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EDITORIAL

Causes of failure in acute respiratory distress syndrome modeling and treatment in animal research and new approaches

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Abstract

Acute respiratory distress syndrome (ARDS) is a major cause of morbidity, death and cost in intensive care units. Despite intensive research, pharmacotherapy has not passed the experimental stage and mortality rates are still high. Animal models provide a bridge between patients and the laboratory bench. Different animal models have been developed in order to mimic human ARDS, but they have limitations. The purpose of this review was to summarize the properties of the most commonly used experimental animal models mimicking the causes and pathology of human ARDS, the limitations of ARDS models, treatment failure and new therapeutic approaches.

Key words: Acute respiratory distress syndrome; Lung injury; Animal models; Model limitations

Core tip: Acute respiratory distress syndrome (ARDS) is a syndrome with multiple risk factors that trigger the acute onset of respiratory insufficiency. ARDS is still one of the most fatal diseases with a high mortality rate in intensive care units. Mortality rates remain unchanged, pharmacotherapies have a very limited role in the management of ARDS and additional treatments are sorely needed. Animal models provide a bridge between patients and the laboratory bench, but these models have certain limitations and to date, no single animal model reproduces all the characteristics of human ARDS. Despite these limitations, the complex pathogenesis of ARDS makes animal models necessary.

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) was first described in 1967[1], and its description was developed into the Berlin definition in 2011[2]. In the clinical study cohort of the Berlin definition, the mortality rate was 27% for mild, 32% for moderate and 45% for severe ARDS[3]. Although worsening oxygenation is a risk factor for ARDS mortality, patients generally die from multisystem organ failure or a progressive underlying illness; only a minority of ARDS patients (13%-19%) die from refractory respiratory failure[4]. Currently, there is no effective medical treatment that improves the survival of adult patients with ARDS.

ARDS is a syndrome of inflammation and increased permeability of the blood-gas barrier[5]. It is characterized by rapid-onset respiratory failure following a variety of direct (*e.g.,* bacterial and viral infections of the lungs, aspiration of gastric contents and inhalational injury) or indirect (*e.g.,* systemic infections that cause sepsis syndrome, major trauma, pancreatitis, severe burns and blood transfusions) insults to the parenchyma or vasculature of the lungs[5-8]. Pneumonia and sepsis are the two most common predisposing conditions for the development of ARDS[5,6].

There have been a number of studies addressing the pathogenesis of, and therapies for, ARDS (*e.g.,* inhaled pulmonary vasodilators including nitric oxide and prostacyclins, corticosteroids, beta agonists, neuromuscular blocking agents, statins, macrolide antibiotics, aspirin, angiotensin converting enzyme inhibitors/angiotensin receptor blockers)[2,9,10]. However, despite intensive research, pharmacotherapy has not passed the experimental stage and supportive therapies represent the mainstay of ARDS treatment[2-5,9-11]. The current therapeutic strategy primarily emphasizes low tidal-volume mechanical ventilation and judicial fluid management, plus treatment of the initiating insult and any known underlying disease[2-4,9,10]. This dearth of therapeutic modalities is largely due to the complex pathogenesis of ADRS, where multiple overlapping signaling pathways are activated depending on the type of lung injury[2,9,10]. The development of experimental models and therapies is necessary for improving treatment and reducing the mortality rate.

ARDS ANIMAL MODELS

Different animal models have been developed for ARDS research[5-8,12,13]. These models can be divided into two groups: direct, in which the lung is injured directly; and indirect, where models are generally based on the formation of sepsis (Table 1). To create a similar human ARDS model, various injury models can be combined[5,14,15]. Numerous different models have been developed, but there is no animal model which shows all the characteristics of human ARDS[5-8,12-15] (Table 1).

Creating a model to mimic the human ARDS definition is not practical in animals, particularly in small animals. Therefore, using histopathological criteria to define ARDS is a more accurate approach[8]. In humans, inflammatory cell infiltrates, thickening of alveolar septa and hyaline membrane depositions are the main characteristics of alveolar damage[5,10]. There is no animal model which shows all the characteristics of human ARDS, however, lacking one of these factors does not mean that this model is not a form of ARDS[8]. The most important factor is choosing an appropriate experimental model. Before choosing an animal model of ARDS, the target feature to be tested should be determined and then it should be created in the most appropriate model[7]. For example, if the passage of neutrophils into the lung is to be investigated, the lipopolysaccharide (LPS) instillation model characterized by alveolar neutrophilia would be appropriate. If epithelial damage is of interest, the acid instillation model would be considered suitable[7].

Table 1 Animal models of acute respiratory distress syndrome

Direct lung injury	Intratracheal or intranasal delivery of bacteria or bacterial product such as lipopolysaccaride
	Hydrochloric acid or gastric particles to create acid aspiration
	High inspired fraction of oxygen
	Surfactant depletion (0.9% NaCl lavage)
	Lung ischemia/reperfusion
	Mechanical ventilation at high tidal volumes
Indirect lung injury	Cecal ligation and puncture
	Intravenous bacteria or LPS administration
	Mesenteric ischemia/reperfusion
	Oleic acid model
Combination models	Cecal ligation and puncture followed by hemorrhage
	Saline lavage after mechanical ventilation
	Intraperitoneal LPS injection after intravenous oleic acid

LPS: Lipopolysaccharide.

LIMITATIONS OF ARDS MODELS

Animal models of ARDS can mimic the clinical disorders, but there are certain limitations that affect the success of the modeling and treatment options[5-8,12-15] (Table 2).

Despite these limitations, animal models are needed. Matute-Bello *et al*[7] reviewed each model with its advantages, disadvantages and methodologies. Animal models also focus on interactions between systemic (*e.g.,* renal failure, hepatic and hematologic dysfunction) and pulmonary injuries[7].

NEW APPROACHES IN ARDS TREATMENT

In the last decade, significant advances in the molecular mechanisms of ARDS have been recorded. However, these improvements could not be implemented successfully in clinical practice.

When considering new therapeutic opportunities and research, such therapies may come from mesen-

Table 2 Limitations of acute respiratory distress syndrome models

Experiment period	The formation of pathology takes hours or days in humans, whereas the monitored period is shorter in animal models (monitoring difficulties)
Ventilation and fluid management	Ventilation and fluid management supports are lacking in animal experiments (these are crucial in humans)
The degree of pathology	Experimental models generally have milder pathology compared to human pathology
The species and the size of the animals	Larger animals (primates) can more easily mimic human disease, but these experiments require expertise. Smaller animals (mice) are much more widely used (this may allow for the study of complex pathways and genetic studies)
Treatment time	Therapeutic agents in experimental studies are usually given before the onset of acute respiratory distress syndrome, whereas the clinical diagnosis and treatment of ARDS is delayed
Animal age	Animal experiments are performed on young animals with no comorbidities; however, patients with ARDS are mostly elderly and may have many medical problems such as cardiovascular diseases, kidney or liver failure
Changes in response to therapy	The effects of therapeutic agents on survival in humans and animals are different. An agent may be effective on animal survival, but may not be effective in humans (there are many anatomical and physiological differences between animals and humans)
Coagulation and fibrinolytic status	Animal models cannot mimic the coagulation and fibrinolytic system changes during lung injury in humans
Correlation between biochemical markers and their biological activities	Biochemical markers measured in bronchoalveolar lavage fluid, plasma and edema fluid may not correlate with their biological activities
Combination treatment	Combined treatment should be developed. Combined treatment approaches are applied to a lesser extent in experimental models

ARDS: Acute respiratory distress syndrome.

chymal stem cells (MSCs; "adult stem cells") and gene therapies[2].

MSCs could represent a promising new therapy for this syndrome, as recent animal research suggests that MSCs may ameliorate lung injury[16]. MSCs have several features which allow their use in the treatment of ARDS. MSCs are capable of regenerating damaged tissues and can differentiate into different cells. In addition, they can release immunomodulatory and anti-inflammatory molecules. These cells also lack HLA II molecules and this allows them to escape the immune reactions after transplantation[2]. Viral and non-viral methods for gene delivery to the lung have been developed. Recent studies have demonstrated that gene transfer of hemoxygenase-1, IL-10, and keratinocyte growth factor attenuate lung injury[2,17]. With the development of more efficient approaches, the use of therapeutic gene therapy will be safe and efficacious in the treatment of ARDS, leading to urgently needed, novel and safe therapies for ARDS. At this stage, further animal research will maximize therapeutic potency and safety of cell, gene or combined cell-based gene therapies and other pharmacotherapy agents in the treatment of ARDS.

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