

Non-invasive Monitoring of Lung Transplant Viability in a Small Animal Model Using MRI and PET

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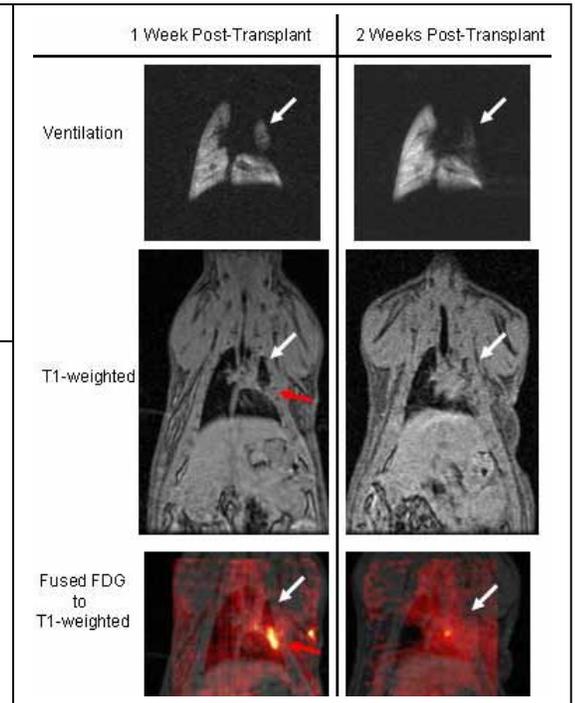
Introduction

Lung transplant (TX) viability can be monitored non-invasively using whole lung spirometry. However, imaging holds promise for longitudinal assessment as it can assess individual organ viability regionally. In the specific case of MRI, use of hyperpolarized (HP) gases in combination with conventional proton and T1-weighted images can allow assessment of ventilation in lung TX [1] and inflammatory infiltrate in small animals [2] without the use of ionizing radiation, making longitudinal assessment of the same animal more feasible. Previous work has demonstrated fusion imaging with HP He-3, T1-weighted proton, and FDG PET for validation of ventilation and inflammation in a small animal model of allergic inflammation [3]. This study extends these imaging techniques to the assessment of lung TX and uses FDG PET to confirm the results of MRI. The hypothesis of this study is that non-invasive MR imaging techniques can be used for early assessment of organ viability in lung TX.

Methods

Three WKY rats underwent syngenic left lung TX. Animals were sedated and intubated to allow computer controlled He-3/air ventilation [3] during imaging studies performed at 1 and 2 weeks after TX to assess organ viability. Animal 2 died prior to PET imaging and was replaced with animal 3. Following the imaging session at 2 weeks, animals were sacrificed and lung pathology was assessed. A standard 1.5T clinical whole body scanner with broadband capability (GE Health Care, Milwaukee, WI) was used for MRI. He-3 gas was optically polarized using a commercial polarizer (GE Health Care, Milwaukee, WI) to ~30% polarization. He-3 images were acquired using a 3D respiratory gated sequence with PROjection acquisition (PR) performed in the coronal plane, and centric encoding in the A-P direction. Imaging parameters included TR/TE = 12.5/2.9 ms, ~7° flip angle, 14 cm² FOV in the coronal plane, 24 x 2.5 mm slices in Z, 8.93kHz BW, 160 readout points, and 10 min imaging time. Data was reconstructed to 12 x 150 ms ventilation phases to enable resolution of the lung structure. T1-weighted proton imaging was performed using a Cartesian acquisition with a 0.5 x 0.5 x 1 mm³ voxel size and 256 x 256 x 36 acquired matrix; and reconstructed to a 0.5 isotropic voxel size. Other T1-weighted imaging parameters included TR/TE = 100/1.9 ms, 21° flip angle, and 8.5 min imaging time. PET imaging was performed using a dedicated small animal scanner (UW MicroPET P4, Concorde Microsystems, Knoxville, TN) at the Keck Laboratory for Functional Brain Imaging (UW-Madison, WI). Imaging was performed during tracer uptake and continued for 90min to detect late trapping of the glucose analogue at a resolution of 0.63 x 0.63 x 1.23 mm. OSEM images from 45-90 min were used for registration and dynamic filtered back-projection images at 10 x 2 min and 8 x 10 min were used to perform Patlak analysis using Spmalize software [4]. Images were fused manually using affine transformations to register common anatomic information.

Figure 1. Imaging results at 1 and 2 weeks post-TX for syngenic WKY rat. At 1 week, ventilation in the left lung is visible (top left) with limited inflammatory infiltrate (middle left) and signal at the edge of the lung, likely due to the surgical procedure (red arrows left). At 2 weeks, ventilation to the left lung is reduced but still present (top right). T1 infiltrate is increased (middle right), although FDG uptake is more diffuse (bottom right).



Results

Imaging results at 1 week post-TX for one of the three animals showed He-3 gas signal in the distal airways of the TX lung suggesting the airways were unobstructed (Fig. 1). Inflammatory infiltrate was limited to the site of the surgical scar. At 2 weeks post-TX, He-3 signal still showed ventilation in the left lung, though relative signal intensity is decreased (Fig 1). Glucose influx Ki (Table 1) was elevated for TX lungs relative to the host organ for all animals. Pathologic assessment of the excised lungs of animal 1 corroborated the imaging results as the TX lung appeared normal with typical compliance. Conversely, at 1 week post-TX in the animal 2, there was evidence of strong inflammatory infiltrate with no detectable ventilation in the small airways of the left lung as only the main bronchi is visible. Similar results were observed in the images 2 weeks post-TX. On pathology, the exterior surface of this lung was hemorrhagic and the organ volume was reduced. Palpitation revealed a firm and unyielding consistency indicative of acute organ rejection. The third animal showed similar imaging features to that of the second animal: strong inflammatory infiltrate, ventilation only in the main bronchi, and glucose metabolism at the sight of the TX lung at 2 weeks. On pathology this lung showed signs of tissue fibrosis, including a rigid consistency at palpitation but with no volume reduction.

Conclusions

This work demonstrates the ability to assess lung TX viability qualitatively using MRI techniques during longitudinal studies in a small animal model. These experiments were performed in conjunction with experiments in this animal model to test the role of collagen V (col V) in autoimmune mediated lung rejection. Due to differences in col V reactivity, 2 of the 3 animals were expected to reject the TX lung [5]. The animal that maintained viability after 2 weeks showed greater ventilation, limited infiltrate, and lower glucose metabolism. Compromised ventilation as well as elevated inflammatory infiltrate were found to correlate with organ rejection on pathology. Future work will further validate these results using histopathology, particularly to confirm fibrotic obstruction similar to bronchiolitis obliterans syndrome (BOS) with a focus on whether BOS can be distinguished from early stage acute rejection. The imaging response in the allergen challenge work was more intense and localized [3], while our preliminary experience in these lung TX cases suggests more subtle changes and future work will look at methods for quantifying these for use in longitudinal studies. Validation in this animal model will guide work to extend the MRI methods to lung TX in humans.

References

- [1] Gast et al. JMRI, 15:268-274 (2002).
- [2] Beckmann et al. MRM, 47:88-95 (2001).
- [3] Holmes et al. MRM, 53:1243-1250 (2005).
- [4] <http://tezipur.keck.waisman.wisc.edu/~oakes>
- [5] Yoshida et al. American Journal of Transplantation, in press.

Week 1	upper-right	upper-left	mid-right	mid-left
TX195	0.00179	0.00437	0.001155	0.010955
TX194	0.001488	0.00912	0.001991	0.017855
Week 2				
TX195	0.001878	0.00692	0.002139	0.008858
TX196	0.002734	0.00465	0.002705	0.008865