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Names and affiliations of applicants (* indicates experimentalists):

Prof. Anssi Sovijärvi, Helsinki University Central Hospital, Finland
Dr. Sam Bayat, Centre Hospitalier de Saint Laurent du Pont, France *
Dr. Leena Kivisaari, Helsinki University Central Hospital, Finland
Prof. Pekka Suortti, University of Helsinki, Finland *

PhD. Christian Nemoz, ESRF *
MSc. Liisa Porra, University of Helsinki, Finland *
MSc. Heikki Suhonen, University of Helsinki, Finland *

Final report 2004-2005

The project was accepted as a Long Term Project (LTP) for the period February 2004 to February 2006. Between February 2004 and November 2005, 4 experiments have been carried out. This report summarizes briefly the results of the project until January 2006.

The background and first results of the project are described in detail in an earlier report covering the period 2001-2003 (experiment number LS-2102).

Aim of the project:

The research program is based on the methods developed in the first phase of the project. An animal model (rabbit) is used to image regional ventilation distributions in normal and pathologic lung. A mixture of oxygen and stable xenon gas is used as the contrast agent, and simultaneous imaging is done by two x-ray beams bracketing the K-absorption edge of xenon. The difference of the two images gives the distribution of the xenon gas. Compared to any other existing imaging method, the present method has superb spatial resolution, it is fast enough for functional imaging, and the results are truly quantitative. The long-term goal is to obtain new dimensions for a better understanding of the patho-physiology of obstructive lung diseases, and study of the effects of medication.

Proposed experimental program of the LTP in 2004-2006:

Four foci of research were defined in the proposal that was submitted in August 2003,

1. Distribution of regional lung ventilation in a model of obstructive lung disease.
2. Effects of mild bronchial provocation with air pollutants and irritants.
3. Methods development for studies of small animals (rat, mouse)
4. Development of 3-dimensional imaging based on a small number of projections.

The emphasis of the studies has been in the first area and in fundamental physiological problems. The second area has turned out to be too vast and require experiments with large populations of animals to be feasible by the use of the present method, given the limitations in the allocated beamtime, cost of experiments and available manpower. Methods development in the third and fourth areas has been started. Experiments and results are described in the following.

1. Distribution of ventilatory gas exchange in diseased lung

An asthma attack can be induced by inhalation of histamine aerosol. This method is routinely used as a diagnostic technique in human patients. It has been known that there are large local abnormalities in regional lung ventilation in response to histamine provocation, but detailed quantitative information has been lacking. The K-edge subtraction (KES) method, which was developed in the first phase of this project, has a spatial resolution of 0.1 mm^3, a CT image is acquired in 2 seconds, and the absolute concentration of the contrast gas is obtained. This imaging technique allows dynamic imaging of xenon concentrations within the lung alveoli, thereby yielding maps of regional lung ventilation with the best spatial resolution currently available. The KES method is also unique tool for quantitative studies of the dynamics of the asthma attack, by allowing the direct measurement of airway calibers and their changes in time in response to bronchoconstricting agents, and the spontaneous or medication-assisted recovery.

As a precursor for the studies of experimental asthma the effects of the depth of breath (tidal volume) was studied (Porra et al., 2004). Severe asthma is characterized by narrowing and obstruction of airways resulting in a reduction of ventilation. We have previously shown that the abnormalities in regional ventilation are bimodal and spatially heterogeneous (Monfraix et al. 2002). Since then, these findings have been confirmed in human patients using PET (Venegas et al., 2005). One supportive treatment strategy in severe asthma is mechanical ventilation, the parameters of which should be optimized to reopen poorly ventilated lung zones. However, little is known on the effects of changes in mechanical ventilation parameters such as Tidal Volume (depth of breath), frequency, or Positive End-Expiratory Pressure (PEEP) on regional lung ventilation at the alveolar level. It was found that the specific ventilation becomes more uniform with increasing tidal volume, as the distal parts of lungs are recruited in normal lung. Similar studies in constricted lung have been started, the data of which would be of highest clinical and physiological interest.

3-dimensional imaging of ventilation distributions was developed further, using both spiral (helical) and multi-slice scanning. The technique was applied to the measurement of the regional lung gas volume and the imaging of the bronchial tree of normal lung and lungs during an asthma attack. Preliminary results were given in the previous report (LS-2102; 2003), where the ventilated lung volume is shown by surface rendering the contrast agent concentration. An important findings are that:

1) static regional lung volume is severely redistributed from constricted to open lung zones. The clinical significance of this finding is that aerosolized drugs are directed to the healthier lung zones in acute asthmatic states,

2) the effects of histamine are not completely reversed during spontaneous recovery, but the effects migrate spatially as a function of time. Total closing of some of the bronchi is illustrated in Fig. 1,

3) quantitative measurement of static regional lung volume at different levels of lung inflation allowed the calculation of a "regional lung compliance ($\delta V/\delta P$)" giving an indication on the regional elastic properties of the lung and chest wall These results have been published (Monfraix et al., 2005).

A systematic study of the dynamics of airway narrowing during an asthma attack was carried out by imaging the lungs at different anatomic levels. The lumens of bronchi were determined as a function of time, and it was found that the response to provocation is strong and immediate in peripheral lung, which is served by small bronchi, while the large bronchi react much slower, but the effects prevail also longer. The changes in the bronchi and the dynamics of airway narrowing are shown in Fig. 2 and 3. The results suggest that narrowing is due to different mechanisms in proximal and distal parts of the airways. This is an important question for understanding asthma as a disease and the possibilities of treating it. The present results give some indications of the origins of the different reaction mechanisms, but further studies are needed. The results are being published (Bayat et al., 2006). In the last experiment (Nov 2005) the effects of PEEP in constricted lungs

were studied. The results have not been analyzed yet, but even the first images indicate that PEEP improves uniformity of ventilation.

In search for the mechanisms of the physiologic control of regional ventilation distribution, L-Name was administered in normal lung and prior to histamine inhalation. L-Name blocks the production of Nitric Oxide (NO), a mediator that is known to relax bronchial smooth muscle, involved in the regulation of bronchial caliber. The results have not been analyzed yet, but it seems that there are local variations in ventilation on the acinar level.

Ventilation and perfusion are optimally matched in healthy normal lung. Ventilation-perfusion mismatching leads to serious acute or chronic hypoxia, or lack of oxygen in arterial bood, in obstructive lung diseases. Only global or indirect evidence is available by the methods that have been used so far. The KES method can be used to study the ventilation distributions when the energies of the imaging x-ray beams bracket the xenon K-edge, and the distribution of the iodine contrast agent in blood when the energies are tuned to the iodine K-edge. Both successive and simultaneous imaging of the ventilation and blood volume distributions have been carried out for normal lung and under histamine challenge. The method needs further development, but it has potential of addressing the fundamental question of the regional lung ventilation/perfusion ratio.

3-4. Methods development

A series of experiments on small animals (rats and mice) was carried out using the high-resolution detector FReLoN. The 50 micrometer spatial resolution is sufficient for imaging the airways and other structures, and effects of histamine were observed. However, the read-out of the detector is still too slow for functional CT imaging (one image in 15 s), and the noise level is too high and blurs the images. In addition, there were some distortions and non-uniformity of the detector response, which hamper the reconstruction of the CT images. The performance of the high-resolution imaging system has been improved since the experiment, but it was concluded that it is not feasible to extend the KES method of functional imaging with the FReLoN detector. Nevertheless, study of genetically well-defined populations of small animals is an important field of research, and it is hoped that in the future high-resolution KES imaging becomes possible.

Stereo images were acquired of phantoms resembling the rabbit lung, and on one animal. The angle between the images was 5 degrees, and when properly colored and viewed through a pair of red/green glasses 3-dimensional images were seen. The actual reconstruction is being developed using existing imaging programs.

References:

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Figures:

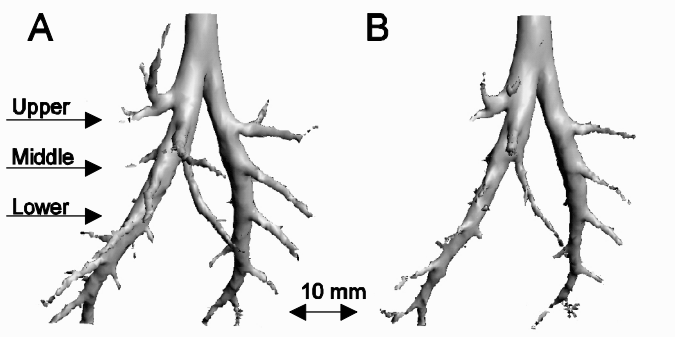

Figure 1: 3D reconstruction of the bronchial tree in one rabbit before (A) and 1 hour after (B) histamine provocation. 3D images were reconstructed from 80 CT slices, the vertical step was 0.7 mm and the total image height 56.0 mm. Images were thresholded based on the xenon density and surface-rendered. Marked airway narrowing is observed following histamine inhalation. Disappearance of some medium sized airways may be due to the 3D rendering technique as narrowed airway calibers approached the resolution limit of the technique Upper, Middle and Lower imaging cross-section levels are marked with arrows (Bayat et al. 2006).

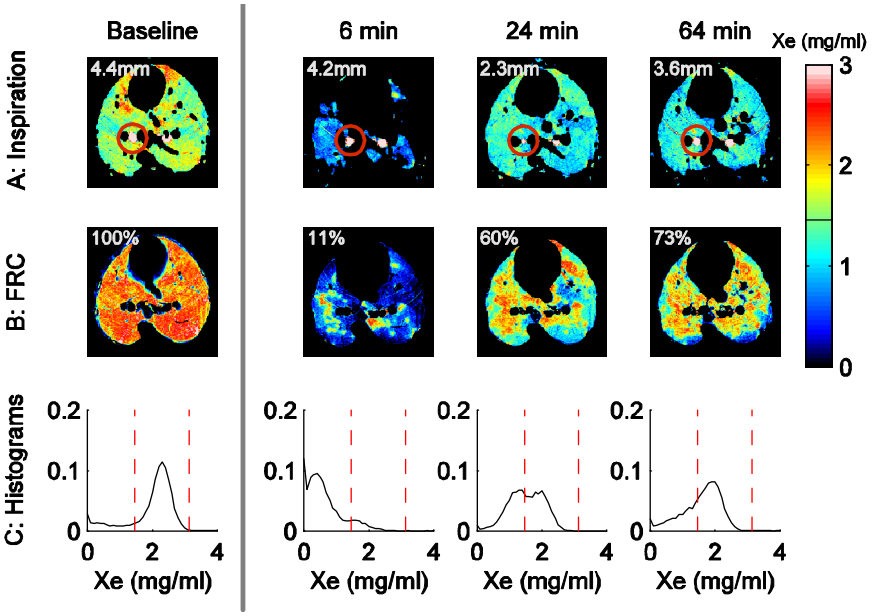

Figure 2. : Xenon distribution in the middle lung cross-section level at baseline and 6, 24 and 64 min after histamine inhalation in one rabbit. **A**: changes in proximal airway caliber. **B**: changes in the effectively ventilated alveolar area. The diameters of circled airway area in **A**, and the ventilated alveolar area in **B** are marked in the upper corner of each image. **C**: Histograms of xenon density based on the images presented in **B** show uniform distribution at baseline. Ventilated alveolar area was calculated based on the histograms. Dashed lines present the ± 2SD threshold limits. After histamine, the histograms became bimodal, later showing a gradual recovery (Bayat et al. 2006).

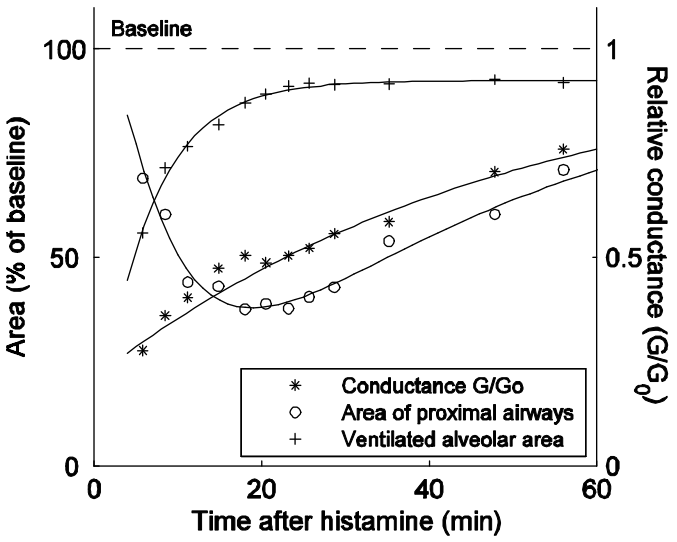

Figure 3. Relative changes in overall respiratory system conductance relative to baseline (G/G_0), luminal area of proximal airways at the lower cross-section level where the largest response to histamine was observed (% of baseline), and ventilated alveolar area after inhalation of histamine aerosol (% of baseline). Data are means from all six rabbits (Bayat et al. 2006).