Should we shift the paradigm of preclinical models for ARDS therapies?

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The acute respiratory distress syndrome (ARDS) is characterised by diffuse impairment in gas exchange that can result from heterogenous aetiologies. ARDS causes 10% of intensive care unit admissions worldwide with inpatient mortality rates ranging from 35% for mild cases to 46% for severe cases.[1] Despite being a common and frequently fatal process, there are no widely accepted pharmacological therapies available to treat ARDS, the management of which primarily rests on appropriate mechanical ventilation and supportive care.[2] Unfortunately, numerous promising pharmacological therapies that demonstrated benefit in preclinical models or early clinical investigation have failed to demonstrate reliable improvement in clinical outcomes.[3–7] In the context of a persistent clinical problem that has vexed state-of-the art investigative therapies, there have been thoughtful proposals on how to improve the investigation of potential ARDS therapies in experimental animal models of acute lung injury (ALI).[8–10] A 2011 American Thoracic Society (ATS) statement defined experimental ALI as an acute process (ie, sequelae develop within 24 hours of exposure) with increased permeability of the alveolar-capillary membrane, frequently with histopathological correlation, leading to impairments in lung physiology.[8] Building on these earlier proposals, Oakley and colleagues[11] propose in this issue of *Thorax* two broad, fundamental changes in the philosophical framework for the investigation of novel therapeutics in preclinical ARDS models.

The first fundamental change to the 2011 ATS definition proposed by Oakley *et al*[11] is that experimental animal models used to assess the clinical efficacy of proposed ARDS therapeutics should be clinically relevant. Specifically, the authors highlight three criteria to define an effective model based on the notion that the clinical conditions of animal models should reflect as best as possible the clinical conditions of human patients that would receive the experimental therapy. First, ARDS therapies should be tested in lungs with pre-existing injury because patients with ARDS do not typically present for treatment until the underlying pathophysiological process of lung injury is already initiated and likely progressing in severity. The authors make an important distinction here between prophylactic and rescue therapies as many experimental models use either pretreatment or peri-injury approaches to prove benefit, which can be difficult to execute in a clinical syndrome that may present days after the incident injury.[9 12] Second, mechanical ventilation should be incorporated into animal models of investigational therapies because ventilation has the potential to exacerbate injury, and most patients with ARDS will require mechanical ventilation during their treatment course even with increasing use of high flow nasal cannulae. Third, potential therapies should be evaluated for their efficacy at either restoring, or preventing deterioration in, physiological lung outcomes such as oxygenation or lung compliance rather than potentially intermediate outcomes such as lung inflammation. As an example of a model that fulfils these criteria, the authors propose a two-hit murine model using inhaled lipopolysaccharide (LPS) as a lung injury stimulus followed by mechanical ventilation initiated at the time of worsening clinical status and use measurements of lung oxygenation and compliance to monitor the efficacy of the therapies tested. The second fundamental change proposed by the authors is to use failed therapeutics as a negative control for assessing the potential efficacy of a novel intervention. That is, a therapeutic should be tested for its ability to perform measurably better than a therapy known to have failed in human trials. This is an intriguing proposal that is buttressed by data demonstrating that one failed human therapeutic, terbutaline, was ineffective in their two-hit mouse model of LPS injury followed by mechanical ventilation. Compared with their negative control, the authors showed marginal improvements in lung oxygenation and compliance in mice treated with an antibody targeting tumour necrosis factor receptor-1 (TNFR-1), which is consistent with their prior work using a slightly different model.[13]

Taken together, the shift in investigative framework that the authors propose is logical, informed by clinical medicine, and provides concrete strategies to address the well-known need to improve preclinical ARDS models. However, 'the devil is in the details', and there are some important weaknesses in the proposed paradigm. First, determining whether a preclinical model is 'clinically relevant' is more complex than it may seem. For example, what is 'clinically relevant' may differ greatly between a level 1 trauma centre and a paediatric hospital in a resource-limited setting. Therefore, the ability of preclinical testing to reliably predict beneficial therapies in heterogenous entities such as ARDS is dependent not just on the details of the model used but also on the clinical population selected for subsequent clinical trials.[9 10] Furthermore, there is no existing animal model of injury that accurately reproduces all features of human ARDS,[8 9] and there are important interspecies differences between mice and humans. For example, mice lack interleukin-8, the most important neutrophilic cytokine in humans. Similarly, most preclinical studies test healthy in-bred juvenile animals that are genetically identical, whereas patients with ARDS are typically older, suffer from various comorbidities (eg, diabetes and heart disease) and have extensive genetic variability, all of which may affect their response to an intervention. Finally, the clinical endpoints used to evaluate ARDS therapies such as 28-day mortality or ventilator-free days are difficult to recapitulate in animal models.[9] Although there may be varied opinions regarding the clinical relevance of any specific model, the basic concept of being 'as clinically relevant as possible' remains important. Perhaps drug development in preclinical models could follow an iterative approach, testing progressively more 'clinical-like' scenarios depending on the effectiveness shown at each step. For example, testing could begin with a 'high throughput' model such as LPS followed by a more 'clinically relevant' model such as two-hit ventilation prototype and, finally, confirmation on outbred animals. It appears that an open discussion about this topic aimed at achieving recommendations, perhaps at the level of relevant scientific societies, is urgently needed.

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Regarding the usefulness of failed interventions as a negative control, this is also a tantalising idea but a complex one as well. ARDS is a syndrome that likely represents a stereotypic lung response to a number of different pathogenic mechanisms, making it unlikely that any single intervention will work in all cases of ARDS. In fact, differential treatment response to ARDS interventions has already been suggested by Calfee *et al*.[14 15] Therefore, some might argue that using a failed therapeutic as a minimum threshold for a new therapy to surpass for 'success' is overly simplistic and risks adding unnecessary complexity to preclinical testing.

The difficulties mentioned above can also be applied to the specific model proposed by Oakley *et al*.[11] Even accounting for the complexities of modelling human ventilation in mice, it is unclear whether 20 mL/kg is an appropriate volume given conflicting existing evidence whether this volume itself is injurious in mice.[16 17] Furthermore, the reliance on a single domain (ie, physiological parameters) to measure lung injury limits the conclusions that can be drawn. ATS recommends using multiple domains including alveolar-capillary permeability, histopathology and lung inflammation in addition to physiological parameters such as gas exchange and compliance to assess lung injury in experimental animal models.[8] In addition, the short time course—minutes to hours—of the therapeutic phase of their model may impair translation into humans. Finally, and perhaps most importantly, the authors do not address the absence of mechanistic data to explain potential benefits in their model. For example, does TNFR-1 antibody administration prevent endothelial injury as others have proposed in healthy human volunteers exposed to inhaled LPS[18] or is there another mechanism that maintains gas exchange in their model? Perhaps it would be beneficial to add a third component to the proposed paradigm shift, that is, to better define the cellular mechanisms underlying the benefit of ARDS therapies in preclinical models, which may improve selection criteria or therapeutic strategies for subsequent clinical trials in humans.

Despite the limitations mentioned above, it is clear that we have to rethink our approach to preclinical testing in ARDS, and the framework proposed by Oakley *et al*[11] deserves a thorough discussion. In particular, their overall proposal that preclinical models should attempt to be clinically relevant by modelling how potential therapeutics would be used in humans is highly relevant. It follows that we should test the ability of 'rescue' therapies to rescue gas exchange when delivered at a time of clinically meaningful decompensation rather than the more commonly used peri-injury approach. Similarly, prophylactic therapies that show promise for human translation should only be tested in humans using a prophylactic approach unless they also demonstrate benefit when used as a preclinical rescue therapy. Finally, we propose that experimental animal models should be used to identify the mechanisms by which potential therapeutics provide benefit to better inform the design of subsequent clinical trials. While it is unclear that the model proposed by the authors can achieve these goals, the points raised remain valuable. Given the vexing history of investigational ARDS therapies, we applaud the authors for their contribution to a conversation that should be continued by professional societies, journal editors, grant reviewers, scientists and clinicians as we seek to improve the care of patients with ARDS.

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