The effect of locally administered glucocorticoid budesonide on ovalbumin exposed rats assessed by HP [3]He MRI

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Introduction: Asthma is a heterogeneous disease affecting the airways and is characterized by an inflammatory response and airway remodeling. The inflammation induced by ovalbumin (OVA) is a well-established model of asthma in rodents, and ^{1}H magnetic resonance imaging (MRI) has been used to assess the amount of induced oedema in that model.[1] Additional information of the lungs can be obtained by MRI using hyperpolarized (HP) [3]He gas. For example the alveolar structure can be assessed by measurement of the apparent diffusion coefficient (ADC) of inhaled HP [3]He. The aim of the present study was to assess, in-vivo, the effect of a glucocorticoid steroid (budesonide) on inflammation induced by OVA exposure, using HP [3]He ADC imaging as read-out.

Materials and Methods: Rats were divided into 4 groups; group 1: control group sensitised with OVA and challenged with saline and treated with vehicle (n = 6); group 2: sensitised and challenged with OVA and treated with vehicle (n = 6); group 3: sensitised and challenged with OVA and treated with low dose (0.1 mg/kg) of budesonide (SigmaAldrich, Sweden) (n = 6); group 4: sensitised and challenged with OVA and treated with high dose of budesonide (1.0 mg/kg) (n = 6). The rats were treated twice daily with start two hours prior to OVA challenge. 48h after OVA inhalation, the animals were anaesthetized and a tracheal intubation was performed. Additionally, a muscle relaxant was administered to enable breath-hold imaging. The animals were connected to a ventilator (Servicios de Eléctrónica y Programación Dedicados, Madrid, Spain) set to 65 breaths/minute at a tidal volume of 2.5 ml.

The MRI experiments were performed with a BioSpec 47/40 4.7 T MR scanner (Bruker BioSpin, Ettlingen, Germany) using a double tuned ^{1}H and [3]He coil. HP [3]He was delivered from the University of Mainz, Germany. After HP [3]He administration and during one breath hold cycle (P=20 mbar), coronal projection images of the lungs with four b-values were acquired, from which ADC maps were calculated. Diffusion encoding gradients had sinusoidal shape and 1.5 ms duration. After the imaging procedure a broncho alveolar lavage (BAL) for a cell count was performed.

Results and Discussion: The OVA challenged animals treated with budesonide resulted in a significant decrease of eosinophils (Fig. 1).The efficacy of treatment was 57% with low dose and 97% with high dose. We also observed significant differences between the doses of budesonide ($p < 0.001$). The [3]He ADC parameter maps showed heterogeneous distribution of ADC in vehicle treated animals (Fig. 2A), whereas in budesonide treated animals the ADC was homogenously distributed (Fig. 2B). The overall mean ADC in each animal is presented in figure 2C. In OVA challenged animals treated with vehicle, the measured ADC values decreased ($p < 0.01$). The ADC for animals treated with high budesonide dose were significantly higher compared to OVA/vehicle treated animals ($p < 0.05$).

In our model, inhalation of OVA causes functional changes in the lungs manifested by the presence of small airways obstructions, remodeling and presence of fluids in the lower airways. The ADC was significantly smaller in OVA challenged rats, indicating a reduced available airspace in the alveoli, possibly due to plasma leakage into the alveoli. Treatment with budesonide decreased the level of inflammation, as indicated by the reduced number of eosinophils, and accordingly the ADC values were greater than the vehicle animals. In the OVA model, the measurement of ADC with HP [3]He MRI indicates disease severity, and this method might be a useful tool to study the effects of novel medicines on alveolar function.
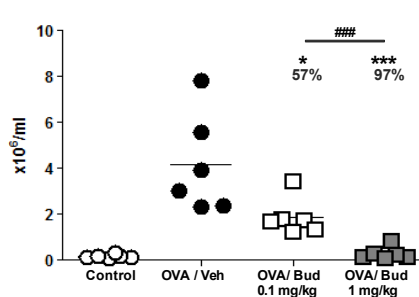

Figure 1. The amount of eosinophils decreased in budesonide treated groups with efficacy of 57% and 97%, low dose respectively high dose. Both budesonide treated groups are significantly different from vehicle treated group (t-test: *** $p < 0.001$,* $p < 0.05$); ### refers to comparison between two budesonide doses ($p < 0.001$). Veh=vehicle; Bud=budesonide
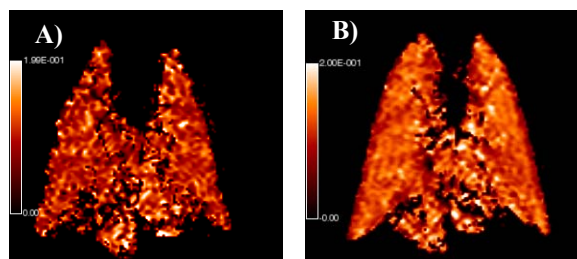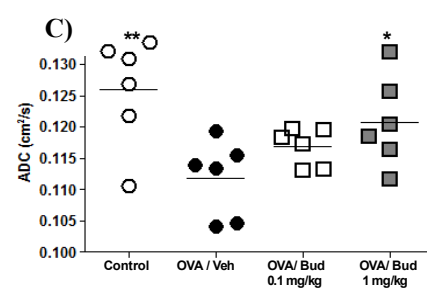
Figure 2. ADC parameter maps of representative animals. A) OVA/vehicle rat (ADC = 0.104 ± 0.041 cm²/s) and B) OVA/budesonide (1.0 mg/kg) rat (ADC = 0.121 ± 0.033 cm²/s). C) A decrease in mean ADC in vehicle treated animals was found. The control and high budesonide dose treated group are significantly different from the vehicle group (t-test: ** $p < 0.01$, * $p < 0.05$). Veh=vehicle; Bud=budesonide.

Reference: 1) Beckmann et al., Magnetic Resonance in Medicine 48:88-95, 2001.