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Utilizing Cytokine Adsorption to Reduce Primary Graft Malfunction Both During Organ Preservation and After Lung Transplantation

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Abstract

Despite advancements, lung transplantation remains hampered by both a scarcity of donor organs and by mortality following Primary Graft Dysfunction (PGD). Using lipopolysaccharide, and caused mild to moderate Acute Respiratory Distress Syndrome (ARDS) in 16 donor pigs. Then, Ex Vivo Lung Perfusion (EVLP) and/or extracorporeal hemoperfusion were used to treat the lungs with or without cytokine adsorption. The medication dramatically reduced post-transplant immune cell counts as well as cytokine levels during EVLP. The incidence of PGD was dramatically decreased in treated mice, and histology showed fewer symptoms of lung damage during both treatment periods. Overall, lung transplantation with cytokine adsorption was successful in restoring lung function and lowering PGD.

Keywords: Primary Graft Dysfunction (PGD) •Acute Respiratory Distress Syndrome (ARDS) • Ex vivo lung perfusion

Introduction

Organ transplantation is still a crucial weapon in the arsenal of treatments for advanced illness, but the field is still constrained by a lack of available organs. The World Health Organization (WHO) notes that just 10% of the world's demand for organ transplantation is being satisfied, which it considers to be a public health crisis. According to estimates, only 40% of possible donor lungs are chosen for transplantation because of donor lung damage and concern over the possibility for Primary Graft Dysfunction (PGD), in striking contrast to the 83% of potential donor kidneys that are transplanted. Despite scientific progress, PGD continues to be the main cause of early death and is a major factor in the development of Chronic Lung Allograft Dysfunction (CLAD), which is the main cause of late mortality. Due to lung damage, rejected donor lungs are frequently considered irreversible. Acute Lung Injury (ALI) and the more severe Acute Respiratory Distress Syndrome (ARDS), which can also damage donor lungs from aspiration, infection, or neurogenic edoema, are common causes of severe respiratory failure. An inflammatory injury at the alveolar capillary barrier and edoema in the airspaces define the damage. Interleukin-6 (IL-6) and other cytokines, such as interleukin-1 (IL-1), and Tumor Necrosis Factor (TNF), are essential signaling molecules that start, increase, and maintain inflammatory reactions both locally and systemically in ALI and ARDS.

Orthotopic heart transplantation has been demonstrated to benefit from cytokine reduction via adsorption, and delayed graft function after kidney transplantation has also been shown to decrease.

Despite evidence that cytokine adsorption does not improve patient survival in septic shock, there is still disagreement on its effectiveness. By lowering the amounts of cytokines like IL-6, IL-1, and TNF-, cytokine adsorbers have been used to treat sepsis or ALI. Although cytokine adsorbers are being researched for their potential in ARDS patients, their ability to save donor lungs from ARDS damage for subsequent transplantation has not been completely investigated. Ex Vivo Lung Perfusion (EVLP), a revolutionary method for evaluating donor lungs that were previously unsatisfactory has been employed in the successful transplant of lungs that had been assessed using the EVLP system. Recently, cytokine adsorption has been tested in pre-clinical conditions in conjunction with EVLP and used as a treatment for healthy lungs exposed to prolonged cold ischemia storage. The restoration of the tissue from exposure to protracted ischemia by cytokine adsorption would allow for longer transportation durations and ease the scheduling of surgeries given that the tissue was healthy at its origin. This would be distinct from looking at lungs that were already damaged at the time of explantation in an effort to increase the number of donor lungs that are still viable for transplant.

In the current study, cytokine adsorption in the recipient during and after the transplant to assess the potential for transplanting lungs with ARDS, with the PaO_2/FiO_2 ratio serving as the primary endpoint to assess lung function was used. Using an extracorporeal cytokine hemoadsorber, this treatment was either given in two stages—at EVLP and post-transplantation or it was given only after the transplant (one-step treatment). Comparing treated patients to untreated recipients, clinically significant and molecular outcomes during EVLP and in the days following transplantation. We postulated that a cytokine adsorber would restore ARDS-affected lungs and lessen the likelihood of PGD.

Discussion

In order to restore the lungs transplantability after ARDS injury, the current study investigates the use of a cytokine adsorber in treatment. According to the findings, using a cytokine adsorber
(i) recovers pulmonary function and inflammation during EVLP.

(ii) restores pulmonary function and lowers inflammation in the 48 hour follow-up post-transplantation.

(iii) was associated with a lower incidence of PGD in recipients.

The importance of this method is based on the interest in repairing damaged lungs. Cross-circulation may be used to repair damaged human lungs, but implementing xenogeneic or allogenic cross-circulation may be difficult in practice. In contrast, using EVLP is a tried-and-true technique that by itself can lessen acute lung injury. EVLP can be used to treat healthy lungs subjected to prolonged cold ischemia storage when combined with a cytokine adsorber. However, the results of employing cytokine adsorption on ARDS-damaged lungs that are then transplanted and assessed for Primary Graft Dysfunction (PGD), the gold standard for determining the effectiveness of possible therapies in the clinic, have not been studied using this technique.

Lungs from donors that had an ARDS injury from LPS were transplanted and given cytokine adsorption therapy. After being administered intravenously, LPS, which is made from gram-negative bacteria's outer membrane, damages the lung's endothelial cells. An inflammatory response across the body also contributes to the damage. The endothelium lining of the lung's vessel walls interacts with the bacterial toxin to cause programmed cell death, which is thought to be crucial to sepsis pathogenesis. Given that the condition has the potential to be clinically translated, this method of producing ARDS has been investigated in large animal models. Oleic acid and other methods of inducing ARDS also cause lung disease, but they do so by using pathways that are not the same as

those identified in ARDS patients in humans. The use of endotoxins has benefits such as technical repeatability and a pathophysiology similar to clinical ARDS. Given the significant number of organs that are rejected owing to acute lung injury, using an LPS-induced ARDS model gives an opportunity to investigate the extension of the donor pool. Numerous factors, including infection, neurogenic edoema, and trauma, may lead to the development of ARDS. Damage to the central nervous system results in extreme stress that activates ARDS40 in neurogenic edoema. In spite of the variations among various causes of illness, they all contribute to damage to the lung epithelium, which raises permeability and causes pathological pulmonary edoema and failure of the lung to undergo adequate gas exchange. To test treatments that lessen or completely reverse the harm brought on by cellular injury, an ARDS model that accurately mimics this pathology must be used. The focus on prolonged cold ischemia storage in other EVLP and cytokine adsorption research has led to the conclusion that lung tissue may be perfused for longer but has not addressed a scenario in which the lung is already injured.

All donors in the pathologies created in this investigation developed mild to moderate ARDS, and the PaO2/FiO2 ratio before lung harvest revealed considerably decreased gas exchange capabilities. This is consistent with the Berlin criteria of the syndrome, and histological evidence further supported the diagnosis of ARDS. Diffuse alveolar injury, in which hyaline membranes conspicuously line alveolar gaps, has previously been used to describe ARDS pathologically. Endothelial cells and pneumocytes may necrotize, resulting in edoema and alveolar bleeding. The tissue recovered after LPS injection in the study's model showed a slight hyaline membrane development. The blinded scoring procedure, which scored samples based on proteinaceous debris, thickening of the alveolar walls, bleeding, and atelectasis, and demonstrated considerable histological damage in LPS-treated lungs as compared to controls, added additional proof of the start of ARDS. Additionally, all donors' levels of early response cytokines—specifically, IL-6, IL-8, IL-1, and TNF-—dramatically increased after receiving LPS. These cytokines have been shown to rise during ARDS in the past. TNF-, IL-1, IL-6, IL-8, and IL-18, proinflammatory cytokines, have even been proposed as ARDS19 biomarkers of morbidity and death. TNF- has been identified as a pro-inflammatory cytokine involved in the aetiology of ARDS that functions downstream of pattern recognition receptors, and IL-6 has been investigated for its relationship to morbidity and death in ARDS. A hyper-inflammatory phenotype with elevated plasma levels of inflammatory biomarkers was discovered to have a distinct therapeutic response and to be associated with greater mortality rates during a discussion of possible sub-phenotypes of ARDS.

Harvested lungs were tested for recovery of function after cytokine adsorption was finished during EVLP for four hours following the development of ARDS. While the PaO_2/FiO_2 ratios of treated lung had enhanced gas exchange capacity and most of them obtained a PaO_2/FiO_2 ratio above 300, those of untreated lung did not reach values that were suitable for transplantation. In addition, compared to untreated lungs, the treated group's lungs had considerably lower BALF levels of IL-1. Throughout the whole EVLP, other cytokines also generally reduced. Comparing the two circumstances shows that there is less inflammation, which is further confirmed by the fact that the treated lungs had less immune cells and more atelectasis than the untreated lungs did. Given that IL-1 was previously identified as a predictive predictor of non-recovery after EVLP, the discovery of lower levels of IL-1 is particularly noteworthy. These outcomes imply that the treated lungs' pulmonary function has been restored.

In the context of numerous surgical disorders linked to elevated inflammatory cytokines, the use of extracorporeal blood purification methods to lessen tissue damage has been investigated. Cytokine adsorbers are a class of commercial items that absorb chemicals using polymer beads. These tools reduce the amounts of various cytokines by concentrating on molecules with a moderate and low molecular weight. They have so far been used in vivo in settings for human kidney and orthotopic heart transplants. The gadget was said to have decreased the levels of IL-6, IL-8, IL-1, and TNF- in patients with severe sepsis and acute lung damage. Adsorption was used in the trial to see if it could save donor lungs from ARDS after it was discovered that it helped heal healthy lungs injured by ischemia.

The transplanted lungs were observed for 48 hours to examine the effectiveness of the adsorption in this situation. It was discovered that both the one-step and two-step treatments resulted in higher hemodyna-mic stability and a decreased requirement for inotropic support. This is consistent with studies on cytokine adsorption in patients with septic shock, in whom the therapy resulted in lower noradrenaline doses. Additionally, lowering IL-6 levels in a randomized controlled study on septicemia demonstrated reduced inflammation. Recipients in this model were also shown to have lower cytokine levels, and the treated groups neutrophil and total white blood cell counts both decreased significantly.

The inflammatory response in ARDS is mediated by activated macrophages, which release TNF-, which in turn activates neutrophils and, along with other mediators, causes the recruitment of inflammatory cells to the alveoli. Histological analysis of the study's treated lung tissue revealed a decline in accumulated immune cells. This supports the conclusion that cytokine adsorption aids in the reduction of inflammation. It is important to note that the lung injury score for the one-step treatment was comparable to the scores for the two-step and control groups, and this difference was reflected in the TUNEL staining. This would suggest that the cytokine adsorber, when given both during EVLP and post-transplantation as opposed to only after transplantation, has an additive impact.

Due to anatomical restrictions on the right bronchus, double LTx in pigs is not possible; instead, a left LTx was performed in this model. The result was a right-sided pneumonectomy to assess the function of the transplanted lungs. Surprisingly, there was no difference in the groups gas exchange capacities on the first post-transplantation day. But on the second day, and particularly after the right pneumonectomy, there was a noticeable difference in gas exchange between the two-step treated and untreated groups, with the treated lungs functioning better. It may be inferred from the ratio in the one-step treatment and the results of the histological and apoptotic scores that the effects of the cytokine adsorber are amplified when applied at two different time points. The graft transplantation responses of the various treatment groups varied, indicating the broad range of the cytokine adsorber's effects. Three transplant recipients exhibited septicemia symptoms after the procedure. Eight hours after the transplant, one patient in the two-step treatment group experienced bacteremia, but she later recovered with no further symptoms. Another transplant recipient in the untreated group also experienced post-transplant septicemia that was untreatable despite sophisticated intensive care and died nine hours later. One patient who had one-step treatment experienced mild septicemia and a severe tachyarrhythmia. Albumin, a magnesium infusion, potassium, and intravenous lidocaine were all administered to the patient without any results. Within an hour of the hemo-adsorber being created, the tachyarrhythmia normalized and disappeared. The likelihood of the treated recipient suffering fatal septicemia may have been reduced by the use of cytokine adsorption. Reductions in cytokine levels may also explain why treated recipients require less inotropic assistance and have higher hemodynamic stability.

It's interesting to note that after 2 hours of EVLP, the graft in one recipient in the two-step treatment group dramatically edematized the lungs. Following EVLP, the trachea could be drained of up to 1.2 litres of fluid, and during the transplant, adjustments were made to fit the expanded graft into the patient's chest. Nearly all of the edoema had been reabsorbed by the conclusion of the post-transplant monitoring period, and the graft displayed excellent gas exchange capacity and no symptoms of PGD, indicating that the cytokine adsorption was particularly significant during hemo-perfusion post-transplant. In addition, there was a decrease in the wet-dry ratios of the lung tissue between the end of EVLP and the end of LTx. The use of a cytokine adsorber minimizes fluid buildup in the tissue, according to evidence from the wet-dry ratio assay, which was used to assess the level of pulmonary edoema in the biopsies. These cases of septicemia and edoema show how the inclusion of a cytokine adsorber may help restore unacceptably damaged donor lungs in the crucial days just after transplantation.

Conclusion

It has been demonstrated in this study that cytokine adsorption in the context of ARDS-damaged lungs can

(i) Reduce inflammation and restore pulmonary function during EVLP.

(ii) Restore function and decrease inflammation after transplantation.

(iii) Lower the incidence of PGD in transplant recipients.

The work described here shows how the cytokine adsorber is used in the context of lung transplantation using donor lungs that have suffered serious damage. Adsorption is therefore considered to be a potential strategy that might result in the acceptance of more lungs for transplant.

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