Quantitative Gd-DOTA-based Aerosol Deposition in Asthmatic and Emphysematous Rats using UTE-MRI

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PURPOSE: Asthma and emphysema are chronic respiratory diseases, which are commonly treated with inhaled therapy[1]. Asthma involves chronic inflammation, airway remodelling and bronchoconstriction. Emphysema is characterized by alveolar wall destruction leading to distal airspace enlargement. Aerosol deposition patterns are difficult to predict as they depend on airway geometry, breathing parameters, aerosol and gas properties. *In vitro* and *in vivo* studies have been performed to better understand deposition mechanisms and to improve inhaled drug delivery[2]. Here, 3D UTE-MRI combined with spontaneous nose-only inhalation of aerosolized Gd-DOTA was implemented at 1.5T to map the distribution of aerosol deposition and to characterize the aerosol lung clearance[3] in asthmatic and emphysematous rats.

METHODS: *Animal model*: For asthma, 6 female Wistar rats, (294±21)g, were sensitized to ovalbumin (OVA; 1mg/rat) by an intraperitoneal injection emulsified in aluminium hydroxide. Sensitisation was verified by plethysmography following OVA challenge with an increase of the enhanced pause indicator (PenH) that correlated to airway resistance[4]. Two rats (312g) were used as controls. For emphysema, 8 female Wistar rats, (272±18)g, were endotracheally instilled with Porcine Pancreatic Elastase (PPE; 25UI/100g BW) and 6 control rats, (268±20)g, with saline (0.2mL/rat). MRI was performed 19 weeks (OVA) and 9 weeks (PPE) after induction. Before imaging, OVA and control rats were challenged (20min nebulization of OVA and saline, respectively). Asthmatic symptoms appeared after 2h and lasted more than 2h. *Imaging and nebulization protocols* were implemented on a clinical 1.5 T [Philips Achieva][3]. Rats, in prone position, were anaesthetized (isoflurane-100%O_2). A 47 mm-diameter receiver coil was used. Two 3D radial acquisitions (TE_1/TE_2=0.4/1.4 ms) were used for R_2* mapping (pre- and 1 h post-nebulization); 3D isotropic T_1W-UTE radial acquisitions (TR/TE=14/0.4 ms, α=30°, 0.5 mm^3 voxel, T_{acq}=7.5 min) were performed once before, then continuously repeated during nebulization up to 1 h post-nebulization. A fraction of the 7 mL of Gd solution [Dotarem; Guerbet], which was nebulized on line [Aeroneb Solo; Aerogen], was administered to the free-breathing rats (50/32 breath/min for OVA/PPE). The aerodynamic size of the aerosols was measured by laser diffraction [Helos; Sympatec]: MMAD=2.5 µm.

Lung segmentation used baseline signal intensity (SI) to classify voxels corresponding to parenchyma (lower SI) from vessels and surrounding tissue (higher SI). After a coil-sensitivity correction, the histograms of the baseline long TE and 3D UTE datasets were fitted to multi-component Gaussian distributions, providing parenchyma SI mean, *M*, and standard deviation, *SD*. Thresholding at *M*+2*SD* discriminated the lung parenchyma as lower SI and provided an estimate of the lung volume.

Image analysis: Relative signal enhancement $RSE = S(C)/S(0)-1$ were analysed for each time point. RSE at the end of nebulization was converted into concentration maps[5] *C*, with r_1=3.7 $mM^{-1}s^{-1}$ and baseline $T_{1,0}$=1.1 s for rat lung at 1.5 T. Aerosol distribution was evaluated for *C*, SI and R_2* using the corresponding relative dispersion RD = *SD*/*M*. To assess regional distribution, lung was divided into 2 equal volumes (V_1 = V_2) along 4 anatomical directions, left/right (L/R), anterior/posterior (A/P), head/feet (H/F) and central/peripheral (Ce/Pe). Relative *C* deposited in each region were calculated. Group analysis was expressed as mean ± standard error of the mean (SEM). Unpaired two-tail *t*-tests with a significance level of 0.05 were performed.

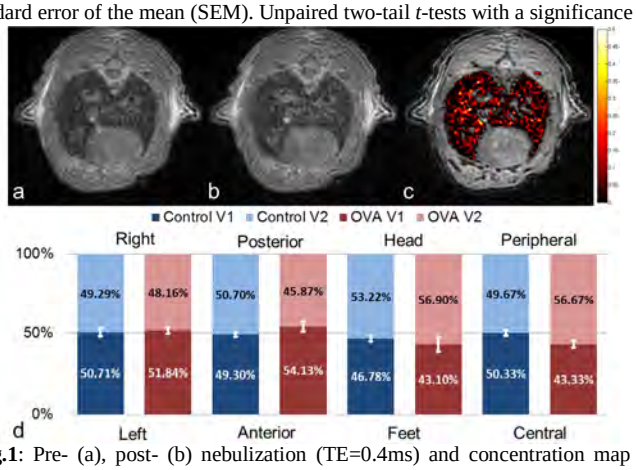

Fig.1: Pre- (a), post- (b) nebulization (TE=0.4ms) and concentration map (c, mM) with heterogeneous distribution in asthmatic rat. Heterogeneity is observed in H/F direction for controls and in all directions within asthmatic rats (d).

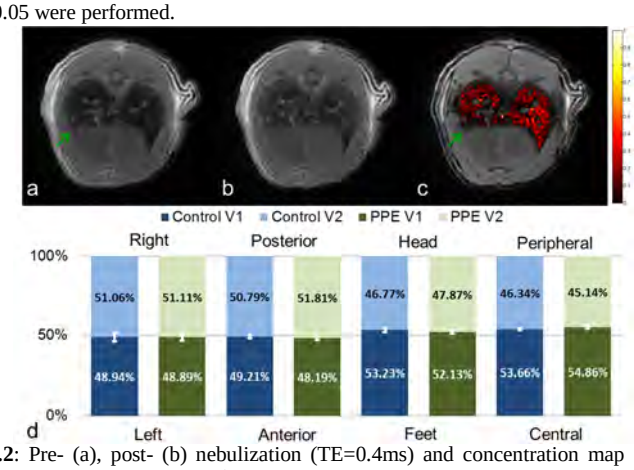

Fig.2: Pre- (a), post- (b) nebulization (TE=0.4ms) and concentration map (c, mM) with parenchymal defects (green arrow) in emphysema. Significant heterogeneity is observed in H/F, Ce/Pe for control and emphysematous rats (d).

RESULTS: Asthmatic rats had larger lung volume, (5.81±0.43) mL vs. (4.28±0.54) mL, lower RSE, (30.27±8.59)% vs. (76.56±16.85)%, and lower deposited aerosol *C*, (0.11±0.03) mM vs. (0.22±0.02) mM. RSE dynamics showed important inter-subject variability within asthmatic rats. Gd redistribution was observed after the end of nebulization. Baseline R_2* was the same between groups and a consistent R_2* reduction after administration was observed. SI was homogenously enhanced for controls while asthmatic rats showed heterogeneous enhancement (Fig.1ab). Heterogeneity was observed in H/F in controls and in all directions for asthma (Fig.1d). A larger RD was measured on *C*, 2.27±0.84 vs. 1.44±0.62 (Fig.1c). A positive correlation was observed between RD and PenH (R^2=0.84, $p<10^{-4}$) in the asthmatic group. Emphysematous rats had a lower baseline SI than controls, 6.59±0.32 vs. 7.22±0.27, and a slightly higher RSE, (60.55±6.50)% vs. (53.31±5.77)%. Lung volumes and baseline R_2* were comparable between groups. Emphysematous rats had visible parenchymal defects in the anterior-lower region (Fig.2a). R_2* variation after aerosol administration was negatively correlated with the baseline SI for emphysematous rats (R^2=0.71, $p<10^{-4}$). On average, a slightly higher deposited *C* (0.19±0.02) mM vs. (0.17±0.02) mM, was found for the emphysema group (Fig.2bc). Some emphysematous rats with smaller estimated deposited concentration showed more visible parenchymal defects on the baseline scan. Some variability was underlined in the control group: 3 animals had identifiable hyper-signal regions within the lung at baseline. The same animals had ~2 times lower total deposition than the other control animals and displayed hot spots with highly-concentrated Gd in the apical right lobes. Finally, no significant difference on RD was observed and regional distributions were comparable between control and emphysematous rats (Fig.2d).

DISCUSSION AND CONCLUSION: Contrast-enhanced 3D UTE combined with nebulized Gd-DOTA was applied to characterize asthmatic and emphysematous rats. The heterogeneity of aerosol distribution observed in asthmatic rats was correlated to PenH suggesting that it can be used as a physiopathological marker for asthma. Baseline SI together with R_2* variation are potential markers for emphysema. The rather low-dose and highly-heterogeneous aerosol deposition recorded in asthmatic lungs can be related to the induced bronchoconstrictions, which result in enhanced velocity and turbulence of the gas flow. The observed subsequent aerosol redistribution may be due to temporal variation of the asthmatic airway resistance. The observed R_2* reduction was related to susceptibility compensation effects; while negative correlation between pre-SI and R_2* variation in emphysema may be explained by the lower susceptibility compensation in enlarged airspaces than in controls, as similar concentrations were measured. It further stresses the complexity of the apparent transverse relaxation within the lungs. Abnormal hyper-signal observed at baseline for some control rats may have been induced by the saline instillation, which may generate lung inflammation[6]. Corresponding symptoms may have been limited for emphysematous rats as comparable RD and regional distributions were observed. Histology or CT could provide complementary insights to challenge our findings and to evaluate the disease severity, as literature results are reporting either higher[7], or lower[8] depositions in emphysema. With 3D UTE, MRI is an efficient tool to measure spatially-resolved aerosol deposition in the lungs. The use of small Gd doses in a clinical MRI system here suggests a potential clinical transfer.

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