Ultra-short echo-time MRI distinguishes ischemia/reperfusion injury from acute rejection in a mouse lung transplantation model

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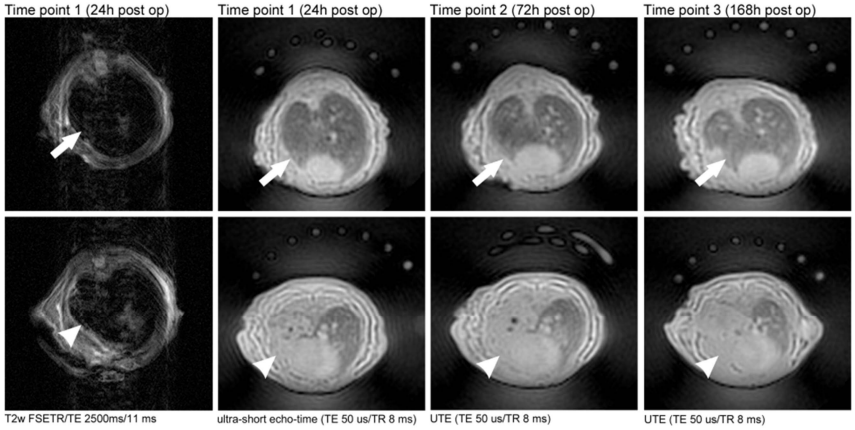
Introduction: In experimental transplantation studies, post-transplantation phenomena such as ischemia/reperfusion injury or allogeneic rejection patterns are intentionally induced to study molecular pathways or test novel agents for the amelioration of graft rejection [1]. The current gold standard for assessment of lung pathologies after transplantation is high-resolution computed-tomography, which suffers from low specificity and, moreover in small animal imaging, requires relatively large doses of ionizing irradiation. In transplant medicine and translational research, early detection and differential diagnoses of acute ischemia/reperfusion injury versus acute rejection may allow for appropriate treatment avoiding transplant failure. Today, MRI of the lung is still challenging due to low proton density and short T2* transverse relaxation time of the inflated lung [2]. The short T2* time is caused by the unique architecture of the lung with air/soft tissue interfaces of the alveoli creating microscopic inhomogeneities of the static magnetic field with a broad intravoxel Larmor frequency distribution. The fast signal decay precludes depiction of lung parenchyma at high field small animal scanners using conventional MRI sequences with echo-time TE in the order of 2-10 ms. Ultra-short TE (UTE) sequences have been shown to provide echo-times below 100 µs and therefore are able to depict signal from lung tissue [3,4]. In this study we investigate whether lung tissue characterization by computation of spin density and apparent T2* relaxation times obtained from ultrashort echo time sequence allow distinguishing postoperative alterations from signs of acute rejection after unilateral mouse lung transplantation.

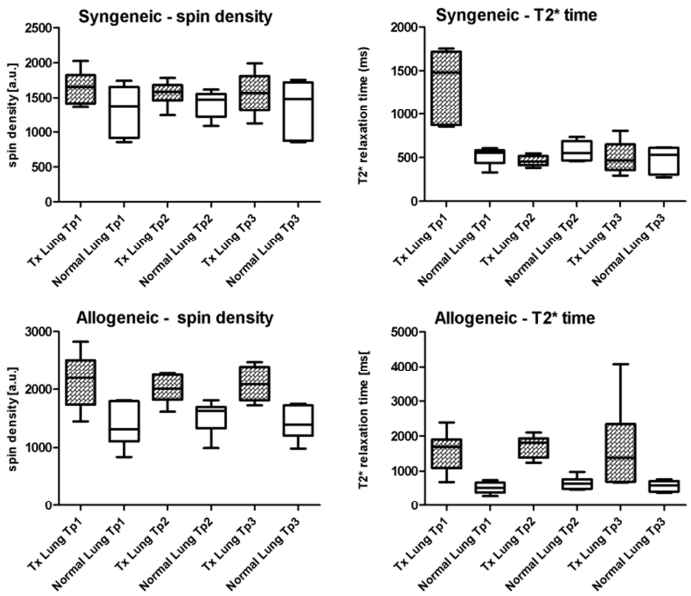
Material and Methods: 12 mice underwent orthotopic left lung transplantation. 6 mice (C57BL/6) received syngeneic (C57BL/6) lung transplants; the other 6 received an allogeneic (BALB/c) transplant. On the 1st, 3rd and 7th postoperative day the mice were scanned using a small animal MR imager operating at 4.7T equipped with a circular polarized 1H mouse whole body radiofrequency coil. In addition to a conventional T1w spoiled gradient-echo (TR/TE 15ms/4.7ms) and a T2w fast-spin-echo sequence (TR/TE 2500ms/11 ms), 3D UTE sequences with echo-times TE=50µs, 75µs, 100µs, 500µs, 1500µs, 3000µs, 4000µs, 5000µs were subsequently acquired (TR=8 ms, matrix 128 x 128). Quantitative T2* values of lung transplant parenchyma as well as relative spin density (normalized to the lung on the right side) were compared by region-of-interest analysis. All samples underwent histological workup.

Results: All twelve mice were used for the analysis. All of them exhibited small pneumothoraces on the left side, these were solely perceivable in the UTE images; adjacent small pleural effusions were best seen in the conventional T2 sequence. Infiltration of lung transplant parenchyma was not visible on conventional fast spin-echo T2 images (image 1) as these ventilated organs exhibited complete signal loss. In the allogeneic group a distinct pattern of alveolar infiltration as a result of the acute? organ rejection was well visualized in the UTE sequences at all three time point. In the syngeneic group there was no difference between the transplanted and the healthy side. Quantitatively these findings were reflected by the spin density (SD) and T2* measurements; where significantly higher values in spin density as well as T2* were measured in the allogeneic group compared to the syngeneic group and healthy lung tissue at the first time point (24h post-operative: Tx allogeneic group SD: 2133.9 ± 516; Tx syngeneic group SD: 1648.61 ± 271 ; $p = 0.0043$; Tx allogeneic group T2*: 1710.16 ± 644 ms, Tx syngeneic group T2*: 577.16 ± 263 ms; $p = 4.63132E-05$). In the syngeneic group, a normalization of both, SD and T2* time was noted on the 3rd (SD: 1561.71 ± 284, T2*: 461 ± 159 ms) and 7th (SD: 1562.66 ± 329; T2*: 501.33 ± 211 ms) time point compared to the allogeneic group were SD and T2* remained high (time point 3 – SD: 2097.05 ± 324; T2*: 1659.44 ± 1246 ms).

Image 1: unilateral syngeneic lung tx (left side, *arrow*): upper row and allogeneic lung tx (left side, *arrowhead*): lower row



Discussion: For this study we used syngeneic and allogeneic transplanted mice in order to the differentiate ischemia/reperfusion injury from acute? rejection with MRI. The syngeneic group offers a model for ischemia/reperfusion injury after organ transplantation and in our study, additionally served as a control group as there is no development of a graft rejection whilst the allogeneic group provides a model for acute ?rejection after organ transplantation. We were able to show that using an UTE sequence changes caused by acute? rejection after lung transplantation can be visualized and characterized as they provide different relaxation properties compared to normal lung tissue as well as syngeneic lung transplants.



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Tp1: 24 hours after unilateral lung transplation
Tp2: 72 hours after unilateral lung transplantation