3D ^{3}He and ^{1}H MR Imaging of Regional Pulmonary Injury Induced by Ozone

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Introduction: Ambient ozone (O_3) is a major environmental air pollutant that significantly impacts public health. Ozone exacerbates lung dysfunction in subjects with asthma and chronic obstructive pulmonary disease **[1]**. While much is known about the deleterious effect of O_3 on global lung function, much less is understood about its effects regionally. To this end hyperpolarized gas MRI could be an ideal means to study the effects of O_3 on regional ventilation as was first proposed by Cremillieux et al **[2]**. However, that study, conducted in rats, was limited to 2D imaging, and despite long ozone exposures revealed only very subtle O_3-induced lung effects. We sought to revisit the effects of ozone on pulmonary function by employing 3D ^{3}He and ^{1}H MRI in C57BL/6 mice.

Methods: Male C57BL/6 mice (8 wks old, n=5) were exposed for a period of 3 hrs to air containing 1 ppm of O_3. Control animals (n=6) were naïve. Approximately 16-24 hr post-exposure, all mice underwent respiratory-gated ^{1}H MRI at 156×156×256μm^3 resolution and then underwent a 5 minute high-resolution 3D ^{3}He MR image (156×156×256μm^3) using methods outlined in **[3]**. Prior to ^{3}He MRI, mice received a hyperinflation breath to clear any atelectasis. ^{1}H images were evaluated for edematous signals and ^{3}He images were evaluated for ventilation abnormalities. The ^{1}H and ^{3}He images for each mouse were registered to correlate fluid-filled regions of the lungs to ventilated regions.

Fig 1: ^{3}He and ^{1}H MRI in a control mouse showing a) homogeneous ventilation b) absence of fluid in the lungs. c) registered overlay of ^{3}He onto ^{1}H MRI showing that ^{3}He is only excluded in regions of blood vessels (black arrow). d) Maximum intensity projection of whole lung showing normal ventilation.

Results: As shown in **Fig 1** naiive mice show homogeneous ^{3}He ventilation and low proton signal in the thoracic cavity. By contrast, as shown in **Fig 2**, mice exposed to ozone showed regions of dramatically impaired ventilation, bronchial narrowing, and accumulation of edematous fluid on ^{1}H MRI. The ozone-exposed mouse shown in **Fig 2** exhibits a ventilation defect with matching fluid accumulation in one slice (**Fig 2 a,b,c**) but also exhibited impaired ventilation without detectable fluid in other areas. This is illustrated in the maximum intensity projection (**Fig 2d** and was representative of what was seen in other O_3-exposed mice.

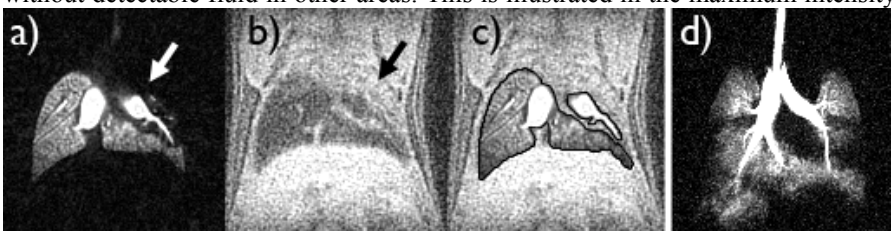

Fig 2: ^{3}He and ^{1}H MRI in an ozone-exposed mouse showing a) ^{3}He ventilation defects and bronchial narrowing b) fluid in the area of the ventilation defect c) registered overlay of ^{3}He onto ^{1}H MRI showing correspondence of ventilation defect and edema in that slice d) Maximum intensity projection of whole lung showing numerous additional defects.

Discussion and Conclusions: Despite experiencing fairly limited O_3 exposure, equivalent to 1-day in Mexico City, the mice exhibited striking regional changes in ventilation. This stands in contrast to more subtle O_3 effects previously reported in rats **[2]**. This is partially attributable to our improved 3D resolution and may also reflect some degree of strain-dependent O_3 susceptibility **[4]**. However, the primary difference is likely to be ozone adaptation. When ozone exposure is repetitive or prolonged, the resultant inflammatory response can become attenuated **[5]**. Thus, both the duration of O_3 exposure and the time after exposure when imaging occurs are important factors. Our work suggests that the combination of high-resolution ^{1}H and ^{3}He MRI done 24-hr after 3-hr O_3 exposure could offer a novel approach to investigate the regional pulmonary effects of this ubiquitous pollutant. Such tools should be useful for testing the efficacy of new therapeutic approaches now being developed to blunt the effects of ozone in vulnerable populations.

References: **1.** J. W. Hollingsworth *et al.*, *Proc. Am. Thorac. Soc.* 4, 240 (2007). **2.** Y. Cremillieux *et al.*, *J. Magn. Reson. Imaging* 27, 771 (2008). **3.** A. C. Thomas *et al.*, *NMR Biomed.* 22, 502 (2009). **4.** L. Y. Zhang *et al.*, *Exp. Lung Res.* 21, 503 (Jul-Aug, 1995). **5.** W. J. McKinney *et al.*, *Am. J. Respir. Cell Mol. Biol.* 18, 696 (May, 1998).
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