Perfluorocarbon Lung Clearance Evaluated with Dual-Nuclei ^{19}F and ^{1}H MRI in the Context of Total Liquid Ventilation

Ludovic de Rochefort[1], Mourad Chenoune[2], Anis Ben Yahmed[1], Charlotte Alibert[1], Jérémy Pépin[1], Fanny Lidouren[2], Lys Darbera[2], Alain Berdeaux[2], Matthias Korn[1], Rose-Marie Dubuisson[1], Luc Darrasse[1], Daniel Isabey[3], and Renaud Tissier[2]

[1]*IR4M, Univ. Paris-Sud, CNRS, UMR 8081, Orsay, France,* [2]*Inserm UMR 955-3, Univ Paris Est, Ecole Nationale Vétérinaire de Maisons-Alfort, Maisons-Alfort, France,* [3]*Inserm UMR 955-13, Univ Paris Est, Créteil, France*

INTRODUCTION

Total Liquid Ventilation (TLV) is a liquid breathing procedure with high capacities of transport and diffusion for O_2 and CO_2. One application is fast hypothermia using liquid perfluorocarbons (PFC) that has been shown to be cardioprotective [1]. TLV procedure includes a lung filling phase, followed by the ventilation per se, and a final clearance phase during which the PFC liquid is eliminated from the lungs by evaporation or endocytosis. For the potential clinical transfer of such approaches, it is important to select PFCs based on the tolerance of the human organism. The clearance phase may vary with the PFC physical properties such as density, viscosity or saturation vapor pressure. Fluorine imaging of the lung has been advantageously proposed for gas imaging [2], or in the context of partial liquid ventilation [3]. Here, we present the evaluation of clearance from pig lungs for three different liquid PFCs with a quantitative dual-nuclei (^{1}H, ^{19}F) MRI protocol at 1.5 T. The results provide first insights for selecting PFCs that could be used in human.

MATERIAL AND METHODS

Preparation of lung samples: All experiments were agreed by the local ethical committee. Eighteen 30kg-pigs were anesthetized. Intra-pulmonary administrations of 15 mL/kg body weight of perfluorodecalin (PFD), perfluorooctane (PFO), and perfluoro-octyl bromide (PFOB) were performed before simulating the clearance phase of the TLV procedure. A control group was also studied for reference. Animals were maintained anesthetized, intubated and ventilated for 24 h to allow more or less complete PFCs evaporation thus mimicking realistic clinical situations. Animals were kept for 4 days in observation before being euthanized. One sample per lobe (7 lobes per pig) was extracted and kept into formaldehyde for imaging and histology.

MRI protocol: Imaging was performed on a 1.5 T clinical system equipped with the multi-nuclei option. Dedicated transmit-receive radiofrequency switch and pre-amplifier tuned to ^{19}F frequency were designed. A two-port dual-resonant volume coil comprising a 10-cm diameter Helmholtz coil (^{19}F) and a 10-cm long saddle coil (^{1}H) were built and connected to transmit-receive switches. For each pig, the seven lobe samples were imaged at the same time, and 3 samples of pure PFD, PFO and PFOB were added in the field-of-view of the coil for signal calibration and quantification. For parenchyma imaging, a 3D spoiled gradient echo sequence with 1 mm isotropic resolution, TR/TE=8.1/3.7 ms, bandwidth per pixel 191 Hz, matrix size 164×72×72, was applied to get T1-weigthed (flip angle 20°, 1 average) and proton density (flip angle 5°, 8 averages) scans. To evaluate PFCs, fluorine images were acquired using a 3D spoiled gradient echo sequence with isotropic 1.5 mm resolution, TR/TE=12/2.9 ms, bandwidth per pixel 2.2 kHz, matrix size 116×52×52, flip angle 10° and 16 averages. Bandwidth and echo time were chosen such that chemical shift artifact was minimized and that the various peaks of the complex spectra were approximately in phase for all the PFC used.

Data analysis: Each sample was segmented in 3D by manually tracing ROIs using the T1W and proton density images. The ROIs were used to evaluate the lung sample volumes. They were reported on the fluorine images for PFC quantification. ROIs were also drawn over the tubes containing pure PFCs in the ^{19}F images to infer the mean signal therein. Noise was measured as the standard deviation in a region void of signal. Fluorine images were thresholded at 3 times the noise level and converted to concentration using the adequate reference PFC signal from the tubes. The mean concentration within each sample was then estimated.

RESULTS

The signal combination between the different peaks led to consistent ^{19}F and ^{1}H images that can be superimposed without further correction, as show in Fig.1 in which an exemplary ROI (red) delineates fairly well the lung parenchyma in both ^{19}F and ^{1}H images. Sample volumes were 6.3±0.4 mL. SNR in the reference tubes were 53, 87 and 106 for PFD, PFOB and PFO respectively, providing a detection threshold (for SNR>3) of voxels with more than 5.7%, 3.4% and 2.8% for PFD, PFOB, and PFO, respectively. It indicates an enhanced detectability as the spectrum becomes simpler.

Typical fluorine results are shown in Fig.2. As expected, there is no signal detected in the control animal. The PFD group displays a large quantity of signal. The PFOB group has detectable amount of signal, and the PFO group displays only traces. As synthetized in Fig.3, when converted to mean concentration within the samples, the PFO group has no significant amount of remaining PFC (0.1%±0.2% on average, on the order of the control group detectability limit). There is remaining PFOB within the lungs (1.1%±1.3% on average). Large amounts of PFD were detected (6.2%±8.7%).

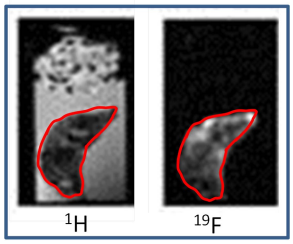

Fig. 1: Typical proton density image displaying a signal hypointensity for the lung sample into formaldehyde. The ^{19}F image indicates a rather homogeneous PFC distribution.

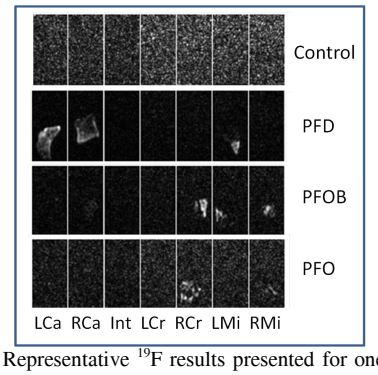

Fig. 2: Representative ^{19}F results presented for one pig of each group (Control, PFD, PFOB and PFO). Acquired 3D volumes reformatted to present the central slice for each lobe (LCa and RCa: Left and Right caudal, Int: intermediate, LCr and RCr: cranial, LMi and RMi: middle)

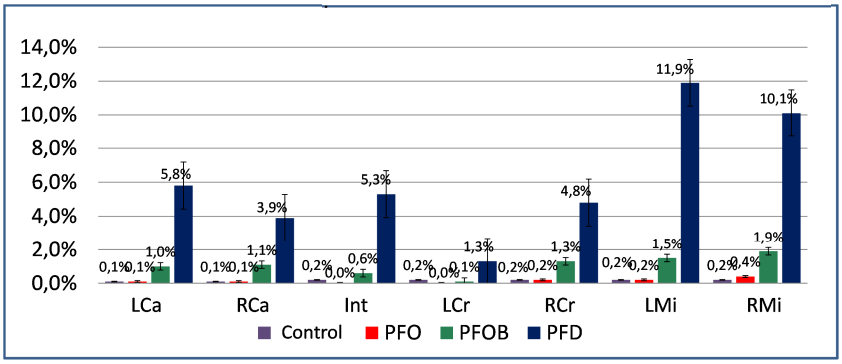

Fig. 3: Remaining PFC concentration in the pig lungs as a function of lobar location (mean±std over animals in the groups). 100% represents liquid PFC concentration. As can be seen, important quantities of PFD remained, with a relatively high variation between lobes.

DISCUSSION AND CONCLUSION

We have presented a sensitive dual nuclei protocol at 1.5 T to quantify remaining traces of PFC in lung samples. Five days after a TLV-like procedure, clearance was shown to be much more efficient for PFO than PFOB and PFD. PFD clearance was clearly much slower. These results corroborate the animal recovery, which was good for the control, PFO, and PFOB groups but not for the PFD group. Further histological analysis should provide insights on the consequences of the slow clearance of PFD.

For ^{19}F MRI of the lungs using liquid PFCs, PFO presents the advantages of a higher sensitivity and a faster clearance.

REFERENCES 1. Tissier R, et al., J Am Coll Cardiol. 2007; 49:601 **2** Schreiber. et al., MRM. 2001; 45:605. **3** Laukemper-Ostendorf. et al., MRM. 2002; 47:82.

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