TRPV4 Channel Inhibition Attenuates Lung Ischemia-Reperfusion Injury and Endothelial Barrier Disruption in a Porcine Lung Transplant Model

Objective: Primary graft dysfunction (PGD) is a major consequence of lung ischemia-reperfusion injury (IRI) and is a leading cause of early morbidity and mortality following lung transplantation. In vitro studies have associated transient receptor potential vanilloid 4 (TRPV4; calcium-permeable cation channel) activation with lung injury via endothelial barrier disruption. Using a murine model, we previously demonstrated that endothelial TRPV4 channels mediate lung IRI and that pretreatment of mice with a selective TRPV4 inhibitor, GSK2193874 (GSK), attenuated lung IRI. Thus, we tested the hypothesis that treatment of the recipient animal with GSK would attenuate lung IRI in a clinically relevant porcine lung transplant model.

Methods: A porcine left-lung transplant model of lung IRI was utilized. Animals were randomized in a blinded fashion to two treatment groups: vehicle or GSK. Donor lungs underwent 30 min of warm ischemia, 24 hrs of cold ischemia, left lung allotransplantation, and 4 hrs of reperfusion. Vehicle or GSK (1.0 mg/kg IV infusion) was administered to the recipient beginning at time of recipient lung explant. Left lung function, lung injury scores by H&E histology, edema (lung wet/dry weight), inflammatory markers (by ELISA), and neutrophil infiltration were compared.

Results: A total of 10 animals were utilized (n=5/group). After transplantation, the GSK group showed a significant improvement in left lung-specific pulmonary vein PO2 at both 3 and 4 hours of reperfusion ($p<0.05$; Figure). Lung compliance trended higher and wet/dry weight ratio trended lower in the GSK group but were not statistically significant. Expression of HMGB1 (damage-associated molecular pattern molecule) and P-selectin (endothelial cell adhesion molecule) in lungs, as well as Ang-2 (marker of endothelial activation or injury) in plasma, were significantly reduced in the GSK group ($p=0.02$). Neutrophil infiltration ($p=0.01$) and lung injury score ($p=0.04$) were significantly reduced in the GSK group.

Conclusions: In this pre-clinical, large animal model of lung transplant recipients treated with TRPV4 inhibitor at time of transplant significantly improved lung function, and attenuated lung injury and endothelial disruption after transplant. Iterative in vitro and in vivo studies conducted by our lab suggest that selective antagonism of TRPV4 channels may be an effective therapeutic strategy to prevent PGD after transplant, leading to improved long-term outcomes.

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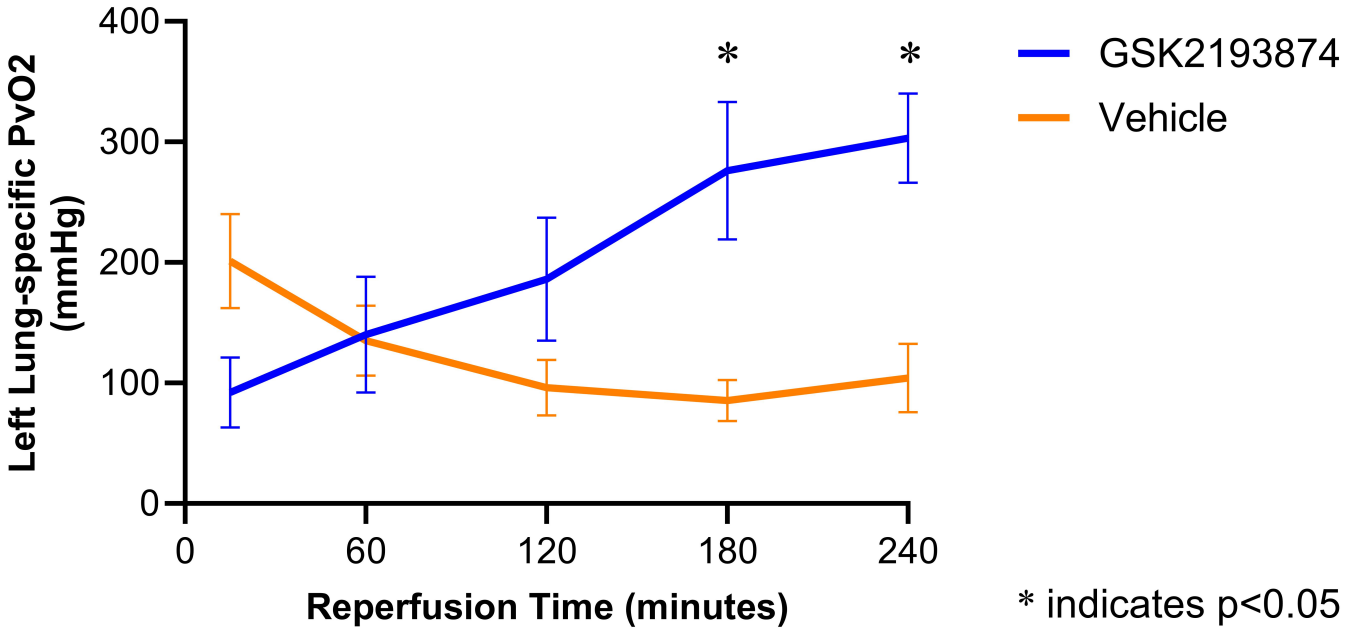
Left Lung-specific PvO2 (mmHg)
400
300
200
100
0
0
60
120
180
240
Reperfusion Time (minutes)
*
*
GSK2193874
Vehicle
* indicates p<0.05