Longitudinal MRI Evaluations of Lung Inflammation within Cystic Fibrosis Mouse Models

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Abstract

Biological variability in transgenic mouse models of Cystic Fibrosis can compromise the evaluation of this pathology using techniques that require serial sacrifice. To address this unmet need, MRI has been used to detect progressive lung inflammation in CF mouse models relative to normal mice. This study demonstrates that non-invasive MRI can provide new opportunities for assessing Cystic Fibrosis mouse models.

Introduction:

The development of transgenic mouse models of Cystic Fibrosis (CF) that are infected with *Pseudomonas aeruginosa* provides new opportunities to investigate the temporal relationship between infection and inflammation, and the effect of therapies directed against this pathology.[1,2] However, the substantial biological variability of implanted infection load and pathological response to the infection can compromise the accuracies of bronchoalveolar lavage measurements and histopathological studies that sacrifice separate cohorts of mice at each time point of a longitudinal study. Therefore, MRI may be a valuable tool for assessing infection and inflammation during longitudinal studies of a single cohort of mice. Problems that confound lung MR imaging must first be overcome, especially the effects of low proton density and respiratory & cardiac motion, before MRI can be routinely applied to assess infection and inflammation in CF mouse models.[3]

Methods:

All mouse studies were conducted according to the guidelines of the Case IACUC. Agarose beads with an average diameter of 100 microns were laden with *Pseudomonas aeruginosa* (PA), diluted in PBS, and implanted in the right lung of transgenic R117H CF mouse models and normal mice to create an initial infection load of 10^5 PA. Each mouse was anesthetized with 2.5% isoflurane in O_2 gas at a 2.25 L/min flow rate, and placed in a customized cradle that incorporated a surface coil with a 2.0 cm FOV. The ECG signal, respiration rate, and core body temperature were monitored using a SA Instruments model 1025 physiological monitoring system. Spin-density-weighted spin-echo scans were acquired with ECG- and respiration-gating, with TR controlled by a respiration rate of ~1.8 sec [TE 9.4 μsec, in-plane resolution 312x312 μm, slice thickness 1 mm, 30 axial and coronal image slices]. Six CF mouse models and six normal mice were scanned each day starting one day prior to implantation and ending 4 days after implantation. All mice were euthanized and processed for histopathological analysis at the end of the MRI study.

Results and Discussion:

PA-laden agarose beads were implanted in the right lung because potential cardiac motion artifacts may compromise image clarity of the left lung. Indeed, artifacts from cardiac motion was evident in ~20% of all MR images, which was attributed to variability in ECG lead placement based on extensive tests with different leads and lead configurations, and from effects of the magnetic gradients on metal leads. Artifacts from respiratory motion were absent, which was attributed to careful control of core body temperature and anesthetization, and obviated the need for forced respiration. The implanted agarose beads couldn't be visualized with MRI, presumably due to the small size of the beads and the low density of mobile protons within the beads. The response to infection was evident 72 hours after implantation of the PA-laden beads, and the evolution of this infection was monitored throughout the longitudinal study (Figure 1). Therefore, a spin-echo MRI pulse sequence with a TE of 9.4 μsec was sufficiently sensitive to detect inflammation while suppressing the background signal of lung tissue, which greatly simplifies quantification of the inflammation. Furthermore, all CF mouse models survived in excellent condition until the final day of the MRI study, and post-mortem analysis revealed only mild infections, indicating that the MRI was able to localize early stages of small inflammations.

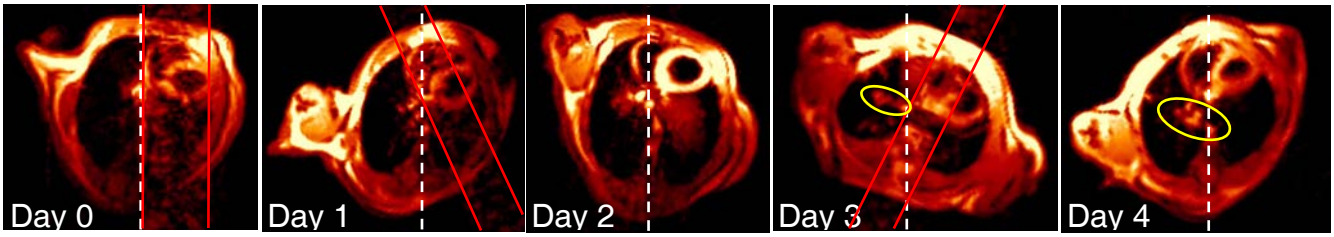

Figure 1. Axial MR images of a CF mouse model acquired after implantation of PA-laden agarose beads in the right lung. Images have been reoriented so that the aorta and spine are vertically aligned (white dotted line). Cardiac motion artifacts are bordered by red lines in the images acquired on day 0, 1, and 3. Inflammation is highlighted by yellow ellipses in images acquired on days 3 and 4. Inflammation in the image acquired on day 2 is inconclusive due to the presence of diaphragm and/or liver tissue within the image slice.

Conclusions:

Inflammation is an important feature of CF pathology and so far has been tracked only using bronchoalveolar lavage and histopathology. These end point measures do not provide temporal information and only limited spatial coverage. MRI can be used to track inflammation with excellent spatial and temporal information in CF mouse models as a compliment to the established techniques.

References:

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