progression as well as the development of ARDS. True protective effect of metformin on the progression of ARDS could be supported by the fact that better outcome would be restricted to patients on the medication. However, treatment with metformin generally is not recommended in critically ill patients because of the potential risk of severe lactic acidosis reported[10]. Therefore, it is unlikely feasible to test the hypothesis of the authors with epidemiologic data from clinical practices. However, the potential risk of lactic acidosis should be balanced against the possible benefits of metformin in future clinical tri-

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als.

Effective pharmacotherapy for ARDS remains extremely limited. Despite decades of clinical trials, no pharmacological treatment has emerged for the treatment of all patients with ARDS. Only lung protective ventilation strategies to date have improved outcomes of these patients[11]. Despite the discouraging results of pharmacotherapy for ARDS thus far, promising therapeutic targets are being explored as our understanding of ARDS continues to evolve.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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