Quantitative Gadolinium-based Aerosol Deposition and Dynamics in Healthy Rat Lung by UTE-MRI

Hongchen Wang[1], Catherine Sébrié[1], Jean-Pierre Ruaud[1], Geneviève Guillot[1], Khaoula Bouazizi-Verdier[1], Georges Willoquet[1], Xavier Maître[1], Luc Darrasse[1], and Ludovic de Rochefort[1]

[1]*Imagerie par Résonance Magnétique Médicale et Multi-Modalités (UMR8081) IR4M, CNRS, Univ. Paris-Sud, Orsay, France*

Purpose: Aerosol toxicology and drug delivery through the lungs require the development of methods to quantify particle deposition, which depends on various parameters such as airway geometry, breathing pattern, aerosol and gas properties[1,2]. The use of intrapulmonary-administered MRI contrast agent combined with lung-specific imaging sequences has been proposed[3] and remains an active preclinical research topic[4-6]. Various administration protocols have been proposed (e.g. nebulization or instillation in conjunction with free breathing, or mechanical ventilation), as well as different pulse sequences such as standard spin-echo or gradient-echo, and more recently ultra-short echo (UTE) sequences[6] that are more adapted for lung parenchyma imaging. Here, we present the use of 3D UTE implemented on a clinical scanner pre- and post- administration of gadolinium-based aerosol delivery in spontaneously breathing healthy rats, thus mimicking chronic particle exposure or free-breathing drug delivery. The method for contrast-enhanced quantification enabled us to follow up lung clearance and map regional heterogeneity of the deposition.

Methods: *Imaging protocol*: Rats (n = 6, male Wistar, 6/7 week-old, 180-200 g) were anaesthetized with 2% isoflurane in 0.8 L/min pure O_2 delivered through a modified nose cone (Rothacher Medical GmbH, Heitenried, Switzerland) and were immobilized in the prone position in a dedicated holder built in-house. They were kept at body temperature using hot water circulation and breathing patterns were monitored (SA Instruments Inc., Stony Brook, NY). MRI measurements were performed using a clinical 1.5 T (Achieva; Philips, Best, The Netherlands) with rat positioned inside a 47 mm-diameter microscopy coil. After localization, a 3D radial sequence with 2 TEs (0.4/1.4 ms) and a pre-contrast UTE baseline scan, Gd-DOTA (Dotarem; Guerbet, Villepinte, France) concentrated at 0.5 mol/L was continuously aerosolized and delivered to the rat during ~14 min using an ultrasonic nebulizer (Aeroneb Solo; Aerogen, Galway, Ireland). The nebulizer generated aerosols with a mass median aerodynamic diameter (MMAD) of 3.4 µm and was inserted in the anaesthetic gas input line. A T_1-weighted 3D isotropic UTE radial sequence was performed with the following parameters: TR/TE = 14/0.4 ms, 30º flip angle, 64 mm FOV, (0.5 mm)^3 resolution, 255 Hz bandwidth-per-pixel and 7.5 min acquisition time. The sequence was repeated during administration and up to 1 hour post-administration.
Image analysis: The lung was automatically revealed from the difference of the pre-administration short- and long-TE datasets. After thresholding, erosion-dilatation and connectivity operations, a region-of-interest (ROI) for the raw lung was defined. The histogram in this ROI was adjusted to a Gaussian distribution (mean m and standard deviation σ) and a finer mask was obtained by thresholding the baseline image to $m+2\sigma$ considering higher intensity as vasculature. The relative signal enhancement (SE) in the reported ROI was analysed on the UTE images at each time point: $SE = (S_{post} - S_{pre})/S_{pre}$. SE was further converted into concentration map using steady-state equilibrium signal and linearity of relaxation rate with concentration[7]. T_2* was assumed not to vary pre- and post- contrast, which was verified for n=3. We further considered a relaxivity of $r_1 = 3.7$ mM^{-1}s^{-1} and relaxation time pre-contrast $T_{1,0} = 1.1$ s for rat lung at 1.5 T. The washout rate was estimated as the slope of the SE decay after administration (given in % decrease per hour) to characterize clearance.
Administered dose evaluation: While the nebulizer reservoir contained 7 mL of Gd, only a small fraction passed through the input anaesthetic gas line. To estimate the aerosol concentration in this line, phantom experiments were done (n = 5) in which the input line was immerged into a tube filled with water. Gd-concentration in the tube was then measured using T_2* mapping after an initial calibration of molar relaxivity r_2*[8]. To further estimate the upper limit of the administered dose, the tidal volume was estimated in 3 rats using a cine sequence synchronized on respiration. Finally, the administered aerosol quantity was evaluated as the product of tidal volume, respiratory rate during administration (38±4 cycles per min), and aerosolized-Gd concentration in the input line.

Results: The signal was significantly and homogenously enhanced in the lungs after aerosolized-Gd administration (Fig.1a&b). The total aerosol deposition in the lung was estimated at 0.45±0.04 µmol (Fig.1c). Some localized spots, generally apical in easily identifiable sub-lobar regions, displayed higher Gd deposition (observed in 4 animals, Fig.1d-f). SE curves (Fig.2) showed individual variability both in maximum enhancement and clearance which may result from breathing pattern, respiratory geometry and physiology. On average, a maximal SE of 50±5%, a time to peak of about 20 minutes (short after the end of administration), and a clearance rate of 14% per hour were observed. The measured tidal volume was 1.62±0.1 mL and the estimated Gd concentration in the input gas line was 36±5.8 µmol/L. These parameters led to the estimation of the upper limit delivered to the rat of 31±6.3 µmol.

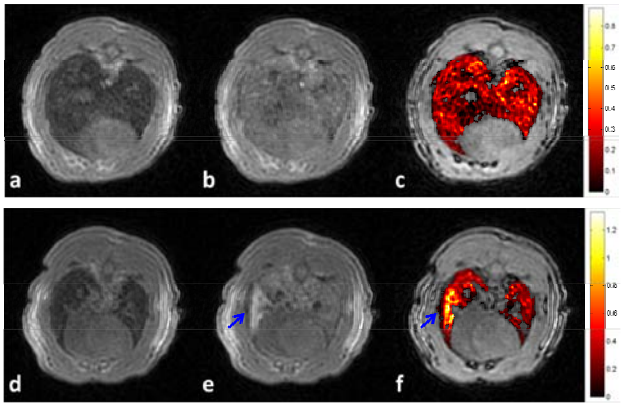

Fig.1: Pre (a,d), post (b,e) aerosol administration and concentration map (c,f, in mmol/L) showing significant SE in a representative region (a, b, c) and in an apical region displaying higher SE (blue arrow; d, e, f).

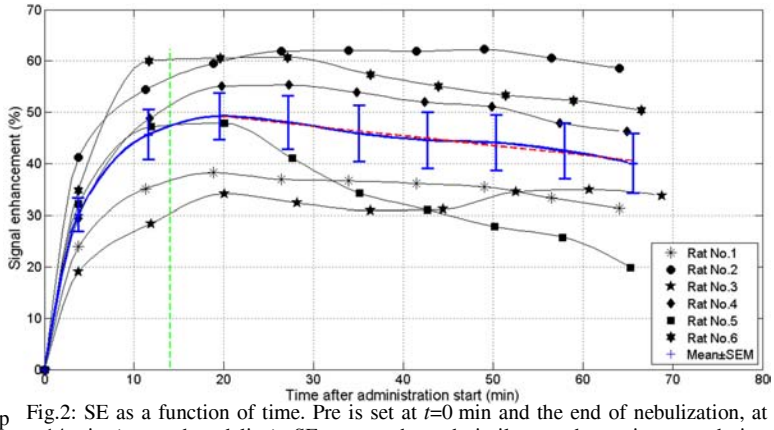

Fig.2: SE as a function of time. Pre is set at t=0 min and the end of nebulization, at t=14 min (green dotted line). SE curves showed similar trends: an increase during administration up to a comparable enhancement followed by a progressive decay, well modelled by a line for the mean curve (red dotted line).

Discussion and Conclusion: A reproducible Gd-based aerosol nebulization in spontaneously breathing rat combined with UTE-MRI on a clinical system was implemented to map aerosol deposition concentration. For quantification, 3D UTE SE sequence was implemented, as it is robust to respiratory motion allowing free breathing during acquisition, it circumvents the issue of short lung T_2* thus increasing pre-contrast signal and does not suffer from slice profile heterogeneity, which makes quantification more difficult[7]. Spontaneous breathing administration is expected to be more representative of chronic exposure to particles than intra-tracheal instillation[6] of acute drug delivery. Indeed, various protocols[6,9] differed significantly from the present study in observed distribution, maximal SE and administration efficiency. Although, in our work, only a small fraction (~1.5%) of the nebulized aerosol was effectively administered and measured in the lung, it is still a much higher quantity than reported in previous studies with longer exposure time[9]. Nebulization efficiency may be limited here by the losses in the circuit and in the extra-thoracic airways. The heterogeneous larger deposition in apical regions may be caused by gravity or airway geometry. The proposed method could be further applied in models of lung diseases such as asthma or emphysema. The experiments were performed in clinical conditions at 1.5 T, providing insights into expected contrast and feasibility in humans.

References: **1.** Sosnowski TR, J Thorac Dis 2011;3:153-155. **2.** Byron PR et al., J Aerosol Med Pulm Drug Deliv 2010;23 Suppl 2:S59-69. **3.** Berthezene Y et al., Radiology 1992;183(3):667-672. **4.** Suga K et al., Acta Radiol 2002;43(3):282-91. **5.** Sood BG et al., Pediatr Res 2008;64(2):159-164. **6.** Bianchi A et al., Magn Reson Med 2013;70(5):1419-1426. **7.** Schabel MC et al., Phys Med Biol 2008;53(9):2345-2373. **8.** Wang H et al., Proc. Intl. Soc. Mag. Reson. Med. 2013; P3841. **9.** Martin AR et al., J Aerosol Med Pulm Drug Deliv 2008;21(4):335-342.

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