In Vivo Monitoring of Mucus Obstruction and Ventilation Malfunction in Mice by Combined 1H and Hyperpolarized 129Xe-gas Lung MRI

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Target Audience Pulmonary hyperpolarized ^{129}Xe MRI; 3D UTE; Cystic fibrosis MRI detection;

Purpose Cystic fibrosis is often characterized by abnormal accumulation of thick and sticky mucus in the lung airways that ultimately leads to airflow obstruction, inflammation, and infection[1]. Mucus hydration and clearance can be improved by the administration of mucolytic drugs, but the efficacy of these drugs is often hard to assess through imaging [2][3]. The aim of this study was to evaluate the combination of anatomical ultra-short echo time ^{1}H lung imaging and hyperpolarized (HP) xenon-gas ventilation lung imaging to monitor mucus obstruction and ventilation function in ß-epithelial Na(+) channel (ENaC)-transgenic (TG) mice (ßENaC mice) that present CF-like symptoms. Findings from ^{1}H and ^{129}Xe imaging studies were analyzed and then validated by post-mortem lung histology.

Methods All images were acquired on a 9.4T Bruker BioSpec scanner (Bruker Copr., Bellirica, MA), using a 35mm dual tuned ^{1}H/^{129}Xe volume coil. For the imaging experiments we used a total of 11 ßENaC-over-expressing mice[4] and 5 wild-type (WT) littermates, all between 4-7 weeks of age. For the imaging study the animals were anesthetized, tracheotomized, and mechanically ventilated at a rate of 60 breaths/minute with a home-made HP-gas compatible and computer-controlled small animal ventilator. The ventilator delivered a mixture of oxygen and natural abundance hyperpolarized xenon gas, in a 25:75 volume ratio, for a total tidal volume of 10 mL/kg. Natural abundance ^{129}Xe was hyperpolarized up to 12% by SEOP using a commercially available polarizer (Polarean Inc., NC). 3D ^{1}H lung images were acquired using an ultra-short echo time sequence (TE=30µs, TR=10ms, matrix size=120x120x120, FoV=2.5x2.5x3cm). Xenon lung ventilation images were acquired using a gradient echo sequence (TE=1.6ms, TR=1000ms, matrix size=256*64, FoV=1.9x1.9cm) triggered to the ventilation-breathing rate. At the end of the imaging study the animals were euthanized and the lungs were excised for histological examination of airway mucus obstruction.

Results Figure 1 shows representative data (^{129}Xe MRI, ^{1}H MRI and histology) from the same ßENaC animal. In all ßENaC animals we observed areas of decreased or impaired ventilation when compared to WT, age-matched littermates. Ventilation defects were more numerous and severe in young ßENaC animals than in old ßENaC animals (figure 1.b vs 1.c). Concomitantly, ^{1}H lung images showed the presence of several spots of increased density compared with the encompassing parenchyma in the same areas of decreased ventilation. These spots had a glassy-like appearance, were present only in one or two consecutive slices, and didn't seem to be connected to other blood vessels or tissues. These spots were found mainly in the main stem bronchi, and more in young than in older mice. The location of these spots correlated well with areas of mucus obstruction found histologically.

Conclusion Our study demonstrates the combination of proton UTE3D and xenon MRI to probe mucus accumulation and ventilation function in CF animal models. In UTE3D images mucus accumulations can be clearly discerned with a careful image analysis, while hyperpolarized xenon images can be used to determine how these accumulations affect ventilation function. The ability to detect both mucus accumulations and ventilation malfunction in a single imaging session represents a clear advantage with respect to CT studies currently used to assess mucolytic drug efficacy in CF patients. As such, this sensitive and non-invasive protocol may provide a useful tool for evaluation of novel treatment strategies in CF patients.

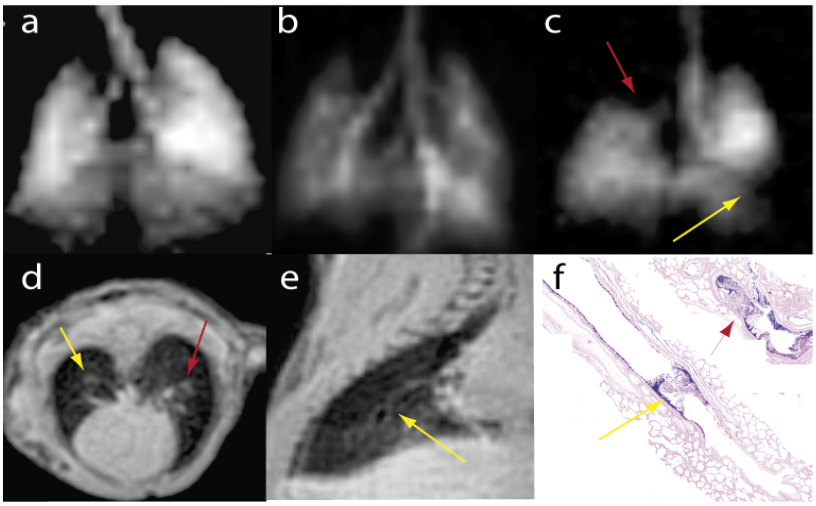

Figure 1. Hyperpolarized xenon ventilation lung images of a 7 week old WT(a), a 7 week old (b), and a 5 week old (c) ßENaC mouse. Ventilation defects are clearly visible in both ßENaC animals but are more severe in the younger animal. Axial (d) and sagittal (e) UTE proton images of the same ßENaC animal as in c show regions of mucus obstruction and bronchiectasis (e) in the same location. (f) Histological slide shows corresponding mucus accumulations.

Reference [1] Butcher, R. C., Annu. Rev. Med., 58 (2007) [2] Donnelly, Lane F., et al., Radiology 212.3 (1999) [3] Wielpütz, Mark O., et al., Journal of thoracic imaging 28.3 (2013) [4] Mall, Marcus, et al., Nature Medicine, 10.5 (2004)