Pulmonary imaging of acute lung injury in mice with ZTE

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TARGET AUDIENCE: Pulmonary researchers

INTRODUCTION: Magnetic resonance imaging (MRI) of the lung is uniquely challenging because of its large air content (> 80% of lung volume): (1) conventional MRI signal is significantly reduced as it relies on tissue proton density, and (2) the T_2^* of the pulmonary parenchyma is extremely short due to the large tissue-gas interface required for optimal gas exchange. To reduce the effects of very short T_2^*, we have utilized the zero echo time (ZTE) technique [1-4] to image mouse lungs at 7T. To evaluate its sensitivity, we used a murine model of acid-induced acute lung inflammation with left lung selectivity [5]. Selective acid instillation to the left lung allows internal comparison with the uninjured right lung. In addition, MRI at different time points after injury characterized the time course of left lung inflammation and its resolution.

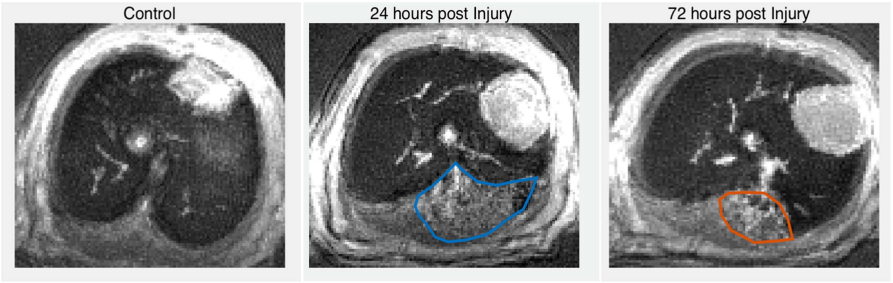

Figure 1. ZTE images of 3 mice: control, 24 and 72hr after HCl intra-tracheal instillation. Although the parenchymal signal is weak, the site of injury is nevertheless easily identifiable and traceable.

METHODS: Hydrochloric acid (HCl, pH 1.0, 0.1N, 50µl, intra-tracheal) was selectively instilled to the left lung of mice (8-10 week old, Balb/c) via tracheostomy, after which the animals were allowed to recover. At pre-determined time points (0, 24, and 72 hrs after acid, n=3 per time point), the animals were euthanized and 700µl (~70% total lung capacity) of air insufflated via tracheostomy, after which the animals were immediately imaged. The measurements were conducted at Small Animal Imaging Laboratory at Brigham and Women's Hospital on a 7T Bruker system. We used an 86 mm volume coil for transmission and a 20 mm surface coil for reception. The imaging parameters were: isotropic resolution at 156 um, TR = 17 ms, flip angle = 10°, 39K spokes.

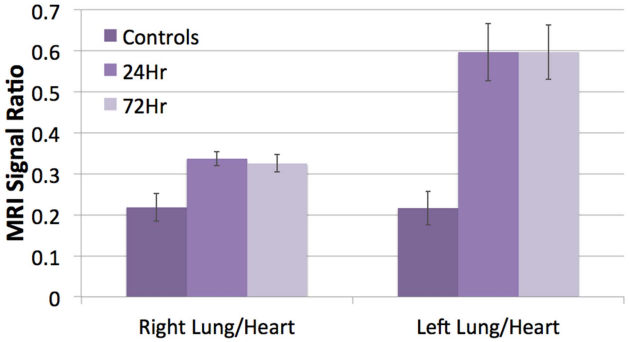

Figure 2. Left and Right lung signals normalized to the signal from the heart. In all cases major blood vessels were avoided

RESULTS: Sample lung images representative of each of the groups are shown in Figure 1. Despite the low SNR in the lung parenchyma itself, the initial inflammation is easily observable, as well as its reduction in 72 hours. In order to quantify the change in the pulmonary signal due to the inflammation, and enable comparison between different mice/imaging sessions, we first identified the inflammatory region in each scan (see ROI outlines in Figure 1) and then normalized the signal to that in the heart. Results are shown in Figure 2. In the control group, we observed ~22% of the heart signal (0.22±0.03 and 0.22±0.04 in Right and Left lungs, respectively). In injured mice, however, both right and left lungs showed higher signal compared to the control mice. Both 24-hr and 72-hr groups had an increased right lung signal of ~30% of the heart signal, while left lung/heart signal ratio was ~60% at both time points.

A significant reduction in injury size was observed in the 72-hr group compared to the 24-hr group. Figure 3 shows the injury area from a sample slice (we chose the slices with the largest injuries for this analysis): for the 24-hr group, the mean injury area was 21.3±1.7 mm^2, while for 72-hr group the value was 8.4±1.8 mm^2.

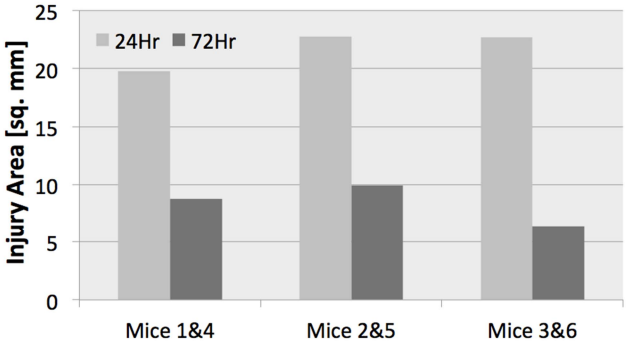

Figure 3. Area of the injury at 24 and 72 hrs in 3 mice from each group. Significant reduction is observed at 72hr in all animals.

DISCUSSION: Zero echo time (ZTE) was used to evaluate the feasibility of the approach for tracking pulmonary inflammation secondary to acid-induced acute lung injury. Despite the presence of radial imaging artifacts, we were able to track relative signal changes in control mice compared to 24- and 72-hr post injury groups. In addition, despite a low signal-to-noise ratio of the images, we observed lung parenchymal signal levels consistent with the density of the lung compared to other tissues. If the density of heart tissue is 1, then since ~80% of the lung is filled with air, one expects to observe a lung-to-heart-tissue ratio of 0.2. Our measurement of 0.22±0.04 is in excellent agreement with this prediction. Of note, the findings of increased left lung density at 24 hrs compared to 0 and 72 hrs correlates with the time course of acid-induced acute lung injury, with peak airway and left lung interstitial neutrophils 24 hrs after intra-tracheal acid [5]. Collectively, these findings underscore the possibility of performing high-resolution MRI of lung during acute inflammation using our novel MRI protocol, with important translational implications evaluation of human acute lung inflammation and its resolution.

REFERENCES: [1] Hafner,et al. MRI,12,1994:1047. [2] Madio, et al.MRM,34,1995:525. [3] Kuethe,et al.,MRM,39,1998:85. [4] Weiger, et al.MRM,66,2011:379. [5] Abdulnour,et al. PNAS 2014: PMID 25369934