Experimental Acute Lung Injury in Animals: With Age Comes Knowledge

To the Editor:

With great interest, we read the recent American Thoracic Society (ATS) workshop update on features and measurements of experimental acute lung injury (ALI) in animals (1). The workshop committee needs to be commended for their ongoing effort to develop a much needed, transparent, and unequivocal framework for animal research studying the complex patho-biological and patho-physiological aspects of ALI. Their "multidimensional" approach must standardize the existing animal models and diminish the bridge between mechanistic, preclinical, and clinical research. However, so far, the influence of age in defining this framework has been neglected.

It is well known that the prevalence and outcome of acute respiratory distress syndrome (ARDS) varies with patient's age (2, 3). For example, children tend to be less susceptible to develop ARDS, and have lower mortality. The current coronavirus (COVID-19) pandemic further magnifies the existence of such age-related differences in ARDS response to a similar clinical exposure. In an effort to adapt the clinical ARDS criteria to young age, both the pediatric-specific ARDS (PARDS) definition in 2015 and later the Montreux definition of neonatal ARDS in 2017, have been developed. However, the influence of age on development and outcome of ALI, but also on specific measurements of pulmonary injury and inflammation, has been less characterized in preclinical studies.

Findings from the current literature involving animal models seem to mirror the situation in humans: increasing age is associated with higher susceptibility to, and severity of ALI in response to an identical trigger (4). More importantly, studies of ALI in animals show the existence of highly differential, age-related pulmonary responses in all of the four key pathophysiological domains (histological injury, alteration of the alveolar-capillary barrier, inflammatory response, and physiologic dysfunction), as identified by the ATS workshop committee (1, 4). For example, in a study with rats treated with intratracheal lipopolysaccharide and mechanical ventilation, adult rats (3–4 months old) showed marked increases in alveolar permeability and inflammation as compared with infant rats (2–3 wk), but these findings were not accompanied by more histopathological lung injury (5). Age in ALI animal models may affect baseline readouts, and as such influence the choices between pathophysiological domains and between outcome measurements within those domains. Age-dependent differences in the levels of biomarkers for inflammation and injury, including those of endothelial dysfunction (e.g., ICAM-1, now further recognized to be of relevance in the current ATS workshop report), are also apparent in the lungs of patients with ARDS (6). Furthermore, the nature and extent of innate and adaptive immunity to pathogens is strongly influenced by age of the host. It is precisely because of baseline differences as well as differential, or even divergent, responses to injurious events, that we believe the age-perspective deserves more attention in the multidimensional approach to experimental ALI.

In conclusion, based on the current evidence we want to emphasize that "age" is an important determinant in all four domains of the host response during ALI, as described by the ATS workshop committee on animal models. We believe it should be considered to adopt the age-perspective in future updates of the multidimensional framework on experimental ALI. Finally, a closer collaboration between pediatric and adult critical care research programs will help better integrate mechanistic and clinical insights across the age spectrum, ranging from neonatal, pediatric, adult, and elderly patients, thereby enhancing the ability to translate knowledge from the bench to the bedside. ■

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