PHIL
Overview of animal models in WPII
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WP2. ANIMAL MODELS

Task 2.1: Pulse sequences and image reconstruction
Diffusion, dynamic imaging, perfusion and MR Protocol definition

Task 2.2: Control animal studies

Task 2.3: Emphysema-induced animals

Task 2.4: Statistical and post-processing studies
Task 2.1. PULSE SEQUENCES AND IMAGE RECONSTRUCTION

Projection-Reconstruction (Radial): both diffusion weighted (four diffusion images) and anatomical imaging

Spiral imaging

Dynamic imaging
COMSPIRA
(COMbined SPIral and RAdial Imaging)

\[ k_x = k_r \cos(\square) \]
\[ k_y = k_r \sin(\square) \]
\[ k_r = k_m \frac{u(i)}{u(n_x \square 1)} \]
\[ \square = \frac{2 \square n_s j}{n_y} + \frac{2 \square n_e u(i)}{u(n_x)} \]
\[ u(n) = n \square \frac{T}{\square} \left(1 \square e^{n\square/T}\right) \]

**COMSPIRA**
*(COMbined SPIral & RAdial imaging)*

Spiral acquisition

- **RF pulse**
- **FID Acquisition**
- **Readout gradients**
- **Gx**
- **Gy**

\[ n_x = 1024; \ n_y = 3; \ n_e = 4; \ n_s = 1 \]

COMSPIRA
(COMbined SPIral & RAdial imaging)

Radial acquisition

RF pulse

FID Acquisition

Gx = G cos φ

Gy = G sin φ

Readout gradients

n_x = 128; n_y = 20; n_e = 0; n_s = 1

SPIRO technique:
ultra-fast ventilation imaging acquisition

Acquisition of fluoroscopic ventilation image series (200 images/s)
SPIRO technique: image series processing

Parametric maps corresponding from top left to bottom right to the gas arrival time, the filling time constant, the average inflation rate (AIR) and the gas volume values.

Tasks 2.2 and 2.3
Control animals and emphysema models
Why animal models for mimic COPD?

- There are many factors implied in COPD that made very difficult to control all variables in developing research protocols. Introduction of multiple drug studies turn it even more complicated.

- Animal model are additionally very important to study:
  - The pathogenic mechanisms
  - The different patterns of pulmonary function
  - Correlation between structure, function, imaging, etc.
Optimal experimental animals

- Small animals: Mice, hamsters, rats (WPII), guinea pigs and rabbits
- Big animals: Dogs
- The answer depends on the susceptibility of each strain more than each species (WPII: Wistar rats)
- In WPII work, additional considerations such as limited spatial resolution, amount of inhaled volume of hiperpolarized gas, etc.
Problems with animal models

- Different response to the substances used
- Difficult to perform Full Lung Function in small animals
- Small animals have important biological differences in comparison to humans
- Experiment costs (elastase, cigarette smoke, $^3$He) in big animals are more expensive
What is possible to measure?

- Almost everything
- Pulmonary function
- Morphometry
- BAL and cellularity
- Molecular biology techniques in pulmonary tissues
Functional Lung studies

- Flow-volume curves
- Quasi-static pressure-volume curves: Steepest slope and exponential “K”.
- Volumes by dilution: RV, FRC and TLC
- Diffusing capacity (using C\textsuperscript{18}O with mass spectrometer)
- Ventilation distribution: Vd and phase III slope (plateau) with 3 different gases (He, N\textsubscript{2} and SF\textsubscript{6})
Flow-Volume Curve

Flow  Volume

Volume

Flow  Volume
Pressure-Volume Curve: Compliance/elasticity
Gas mixing

Human

Animal model emphysema

Phase 2
Dead Space

Phase 3
Alveolar Plateau

% Nitrogen exhaled
expired volume

% Nitrogen exhaled

He
SF₆
N₂
Following the common method in humans:

Lesions are provoked inducing animals to inhale cigarette smoke

Methods to simulate human smoking

Producing pulmonary lesions similar to those found in human, but using different substances or mechanisms (WP2)

Using combined mechanisms: cigarette smoking is used, but with facilitators
WPII: 2 kinds of emphysema

- Elastase (Panacinar)
  - Normal gas mixing
  - Increase of compliance

- Cadmium (Centriacinar)
  - Severe alterations in the gas mixing
  - Decrease of compliance or normal
"Effect on Single-Breath washout and lung function of elastase-induced emphysema in rats"

N. González Mangado, et al.


"N-Acetylcysteine prevents cigarette smoke-induced small airways alterations in rats"

M.L. Rubio, M.V. Sanchez-Cifuentes, et al.

WPII: some results

- Task 2.2: Control animal studies
- Task 2.3: Emphysema-induced animals
- Task 2.4: Statistical and post-processing studies
FIRST $^3$He IMAGES IN MADRID

Madrid, 24 February 2003
GAS DENSITY IMAGING

Cadmium
ADC
(Apparent Diffusion Coefficient)

DC of $^3$He free is about 2 cm$^2$/s

The diffusion in the lungs is not free

ADC is a function of the alveolar size

ADC could be used as a measurement of the alveolar sizes

It should be convenient to have a numerical relationship between ADC and AIA
CORRELATION MRI-HISTOPATHOLOGY

Control
Panacinar
Centriacinar

\[ r = 0.63 \]

\[ r = 0.98 \]
CONCLUSIONS

- First demonstration of correlation between ADC and alveolar sizes ---> possible quantitation of the degree of severity of emphysema

- Detection of early stage of animal panacinar emphysema

Helium-3 MRI diffusion coefficient: correlation to morphometry in a model of mild emphysema

EXTRA ACTIVITIES: GAS ADMINISTRATION AND GAS POLARIZATION
Working with animal models in a MRI environment

- Compatibility with MRI instruments (materials and synchronism)
- No depolarizing materials
- Small dead volume (about 0.15 cm$^3$)
- High time accuracy (less than 1 ms)
- Versatility (free-breath, hold-breath, ...
AUTOMATIC TUNING AND MATCHING OF A SADDLE COIL AT 4.7 TESLA

Multinuclear experiments (He-3, H-1 and F-19)

MRM (2003) submitted
EXAMPLES OF IMAGES ACQUIRED

\[ ^1H \]
\[ ^{19}F \]
\[ ^3He \]
ACKNOWLEDGMENTS

**MADRID-UCM**
- Manuel Cortijo
- Jesús Ruiz-Cabello
- Ignacio Rodríguez
- Rigoberto Pérez de Alejo
- Palmira Villa

**MADRID-FJD**
- Nicolás González-Mangado
- Germán Peces-Barba
- Mª Luisa Rubio
- Mercedes Ortega
- Mª Carmen Martín-Mosquero

**LYON-CNRS**
- Yannick Cremillieux
- Yves Berthezene
- Virginie Callot
- David Dupuich
- Vasile Stupar
Thanks for your attention