Perspectives on Lung transplantation: mechanical ventilation and biomarkers in the development of chronic and acute graft dysfunction

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Abstract

Background
Despite strides made within the last sixty years of lung transplantation, this surgical procedure remains hindered by a high risk of mortality and morbidity. Patients face difficulties including the low availability of transplantable donor organs and high rates of post-operative complications upon receipt of a graft. Both primary graft dysfunction (PGD) and bronchiolitis obliterans (BOS), a form of chronic rejection, are serious threats to the longevity of transplanted lungs. Despite the high proportion of patients who will encounter these disease processes, the factors which either exacerbate or prevent them are not fully elucidated. Furthermore, there are few available methods and markers by which to predict and easily diagnose disease state.

Research questions
The main projects aim to answer the following questions:
1. Do post-operative mechanical settings correlate with the incidence of PGD?
2. Are there novel plasma proteins which can be used as biomarkers of BOS?
3. Can new technology serve as a bedside method of predicting PGD onset?
4. Can an ex vivo model using biopsied tissue recapitulate acute rejection?

Preliminary Results
In a retrospective study of lung transplant patients, we were able to analyze the mechanical ventilation settings and graft size matching to generate hypotheses on associations with PGD development. Looking at plasma samples of these transplant recipients, we also isolated previously described disease markers and identified a novel marker, corticotropin releasing hormone (CRH). CRH was found to be decreased in BOS patients and to decrease as patient disease level became progressively more severe.

In studies that are currently underway, we have used a novel device to both monitor and collect exhaled breath particles from our translational porcine transplant model. We aim to use the collected particles and their rates to further characterize the onset of PGD. From this same porcine model, we have collected tissue which we are using to develop a bench side ex vivo model of acute rejection.

Significance
These projects take clinical and translational data to study the processes that surround the onset and progression of acute and chronic rejection. Given a lack of existing tools, the use of exhaled breath particles and ex vivo models will provide novel methodologies by which to understand postoperative complications. Furthermore, our studies of mechanical ventilation and plasma markers provide clinical insight to inform guidelines on patient care.

Papers to be included in the thesis: