From an invited talk presented at: "Gaz rares hyperpolarisés: des techniques de pompage optique aux applications RMN",
Journée de clôture du GDR 2144 *- Grenoble, 19 Octobre 2004*

Polarised Helium to Image the Lung

Geneviève Tastevin

Laboratoire Kastler Brossel - Paris

http://www.lkb.ens.fr/recherche/flquant

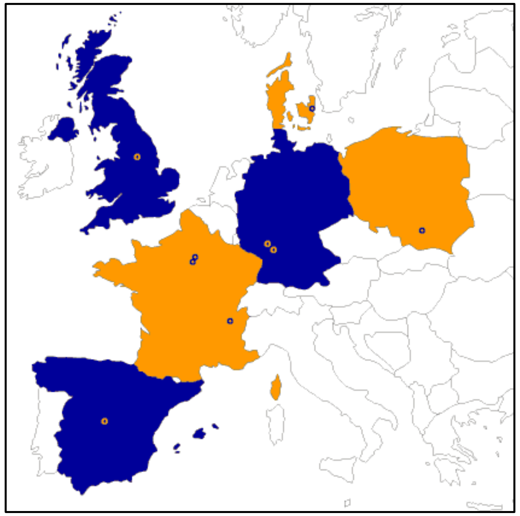
Polarised Helium to Image the Lung

PHIL

Project funded in the 5th Framework Program (FP5)

http://www.phil.ens.fr

Quality of life



A European endeavour

- 9 partners, 6 countries .... w/o pre-existing know-how in ^{3}He-MRI
- born at the 1999 ‘hyperpolarized gases in MR’ meeting in Les Houches

Objectives : validate, develop and disseminate ^{3}He MRI

A European endeavour

Objectives : validate, develop and disseminate ^{3}He MRI

- **Clinical study** : in vivo comparison with established techniques

set up a **large scale, multi-center study**
focused on Chronic Obstructive Pulmonary Diseases

demonstrate **potential as a new tool** for detection, differentiation, staging

=> details and preliminary results in this talk

A European endeavour

Objectives : validate, develop and disseminate ^{3}He MRI

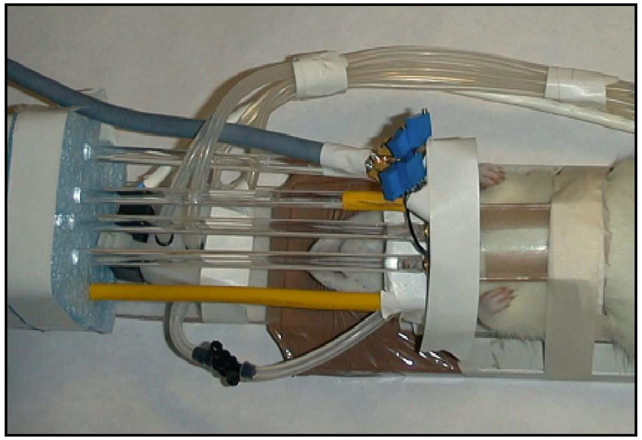
- **Clinical study** : in vivo comparison with established techniques

- **Animal study** : comparison with post-mortem histology

controlled animal models (induced lung injury)

establish positive correlation between
^{3}He-MRI and ex-vivo measurements.

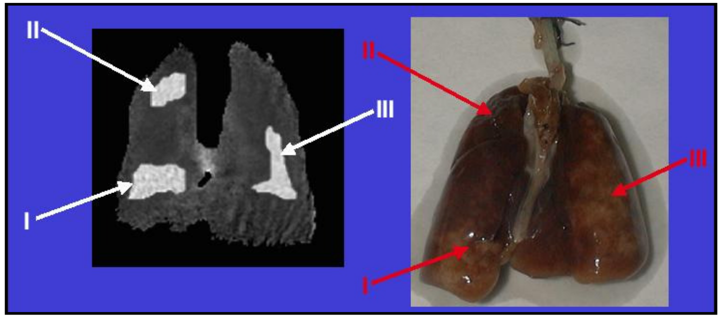
demonstrate potential for early diagnosis
of emphysema (mild injuries)



=> quick start, efficient pilot study
very successful work

Peces-Barba et al, Eur. Resp. J. ***22****, 14-19 (2003)*

(cf Y. Cremillieux's talk)



A European endeavour

Objectives : validate, develop and disseminate ^{3}He MRI

Methodological study

• upgrade and optimisation of gas production and delivery techniques

centralised massive production

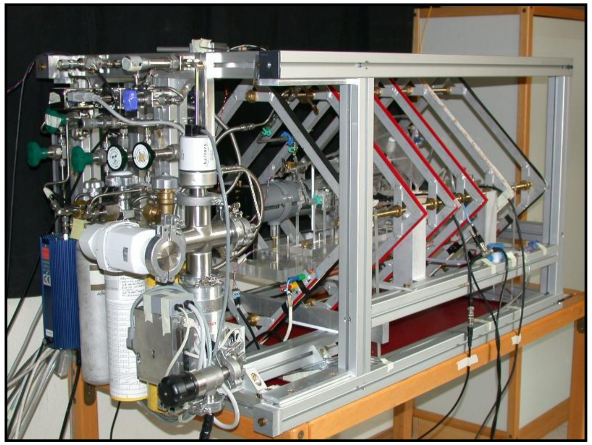
produce and deliver high-grade hyperpolarized gas **to the clinics**

provide accurate control of the gas bolus during administration

on-site production

build table-top polarisers for flexible use

in **animal** or MR **methodological studies**.



$1.1 \times 0.6 \times 0.6$ m^3 unit, Paris

+ push **Metastability Exchange O. P.** to the limits

=> work successfully completed (see later, and GDR'03)

A European endeavour

Objectives : validate, develop and disseminate ^{3}He MRI

Methodological study

- upgrade and optimise gas production and delivery techniques
- improve established ^{3}He-MRI tools and search for new ones

analyse the **magnetic field dependence of SNR and image quality**

systematically investigate **image contrast parameters** to find **new** robust **imaging sequences**

test and clinically implement other **fast imaging** sequences **for improved time resolution.**

assess the standardised PHIL clinical protocol

=> many good and promising results (cf L. Darrasse', Y. Cremillieux' talks)

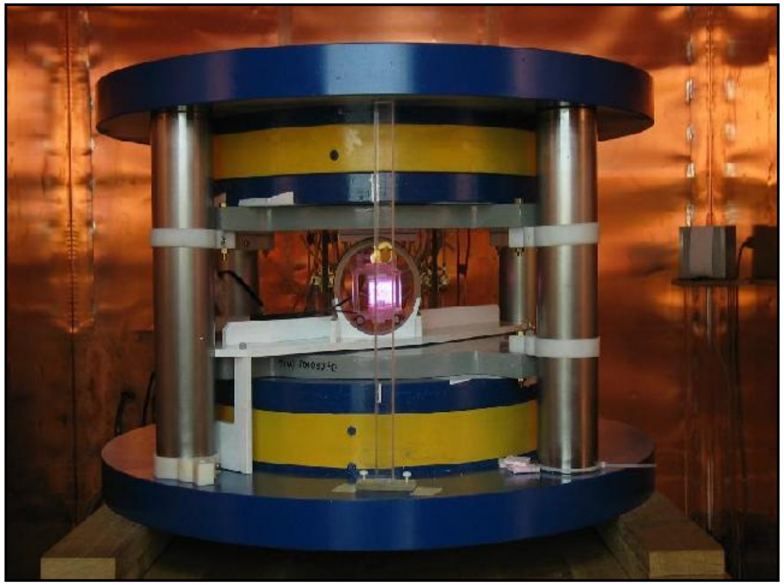
A European endeavour

Objectives : validate, develop and disseminate ^{3}He MRI

Methodological study

- upgrade and optimisation of gas production and delivery techniques
- improvement of established ^{3}He-MRI tools and find new ones
- promotion and test of low field ^{3}He-MRI

build and use **low-cost**, open-access, **dedicated scanner**(s)



0.08T MR scanner
for medium size animals,
Krakow

A European endeavour

Objectives : validate, develop and disseminate ^{3}He MRI

- Create four new ^{3}He-MRI centres (including 1 in Eastern Europe)

  => more expertise and higher training opportunities
- Foster open scientific exchange
- Release information on major outcomes :

  web, media, open scientific meetings, publications...

- Open the way to **massive clinical implementation**
- Initiate **technological development**
- **Transfer robust, dedicated tools to end-users**

A European endeavour

Objectives : validate, develop and disseminate ^{3}He MRI

The PHIL project :

- An <u>academic multi-disciplinary project</u> ...

  Physicists : atomic physics & MR physics

  MDs : radiologists & clinicians, pneumologists, anaesthesiologists,...

  Veterinarians, animal lung physiologists

  + Engineers (hardware + software)

  + Technical MR support from manufacturers

A European endeavour

Objectives : validate, develop and disseminate ^{3}He MRI

The PHIL project

- An academic multi-disciplinary project
  involving close co-operation, multi-center operation, cross-training,...

- Laboratoire Kastler Brossel (**Paris**)
- University of **Sheffield**
- **Copenhagen** Hospital Corporation
- Johannes Gutenberg University (**Mainz**), Klinik für Anesthesiologie, Radiologie, Schwerpunkt Pneumologie.
- Johannes Gutenberg University (**Mainz**), Institut für Physik
- Unité de Recherche en Résonance Magnétique Médicale (**Orsay**)
- Jagielonian University (**Krakow**)
- Université Claude Bernard **Lyon** I, Lab. de RMN
- Universidad Complutense de **Madrid**, Unidad de RMN

Clinical studies
Animal studies
Methodological studies

A European endeavour

Objectives : validate, develop and disseminate ^{3}He MRI

The PHIL project

- An academic multi-disciplinary project
  involving close co-operation, multi-center operation, cross-training,...
- A large work program
  including several scientific and technical challenges

Supported by the 5th Framework Program - Quality of life

- Dec. 2000 - May 2004 : 3 years +6 month extension
- Funding : 1.3 M euros
- Coordinator : M. Leduc, LKB (Paris)

Lung MRI with hyperpolarised ^{3}He gas

Hyperpolarized ^{3}He gas

large, laser-induced (out-of-equilibrium) nuclear polarisations

PHIL : MEOP => high production rates, polarisations up to 92%

(300ml gas bolus diluted in 6.5l TLC imaged with $3 \times 3 \times 10 mm^3$ voxel)

Large MR signals from 0 to several Teslas

from (ultra-)low field to clinical MRI, and high field animal MRI

Safe MR probe, suited for lung imaging

inert gas	no chemical shift	long in vivo lifetime (20-40s)
no side effect	confined to air spaces	exogenous tracer

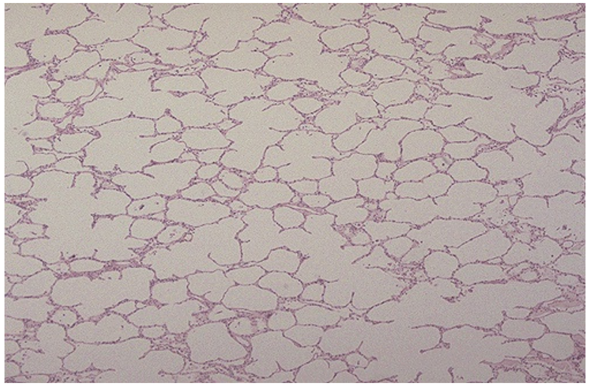
Highly diffusive gas

optimal visualisation and characterisation of (alveolar) air spaces

Lung MRI with hyperpolarised ^{3}He gas

Highly diffusive gas

		^{1}H		^{3}He
Lung parenchyma	low tissue content	☹	mostly air spaces	☺
	free diffusion: $D_H = 10^{-5}$ cm^2/s	☹	$D_{He\text{-}N2} = 0.8$ cm^2/s => 1.3mm in 10ms	
			Restricted diffusion normal lung,std cond.: $D_{eff} = 0.2$ cm^2/s • D_{eff} (alveolar size, $t_{meas..}$)	☺
=> **inhomogeneous local field**	$T_2^* = 1.5 - 3$ ms	☹	**Motional averaging** $T_2^* = 16$ ms @1.5T in $3 \times 3 \times 10$mm^3 voxel • 30-40 times more @ 0.1T !	☺



alveolar size : 0.2 mm

$\chi_{\text{tissue}} = 10$ ppm

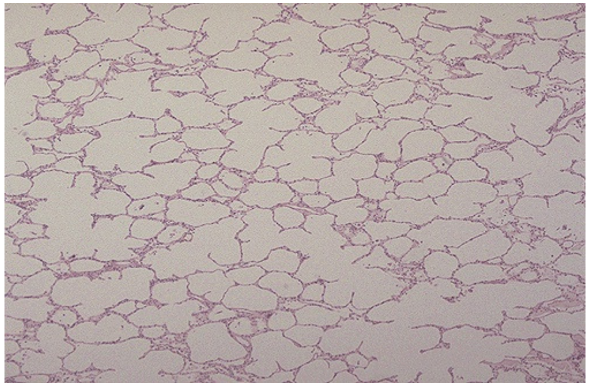
=> **inhomogeneous local field**

NB: Fast imaging feasible & desirable => reduced motion artefacts

Lung MRI with hyperpolarised ^{3}He gas

Highly diffusive gas

	^{1}H	^{3}He
Lung parenchyma	low tissue content	mostly air spaces
		Restricted diffusion normal lung,std cond.: D_{eff} = 0.2 cm^2/s • D_{eff} (alveolar size, $t_{meas..}$)
	T_2^*=1.5 - 3 ms	**Motional averaging** T_2^*=16 ms @1.5T in $3 \times 3 \times 10$mm^3 voxel



alveolar size : 0.2 mm

χ_{tissue} = 10 ppm

=> **inhomogeneous local field**

Ultimate limit on coherence time ?

(local)T_2 : intrinsic relaxation $T_2 = T_1$ at 3mT (LKB, 3mT)

+ diffusion loss in internal gradients physiological contrast

+ diffusion loss in applied gradients limit on resolution

diffusion-weighting

CPMG : G_{app}=0, T_{cp}=20ms
T_2' (0.1T) = 9.2 ± 0.7s
T_2' (1.5T) = 0.14 ± 0.2s
(Orsay)

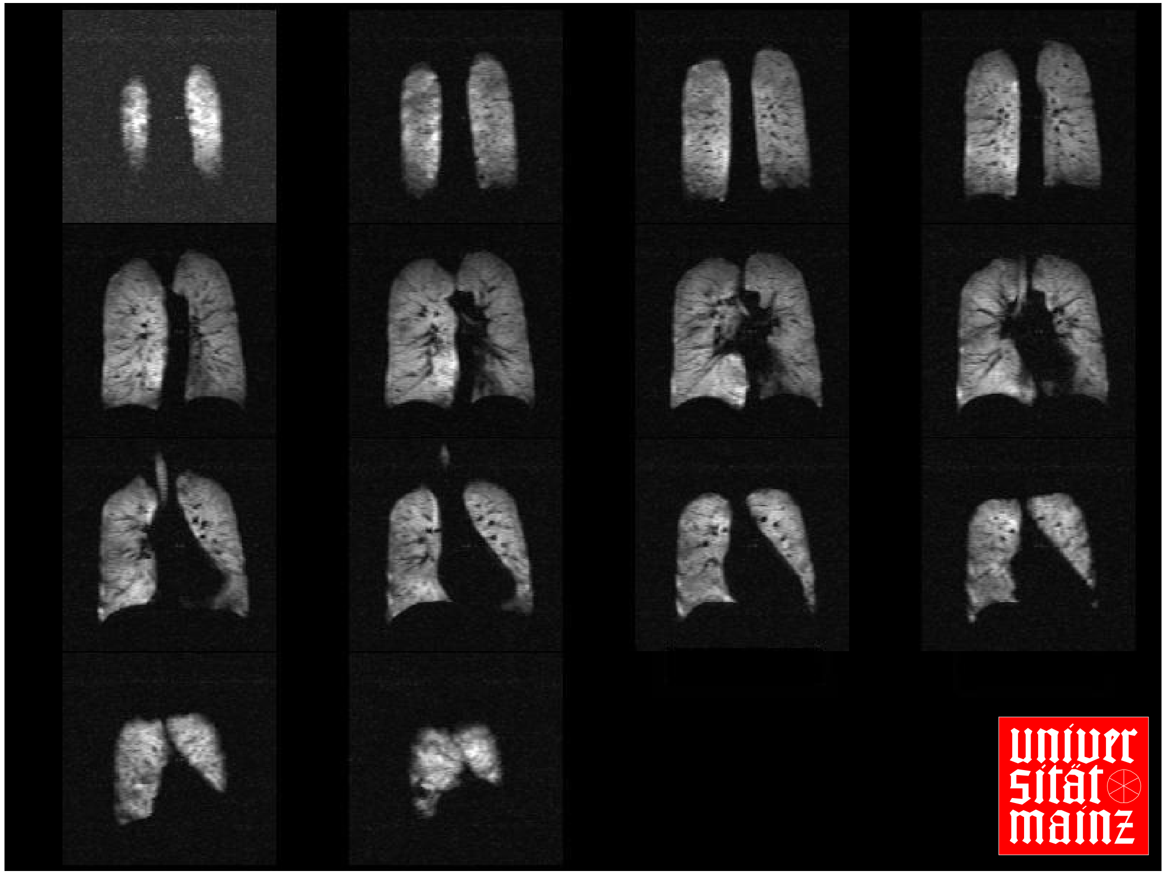
State-of-the-art ^{3}He MRI at PHIL take-off (2000)

1 - High resolution static imaging

Breath-hold acquisition of gas density images (thin slices)

FLASH, with short echo-time *TE* to reduce signal loss due to T_2^* decay

α / TE / TR = 9° / 2.5ms / 7ms
No averaging
128x112 points in FOV=42x37 cm
BW: 244 Hz/pixel (t_s=4096 μs)



Coronal FLASH images - Healthy subject
(300ml ^{3}He bolus with M≈40% polarisation)

10 mm thickness, 3.3 x 3 mm^2

Up to 19 images
can be sequentially obtained
from anterior to posterior.

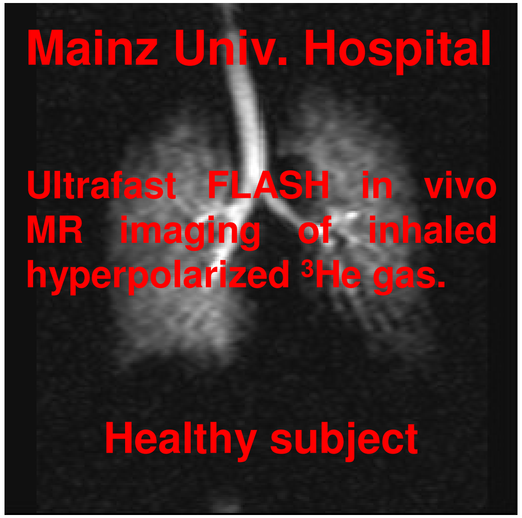
Coronal : reduce breath hold time

State-of-the-art ^{3}He MRI at PHIL take-off (2000)

2 - Dynamic imaging

Ultrafast 2D FLASH to follow the entire respiration cycle:

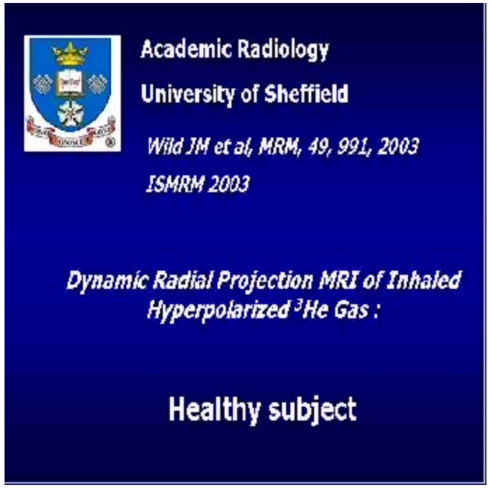
Reduced FOV, minimum TR and TE, minimum BW (data sampling also during ramp-up and ramp-down), no slice selection, low flip angle.



FLASH 2D
No slice selection
α /TR/TE = 1 ° / 2ms / 0.7ms
BW 1527 Hz/Pixel (t_s=800 µs)
75 x 128 matrix
FOV 300 x 350 mm
128 ms/image

4.0 x 2.7 mm^2 in-plane resolution
200 images in 26s

Sheffield Univ.



Coronal projections - Healthy subjects

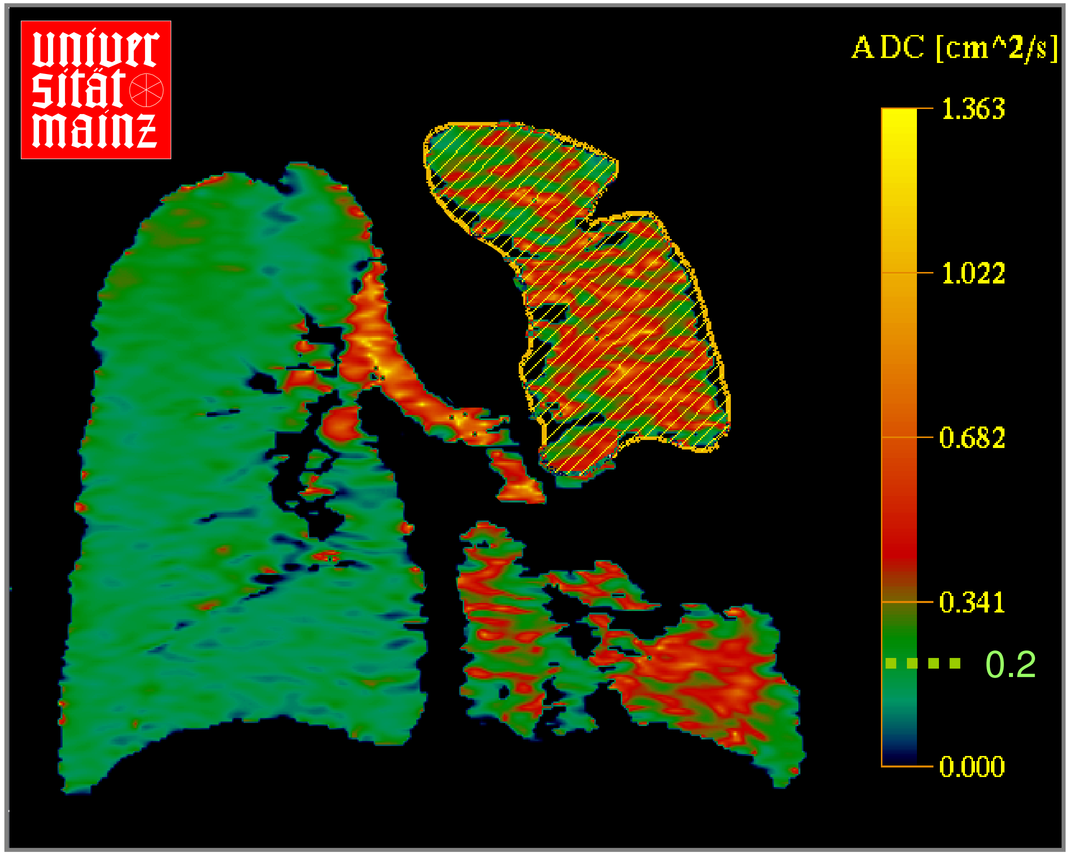
Fast radial imaging
6 ms image refreshment period)

State-of-the-art ^{3}He MRI at PHIL take-off (2000)

3 - ADC maps

Computed from diffusion-weighted breath-hold images (transverse decay)

FLASH,
ADC with b= 3.89 cm^2/s.
(bipolar gradient pair, ±12mT/m, 4.6 ms).
α /TR/TE = 4° / 11ms / 16ms
BW=195 Hz/Pixel (t_s= 5120 µs))
Thickness 20 mm
Matrix 128x 64 in FOV 32x32 cm



Lung Transplant (RL) - Emphysema (native LL) patient

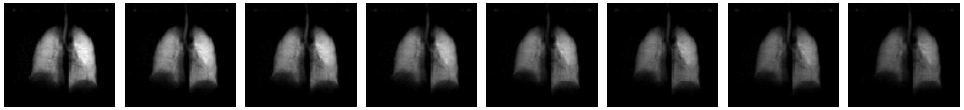
Hanisch et al, ECR 2000, RSNA 2000

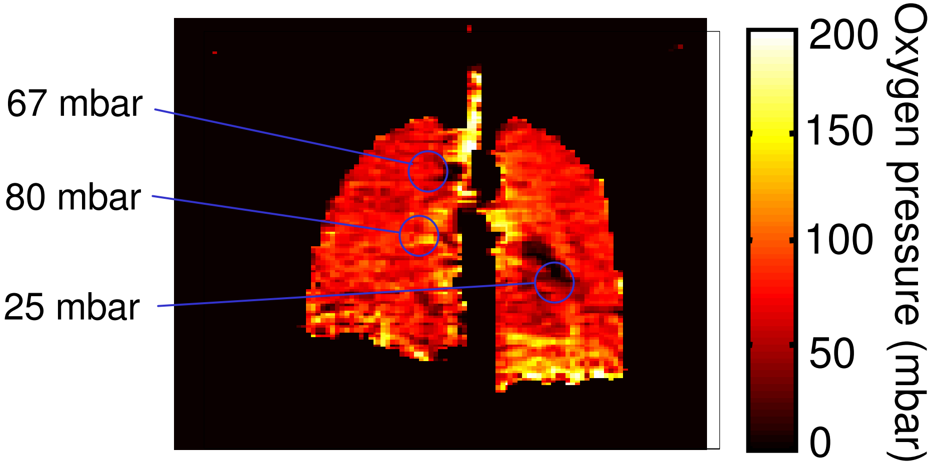
State-of-the-art ^{3}He MRI at PHIL take-off (2000)

4 - Alveolar PO_2 and O_2 uptake maps

Computed from <u>longitudinal</u> decay

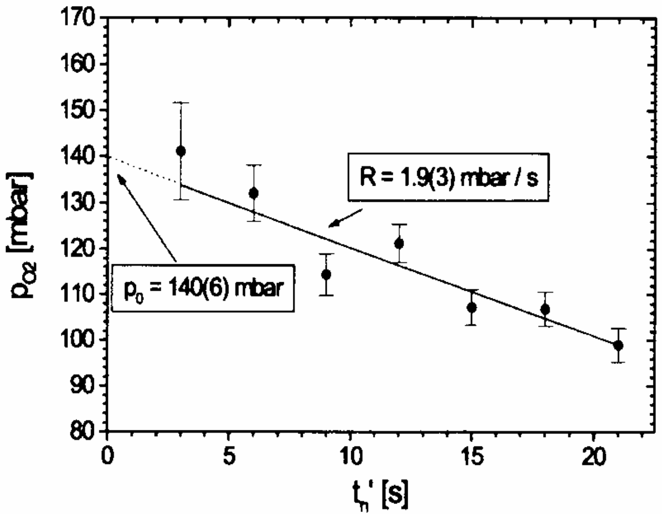
T_1 =2632 s / PO_2[mbar] @37℃ (≈ 13 s in air)





<u>Variation during apnea</u>

= > O_2 uptake



Mainz Univ.

NMR biomed. 2000; 13 : 194-201

PHIL : the multi-center clinical study

Focus on COPD, with emphasis on emphysema

- **large incidence** : 10% of the population in western countries
  1 out of 4 smokers develop COPD
  4th cause of mortality in Europe and the US
- **high social impact** : numerous implicated factors
  - cigarette smoking
  - acute or chronic exposure to dusts, toxic fumes, air pollution, respiratory viruses,...

  huge healthcare cost

Focus on COPD, with emphasis on emphysema

COPD : asthma
chronic bronchitis
emphysema
bronchiectasis
cystic fibrosis
congenital bullous lung disease

both involve irreversible chronic airway obstruction

with considerable overlap between clinical manifestations

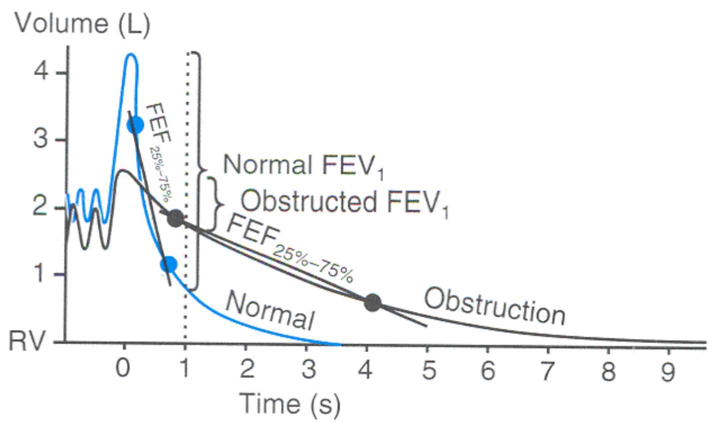
* pathology and pathophysiology are notably different
* required management is also different

=> differentiation is crucial

=> staging is important for prognostic and treatment

PHIL : the multi-center clinical study

COPD : limitation of air flow, in particular expiratory flow



chronic bronchitis

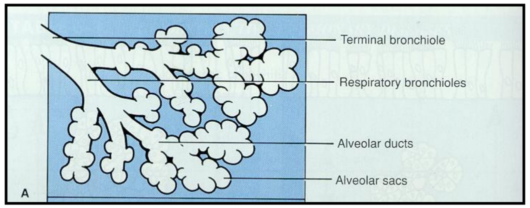
airway wall thickening

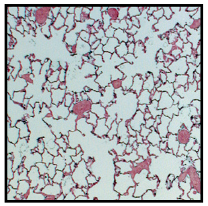
- large mucus gland excess
- inflammation
  (cell hyperplasia, wall edema,...)

mucus hypersecretion

→ narrow airway diameter
→ increased airway resistance

normal parenchyma

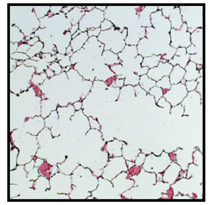




emphysema

enlargement of acini /alveolar air spaces

- alveolar/capillary wall destruction
- elastic recoil reduced

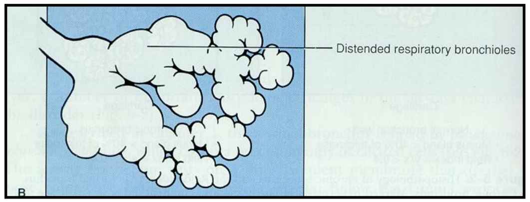


→ increased lung volume
→ increased lung compliance
→ flattened diaphragm

chronic adaptative response

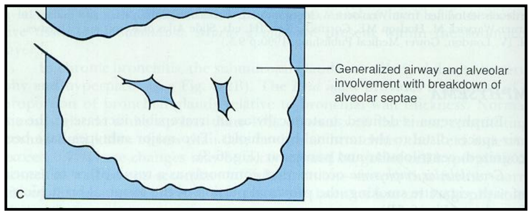
- increased mucus secretion
- contraction of airway smooth muscles

→ increased airway resistance



centrilobular

cigarette smoking



panacinar

aging
α_1- AT disorder

PHIL : the multi-center clinical study

Focus on COPD, with emphasis on emphysema

Method: use a standardised protocol in 3 centres (state-of-the-art ^{3}He MRI sequences)
perform a systematic large scale study

Goal : validation of ^{3}He MRI through comparison with other techniques

- compare with High Resolution Computed Tomography imaging
- use Pulmonary Function Tests as gold standard

\+ add-on shared expertise: Kr scintigraphy (Copenhagen), MIGET (Sheffield)

\+ compile a substantial body of high quality reference data (normal subjects with controlled respiratory conditions).

Population :

120 COPD patients w/o emphysema, incl. 25 with α1-AT deficiency

40 healthy subjects (sex- & age-matched)

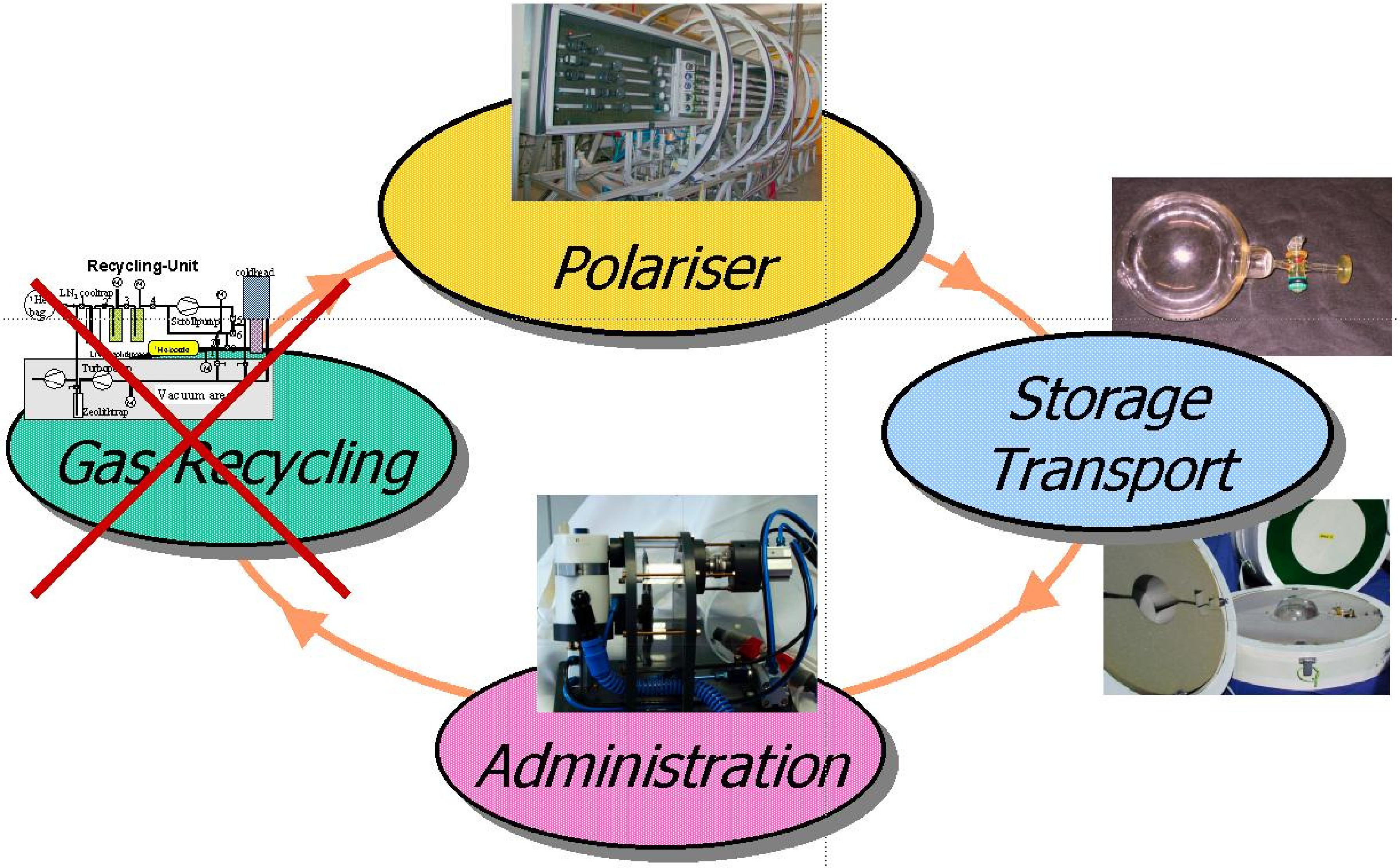
Challenges :

- Get two clinical groups started with ^{3}He-MRI (from scratch!)
- Agree on a protocol (imaging + data processing)
- Implement it identically on all 1.5T systems (2 Siemens, 1 Marconi-Philips)
- Recruit 160 suited subjects, for a demanding series of exams
- Get hundreds of bar.liters of high grade polarised gas delivered on time.

PHIL : centralised gas production and delivery

Technical support to the clinical study

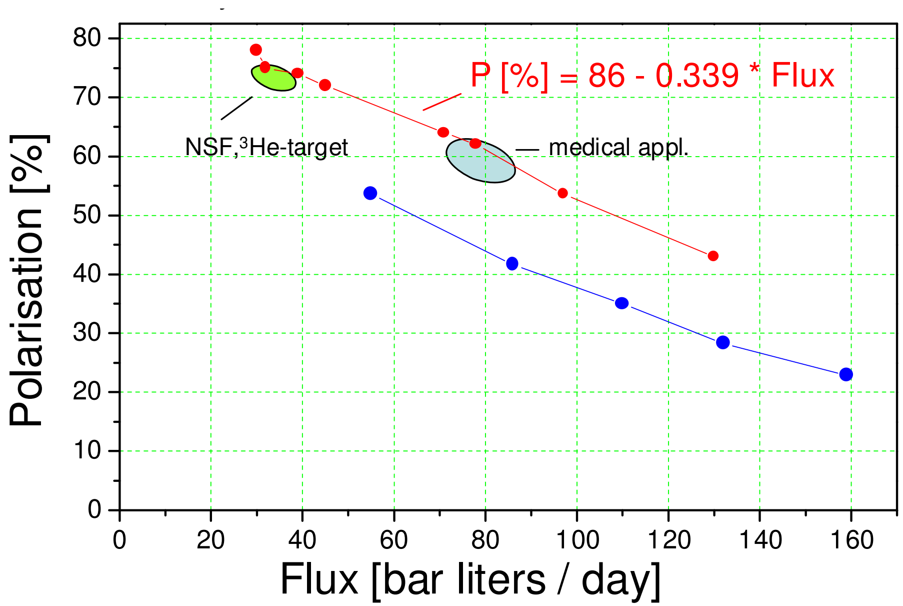
Institute of Physics
EXAKT



PHIL : centralised gas production and delivery

Demonstration of a ^{3}He distribution network :

central production facility + commercial airline transportation



Institute of Physics
EXAKT

Hundreds of ^{3}He bar.liters have been delivered.

Road - air cargo freight - road transportation

250 euros / shipment
transport to imaging : 16-20h (record = 6h!)

T_1^{cell} = 100 - 210h
M_{final} = 30 - 50 %

Phys. Med. Biol. 2002, Eur. Rad. 2003

PHIL : the multi-center clinical study

Inclusion criteria:

Patients with clinically well-established disorders

COPD/Emphysema:

- age > 50 years
- history of COPD (asthma excluded)
- FEV1 ≤ 70%, “no” reversibility
- history of smoking > 20 pack/years.

Homozygous α1-antistrypsin deficiency

- age > 30 years
- α1AT-deficiency syndrome
- FEV1 ≤ 70%, “no” reversibility

Reference

Healthy volunteers:

- age > 50 years
- no history of lung disease
- FEV1 ≥ 80%
- life-long non-smoker

PHIL : the multi-center clinical study

Despite a demanding protocol and straight inclusion criteria...

Total recruited : 122 = 86 COPD (18 α1-AT) [78 m, 38 w; age : mean 62, range 50-79]
+ 36

Inclusion failure : 6 (1) patients due to FEV1
^{3}He-MRI failure : 21 / 116 [withdrawal, obesity,claustrophobia, unstable condition, technical MRI failure]
CT failure : 7 due to radiation

Kr scintigraphy : 35 patients/volunteers
HRCT (in-/exp.) : 109 patients/volunteers
^{3}He-MRI : 95 patients/volunteers

94 / 116 completed CT & MRI = 53 (13) COPD + 28 healthy

36.000 images, 44.000 data files, 9 GB - High quality data (only 5% drop out)

- 120 clinical & visual parameters per subject
- 234 ADC parameters
- 87 ventilation parameters

Final analysis still under way...

PHIL : the multi-center clinical study

Primary endpoint of the study :

Difference in rating, according to PFT classification,

using either ^{3}He-MRI or reference testing (HRCT, Kr scintigraphy, MIGET**).**

1- Pulmonary Function Tests (gold standard)

Complete work-up (spirometry, CO-diffusion, body plethysmography, blood gases...)

=> functional parameters : (FEV1, FVC, $MEF_{25\text{-}75}$), DLCO, (TLC, RV, resistance),..

- FEV1 : airway obstruction
- RV / TLC => hyperinflation / airspace enlargement
- DLCO => capacity to transfer O_2 across lung surface

} parenchymal destruction

Categorization by scores : conventional 1 - 4 rating

(from absolute values, % of predicted ones)

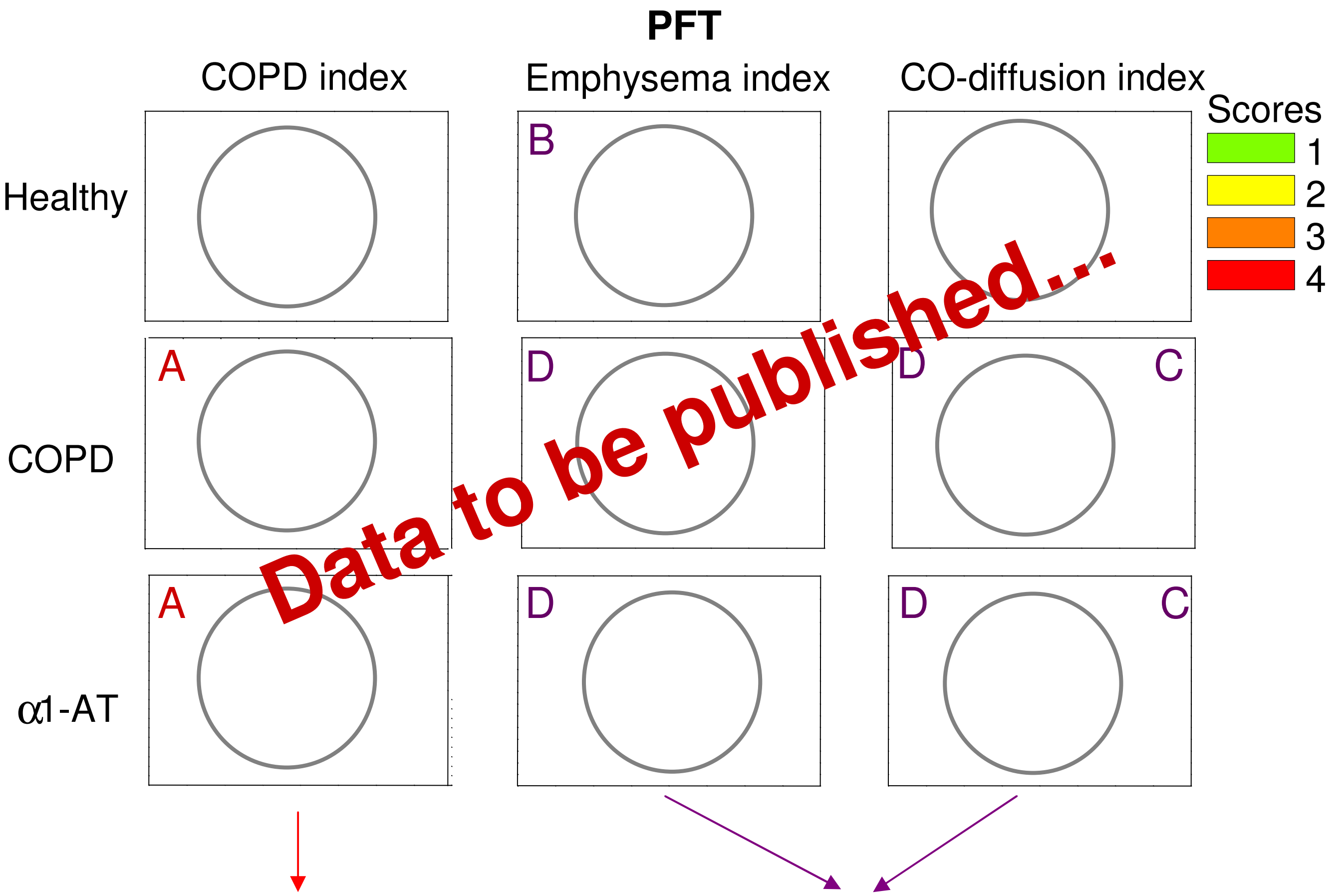
COPD : FEV1/FVC, combined with FEV1 (FEV1<70% = scores 3 and 4)

Emphysema : RV/TLC

CO-diffusion : DLCO

PHIL : the multi-center clinical study

PHIL results : overview of PFT ratings



A ……
75% moderate abnormality
20% severe abnormality

B - EI : …
C …..
=> too much overlap between healthy and diseased
D => no differentiation between COPD and α1AD

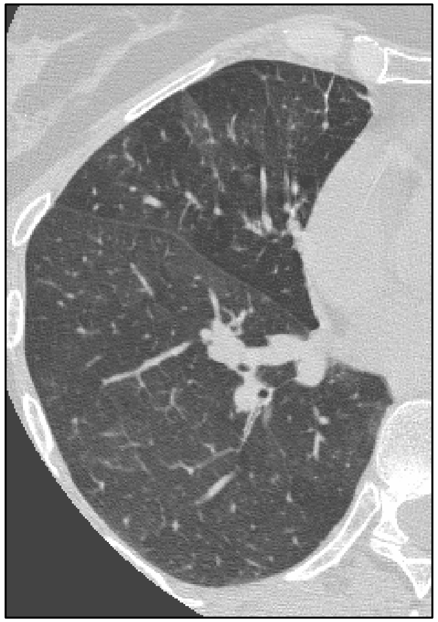
PHIL : the multi-center clinical study

2- High Resolution CT

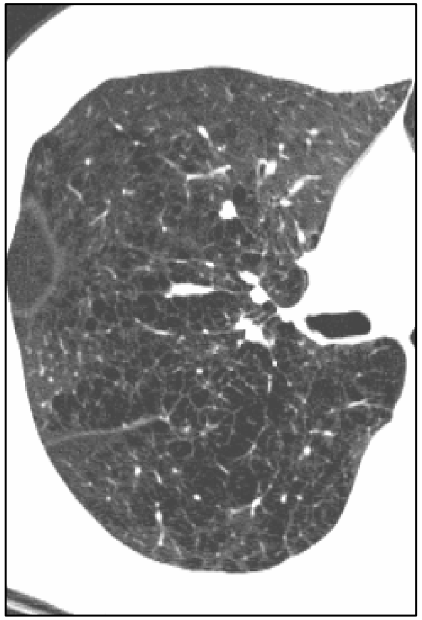
State-of-the art inspiratory and expiratory (axial) scans

- wall thickening
  bronchial dilatation
  air trapping
  } airways
- distribution of opacity
- bullae, fibrosis,...
  } parenchyma (+ types of emphysema)

+ wall thickening



air trapping



emphysema

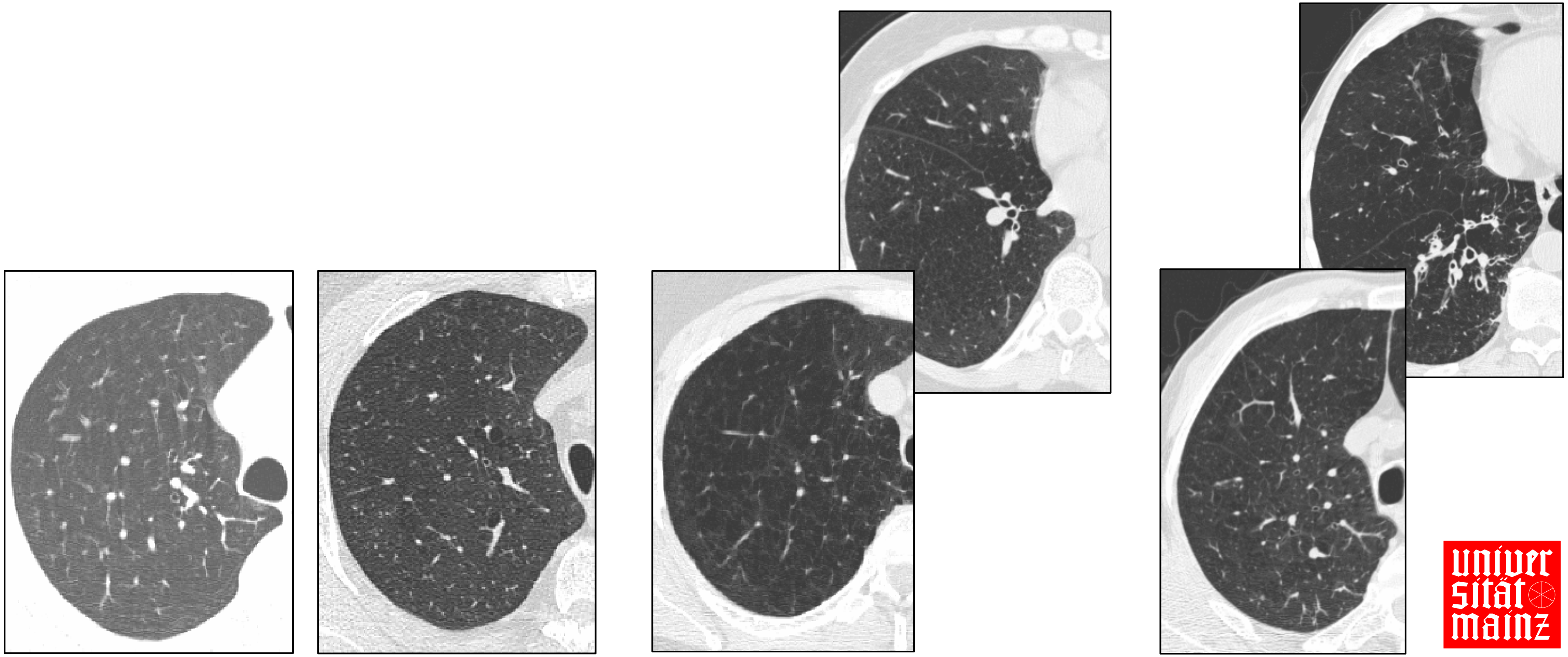
2- High Resolution CT

State-of-the art inspiratory and expiratory (axial) scans

Categorization by scores : 1 - 4 rating

Ventilation : % of diseased lung

Mean Emphysema Index : mean lung density => coarse index!



1 : normal 2 : mild 3 : moderate 4 : severe

PHIL : the multi-center clinical study

2- High Resolution CT

State-of-the art inspiratory and expiratory (axial) scans

Categorization by scores : 1 - 4 rating

Ventilation : % of diseased lung

Mean Emphysema Index : mean lung density

- **Morphological assessment :** definition of 3 main defects (localisation, size, shape)

3 - ^{81m}Kr scintigraphy

[Stanvgaard et al, ISMRM04, ESMRMB04]

4 - MIGET

not discussed here

PHIL : the multi-center clinical study

^{3}He-MRI

Static spin density images

Visual assessment :

- missing signal => non/poorly-ventilated lung
- defect patterns : wedge-shaped, focal, diffuse

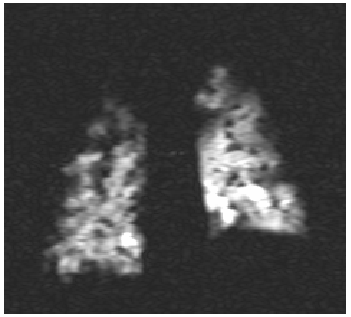
airway obstruction?
parenchymal destruction?

Categorization : scores 1 - 4

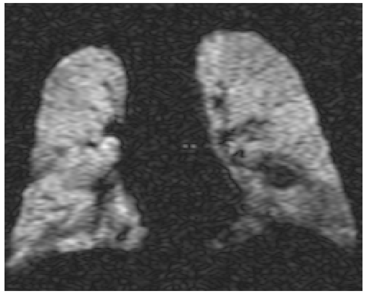
ventilation : % of non-ventilated lung

Morphological assessment : definition of 3 main defects (localisation / size, pattern)

wedge-shaped
(segmental)



focal
(non segmental)



diffuse

PHIL : the multi-center clinical study

^{3}He-MRI compared to HRCT

Visual assessment :

blind reading + cross reading + side-by-side comparison

- corresponding morphology (small / large airways, parenchyma shape)
- corresponding defects + conspicuity

^{3}He-MRI compared to HRCT: preliminary & partial results (1)

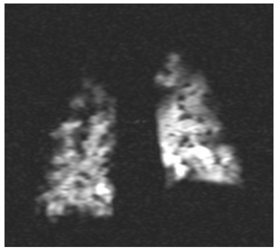
Visual assessment : example of correlation between leading patterns

	CT findings			
CT findings	Emphysema	Air trapping	Bronchial disease	Normal
^{3}He-MRI patterns				

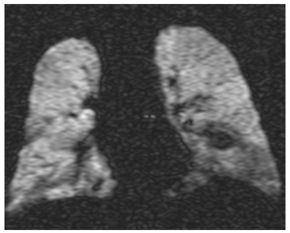
Data to be published…

wedge-shaped

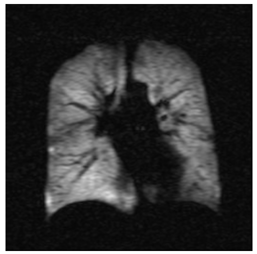
focal



diffuse

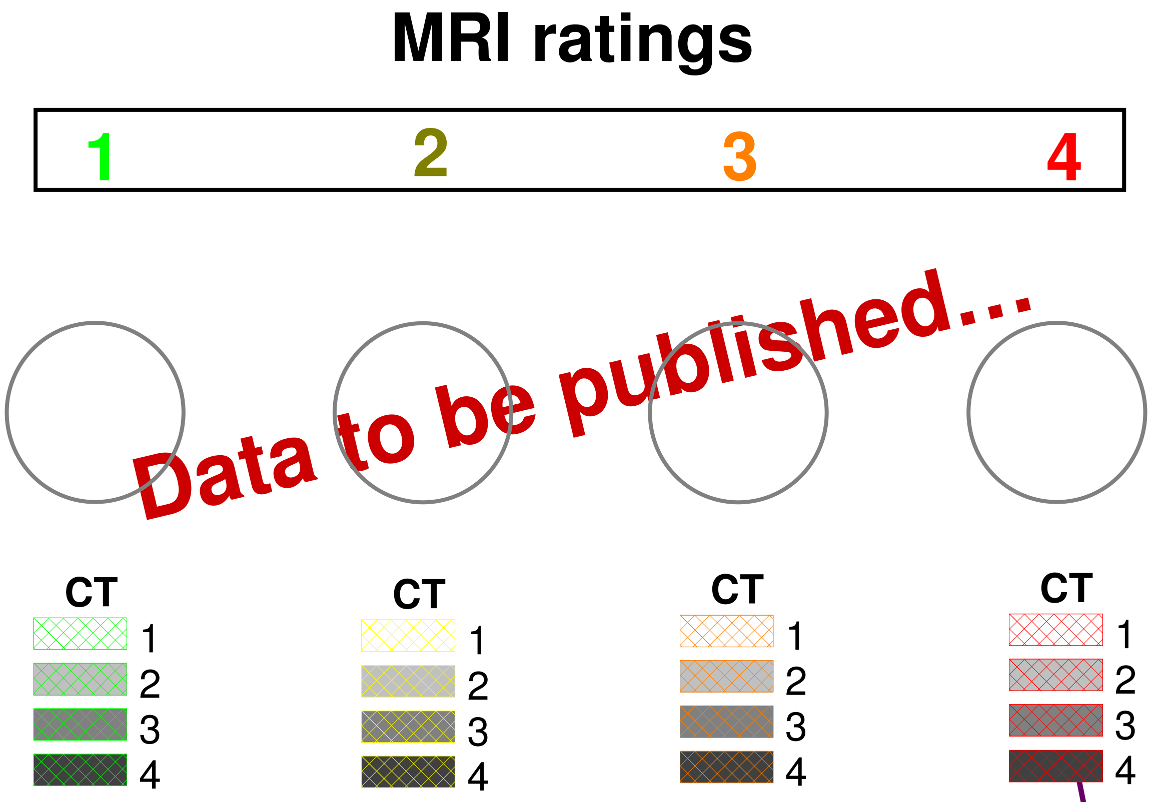


normal



^{3}He-MRI compared to HRCT: preliminary & partial results (2)

Correlation between rating scores



....

COPD : ....

α1AT :.............

=> HRCT more sensitive?

Healthy : ....

=> HRCT ≡ ^{3}He-MRI?

(.....................................)

....

^{3}He-MRI and HRCT compared to PFT dichotomized scores

(normal/mild -moderate/severe)

Preliminary & partial results

- **COPD score**

	^{3}He	CT
Sensitivity (%)	....	....
Specificity (%)	....	....
False P/N (%)	....	....

- **Emphysema score**

	^{3}He	CT
Sensitivity (%)	....	....
Specificity (%)	....	....
False P/N (%)	....	....

Data to be published…

=> **^{3}He-MRI :** higher specificity

much fewer “false positive” / “false negative”

less sensitivity

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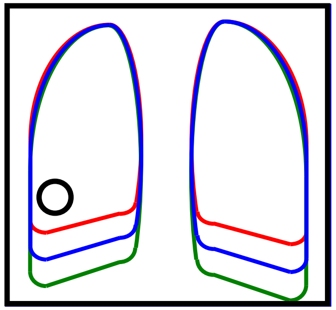
Dynamic imaging

- motion correction to consecutive images



Gast et al.
Invest Radiol 2002, 2003

- mapping of 4 parameters,

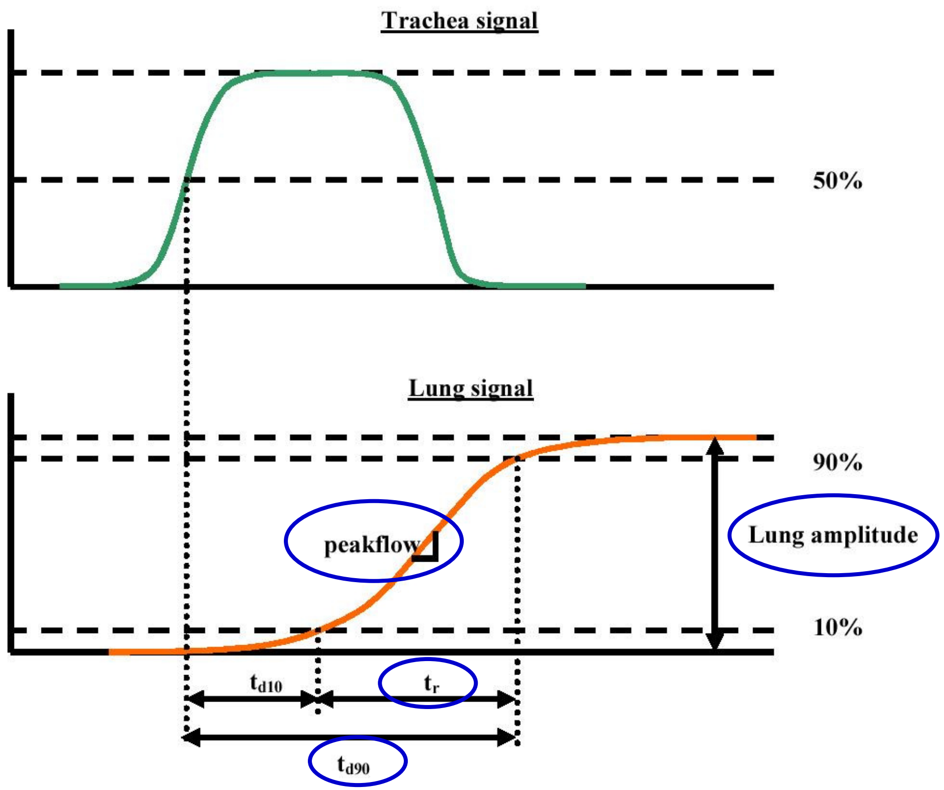
normalised to intake flow of the ^{3}He bolus

maximum flow

90-delay time

rise time

inspired volume/mm^{2}.



- Imaging sequence parameters were kept unchanged during the study.
  (despite progress in temporal resolution...)
- Analysis still under way

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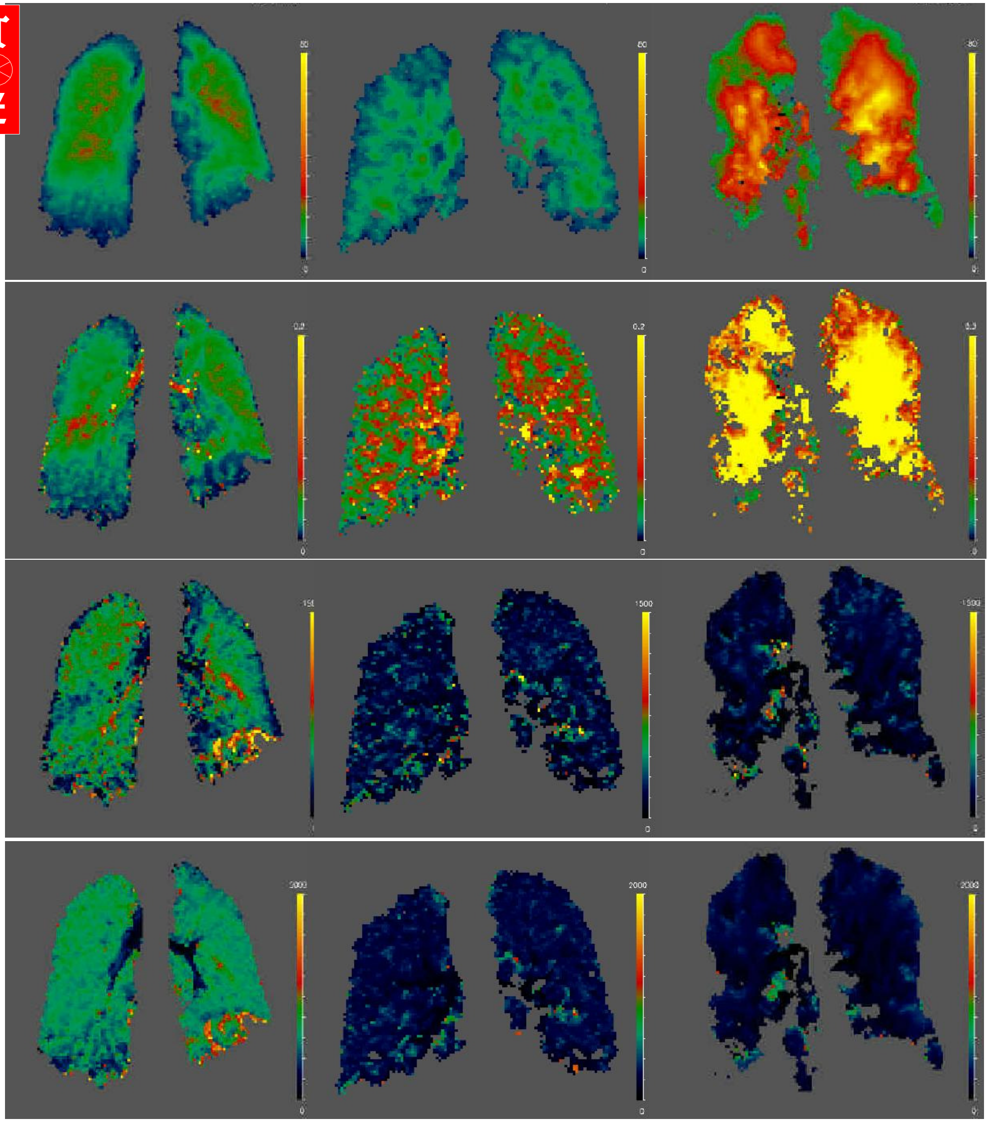
Dynamic imaging :

Normalised functional parametric images



amplitude (µl ^{3}He/mm^2)

peak flow

t_r

t_{90}

Healthy COPD α1AT

=> Distinct abnormal patterns

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Dynamic imaging - Rough summary of preliminary results

Median values and ranges :

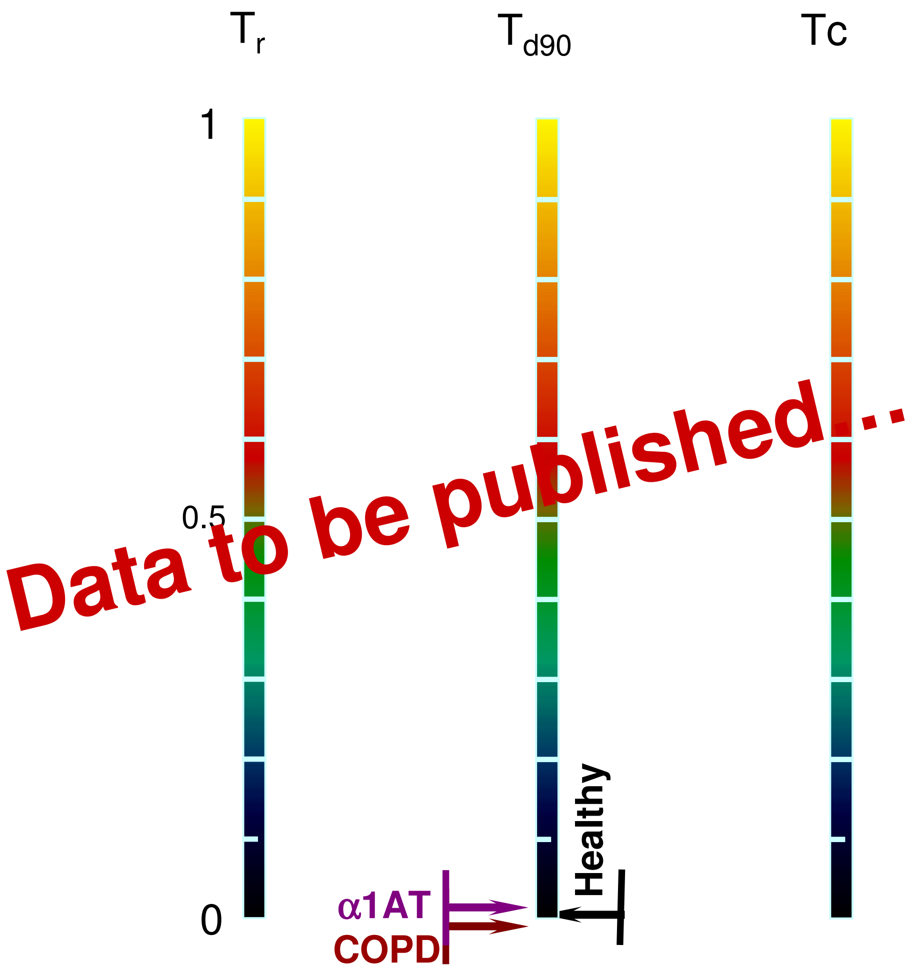
(partial data)

- COPD vs healthy:
  - comparable ranges
  - statistically higher for COPD
  - assess spatial variations?

- α1AT :
  - no overlap
  - systematically lower values

    due to preferential gas flow into upper lobes

=> clear differentiation between α1AT & COPD



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ADC mapping - Rough summary of preliminary results

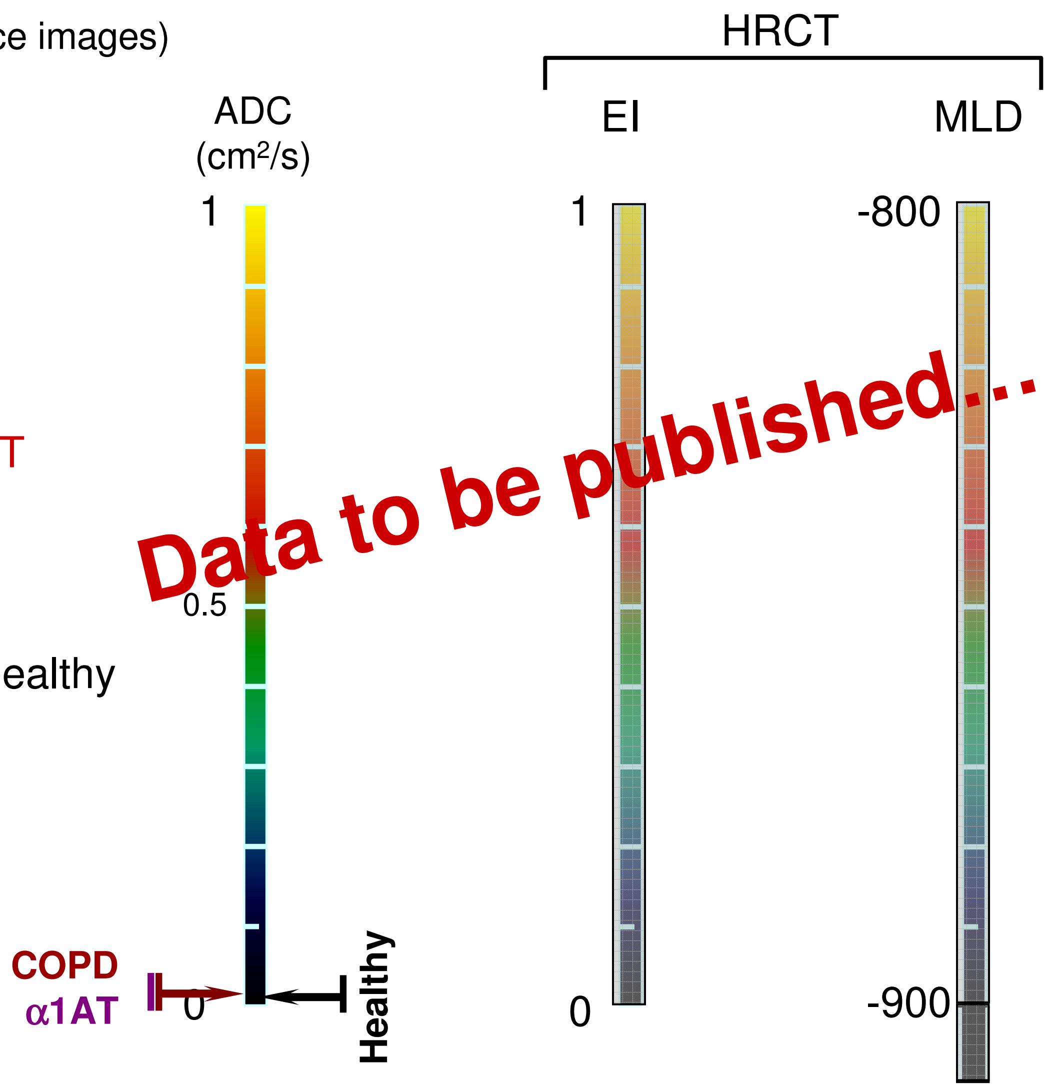
3 axial slices (carina, 3 cm above, and 5 cm below)
Thickness 2 cm, FOV 470 mm.
ADC in x, y, and z axes (+ mean and reference images)

Median values and ranges :
(partial data)

- ^{3}He-MRI mean ADC:
  separates well patients from healthy
  no differentiation between COPD & α1AT
  => assess spatial variations?

- HRCT :
  no differentiation between COPD and healthy
  α1AT is distinguishable

Rather combine the 2 modalities?



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Cross-correlation of scores

Rough summary of preliminary results

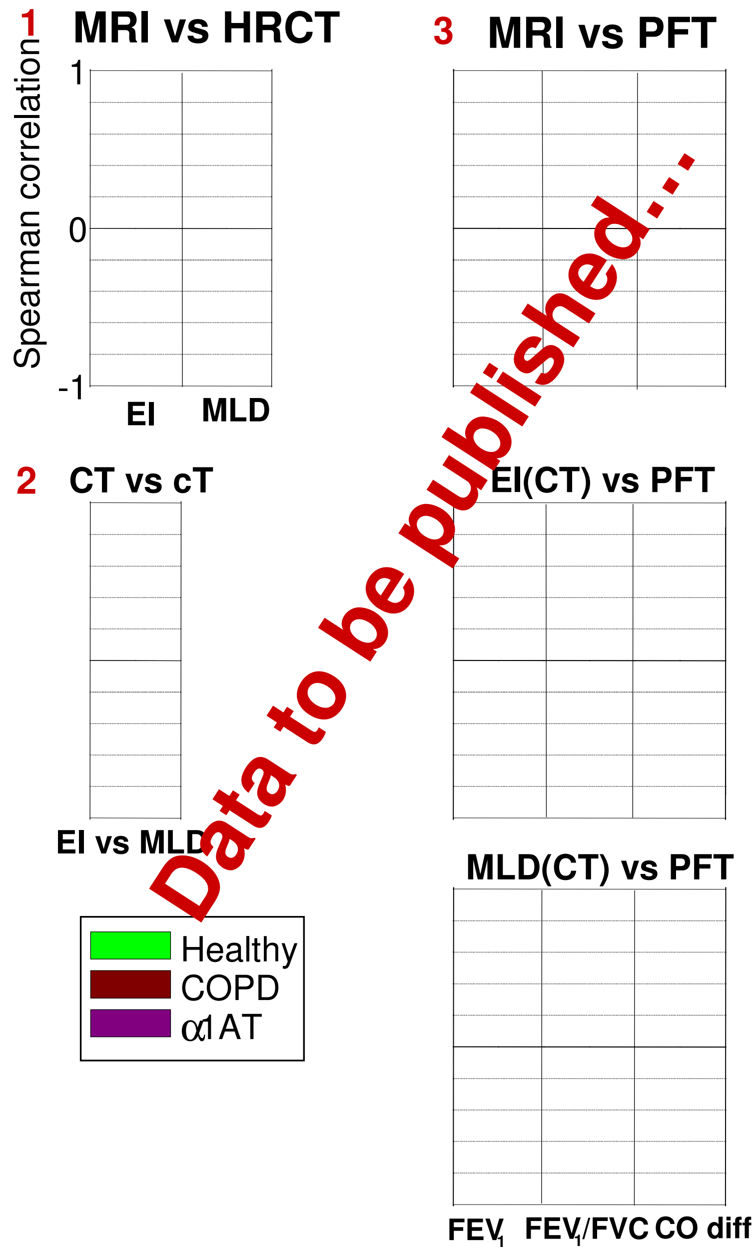
(partial data)

1- ^{3}He-MRI ADC correlates well with CT (both EI & MLD) except for EI in α1AT group

2- EI & MLD, both from CT, correlate very well...!

3- ^{3}He-MRI ADC correlates better with PFT's than CT in patients

=> better representation of lung function by small airway assessment with ^{3}He-MRI



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Conclusions

- Distribution network established (limit start-up costs!)

  (central ^3He production facility + commercial airline transportation)

- Preliminary clinical results

  - ^3He-MRI can distinguish between COPD and α1AT,

    using ventilation + ADC imaging

  - Dynamic imaging can also distinguish between COPD and α1AT,

    <u>but</u>

    poorly correlates with conventional lung function tests so far (COPD)

  - ^3He-MRI correlates better with PFT than HRCT

    <u>but</u>

    morphological information from HRCT is superior to that of ^3He-MRI

  - ^3He-MRI superior to CT in emphysema

PHIL : the multi-center clinical study

Conclusions

- Distribution network established
- Preliminary clinical results
- Many more (detailed) clinical results to come

  - **huge database, available for exhaustive exploitation**

  - > 2 years of work! **Go beyond statistics on global scoring?**
    (intra-individual / spatial correlations within maps, histograms...)

- Progress made in ^{3}He-MRI (methodology + clinics) during the past 3 years

  => **improved protocol to increase relevance and efficiency**
  - try milder COPD?

  => **greater potential interest in other lung diseases?**
  - cystic fibrosis (Sheffield : children 5-15 years)
  - asthma (follow therapeutical interventions)
  - lung transplant (Mainz: early detection of graft rejection)
  - lung volume surgery (better spatial awareness : redundant / non-functioning tissue)
  - radiotherapy planning (Sheffield : reduced damage by combined imaging approach)
  - vertical imaging : better lung function tests? (Paris, Sheffield : low field, open access, multi-orientation dedicated scanners).

PHIL : the multi-center clinical study

Conclusions

- Distribution network established
- Preliminary clinical results
- Many more (detailed) clinical results to come
- Progress made in ^{3}He-MRI (methodology + clinics) during the past 3 years

Perspectives

Dissemination of ^{3}He-MRI

Transfer to end-users

European Research Training Network (FP6)?