ESRF	**Experiment title:** Quantitative imaging of small airways and lungs using stable xenon gas as contrast agent	**Experiment number**: LS-2102
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Shifts: 181	**Local contact(s)**: Dr. Géraldine LE DUC, MSc Sylvie MONFRAIX, Dr William THOMLINSON	*Received at ESRF:*

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Report:

The project was accepted as a Long Term Project for the period September 2001 – August 2003, and it was allocated 180 shifts of beamtime at ID17. Between Sept 2001 and May 2003, 7 experiments have been carried out. This report summarizes briefly the results of the project. A more detailed report covering the allocation period until March 1, 2003 was submitted when a 6 month prolongation (Sept 2003 – Feb 2004) was requested.

Aim of the project

The aim of the project was to develop a new quantitative imaging method for description of the structure and function of lungs. In the recent years, there have been many advances in this field, but the existing methods have some drawbacks and limitations. In particular, good spatial and temporal resolutions, which are prerequisites for imaging local function of small airways and lungs, are not combined in any of the methods. Moreover, none of the existing methods yields truly quantitative ventilation distributions. The long-term goal of the present project is to obtain new dimensions for a better understanding of the patho-physiology of certain common diseases of pulmonary airways and tissues, and study of the effects of medication.

1. New method for quantitative functional lung imaging

Background

The first phase of the project concentrated on development of an imaging method where the limitations of the existing clinical methods are overcome. Lung morphology can be studied in great detail by modern spiral acquisition CT, but in formation on ventilation remains limited. Methods of nuclear medicine (SPECT, PET) can be used for functional studies of low spatial and temporal resolution, and MRI with spin-polarized ^{3}He as the contrast agent and the source of signal measures semi-quantitatively local ventilation and associated parameters with modest spatial resolution. The initial goal of the present project was to develop a method with superb spatial resolution and with a temporal resolution adequate for functional studies.

New tools

The so-called K-edge subtraction (KES) method has found numerous applications in medical imaging with synchrotron radiation [1]. The method is based on recording two images simultaneously using energies that bracket the K-absorption edge of the contrast agent. When the high-energy image is subtracted from the low-energy image on a logarithmic scale the distribution of the contrast agent is observed, and the other structures become invisible. For lung imaging, the natural choice for the contrast agent is the stable Xe gas, which is inert and sufficiently heavy to provide strong absorption. The physiological effects of Xe are well known, because radioactive Xe is widely used in nuclear medicine. The spatial resolution achieved by the KES method is a fraction of mm, there are no motion artifacts in the images, and the concentration of the contrast agent is determined on an absolute scale. The method can be used in projection and CT imaging equally well. These advantages of the KES method make it unique among the medical imaging methods. An example of lung imaging with the method is shown in figure 1.

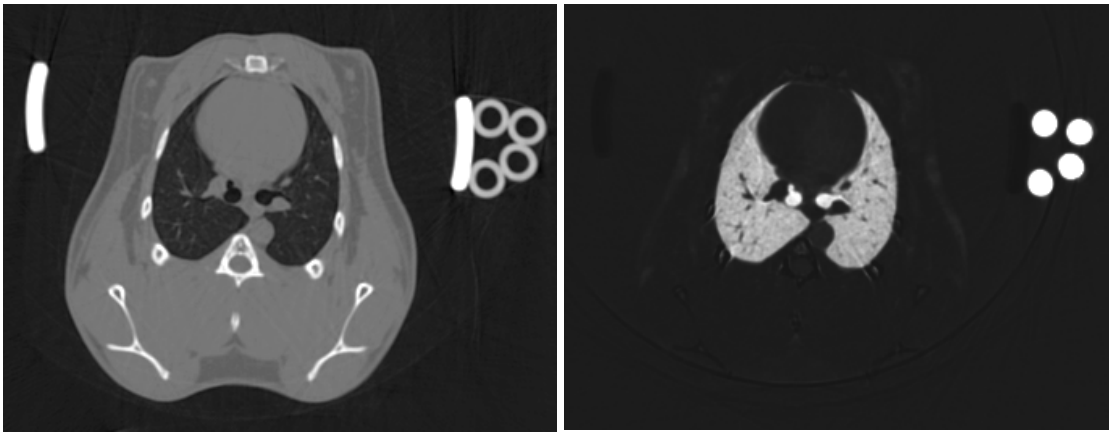

Fig. 1. *Left:* Absorption SR-CT image. Plastic parts of the animal holder and tubing carrying Xe and O_2 are visible laterally. *Right:* K-edge subtraction (KES) image. Only the Xe carrying structures, the bronchi, lung parenchyma, and tubing lumen are visible.

Pilot experiments, where the diffraction-enhanced imaging (DEI) method were applied in studies of rabbit lung, demonstrated very strong refraction and scattering contrast in the peripheral lung. The enhanced apparent absorption due to the large areas of small structures in lungs has been observed previously, but this effect has not been used for studies of lung functions. It is likely that the DEI method will provide direct quantitative information of the effective area of gas exchange in lungs.

2. Scientific goals and results of the project in 2001-2003

Aims

A previous study of the human bronchial tree with Xe as the contrast agent suggested that the KES technique could be used for an early diagnosis of lung cancer [2]. The aims of the present project were set differently. Rather than introducing another diagnostic method, which has limited availability, the objective is to describe the functions of normal and diseased lungs with spatial and temporal resolution using quantitative measures such as the local specific ventilation. The long-term goal is a detailed description of the effect of overt common diseases such as asthma and chronic obstructive pulmonary disease (COPD), and modeling their patho-physiology as well as the effects of inhaled medication (broncho-dilators, anti-inflammatory asthma drugs) on the lung functions in the gas exchanging compartment (silent zone).

Methods development

The original approach, as described in the proposal submitted in February 2001, was to develop 3-dimensional imaging of the bronchial tree by reconstruction from a small number of stereoscopic projection images. It was realized that a large number of line projections could be acquired in 2 seconds, so that complete 2-dimensional sections could be reconstructed. Accordingly, the emphasis was shifted to

development of methods for functional imaging, which was a more ambitious goal than the one foreseen in the beginning of the project.

The first phase of the project concentrated on development of the necessary methods and instrumentation for experiments where animals (rabbits) are used. This required adaptation of different techniques of anaesthesia, monitoring physiological functions, mechanical ventilation to the environment of a synchrotron radiation beamline. Large effort was needed in development of experimental protocols where mechanical motions, detector read-out and sequencing data acquisition were integrated. At the same time, the methods and protocols must comply with the ethical standards covering animal experiments. A schematic description of the experimental protocol, imaging sequence, and instrumentation is given in Fig. 2.

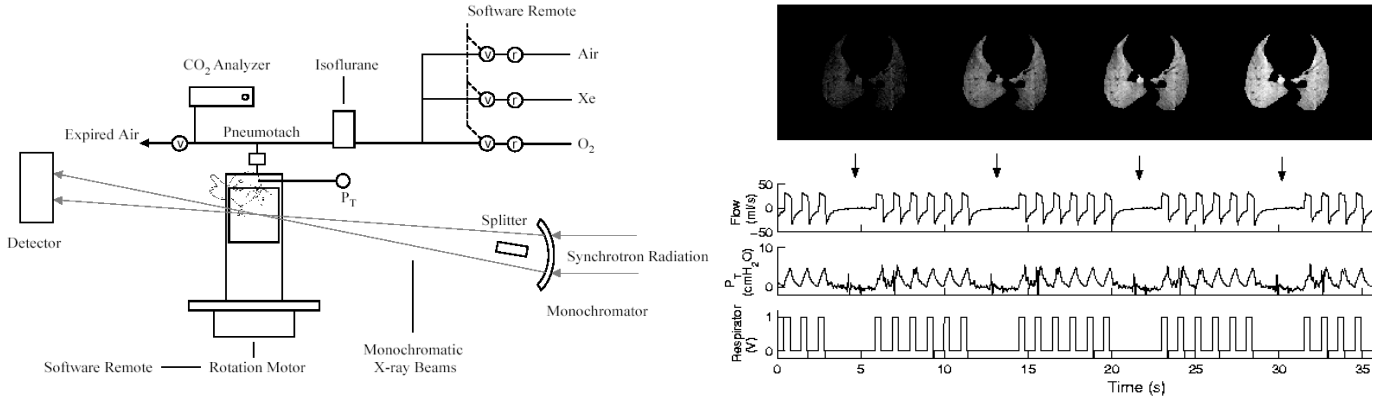

Fig. 2. *Left:* Experimental set-up for mechanical ventilation and CT imaging. A single solenoid valve (v) controls respiration, and three valves are used to switch from one inspired gas mixture to another. *Right:* The sequence of gas flow, tracheal pressure, and opening the respiration valve are shown together with a series of CT images in the wash-in phase.

Results of animal experiments

The time-dependent concentrations of the contrast agent were used for construction of high-resolution maps of specific ventilation (inverse of the local time constant of ventilation). The studies were limited to small animals (rabbits) only, because multi-slice CT imaging could be used. The results with references to publications are described in the following.

1. The method and first illustrations of the results of imaging of pulmonary gas containing compartments have been published [3]. The main results are the following: (a) the spatial resolution is better than 1 mm, which is sufficient for imaging small peripheral airways, (b) the absolute concentration of the contrast gas can be determined in a 2-dimensional section of the lung (cf. Figs. 1 and 2).

2. The effects of the tidal volume on local specific ventilation in normal lung have been studied [4]. The principal findings are the following: (a) at small tidal volumes specific ventilation is non-uniform, the dorsal and lower parts of the lungs of a rabbit in upright position are better ventilated, (b) when the tidal volume is increased within physiological limits ventilation becomes more uniform, and specific ventilation increases, (c) the ventilation distributions retain their shape in the relative scale, which indicates a uniform response of lung to mechanical ventilation (cf. *Physical modeling*). The results may be significant for planning intensive care of lung injury patients and for mechanical ventilation during anaesthesia.

3. 3-dimensional mapping of the contrast agent in the bronchial tree and peripheral lung was developed [5]. The entire lung volume of a rabbit could be imaged by two successive spiral scans during apnea, or by multi-slice scans: (a) by proper respiration and imaging sequences different parts of the airways and peripheral lung can be visualized, (b) lung volume and the recruited compartments can be determined, yielding for instance a detailed picture of the effects of an asthma attack simulated by inhaled histamine

(Fig. 3). The results indicate that the variations of regional ventilation in normal and diseased lungs and airways can be studied in detail and quantitatively.

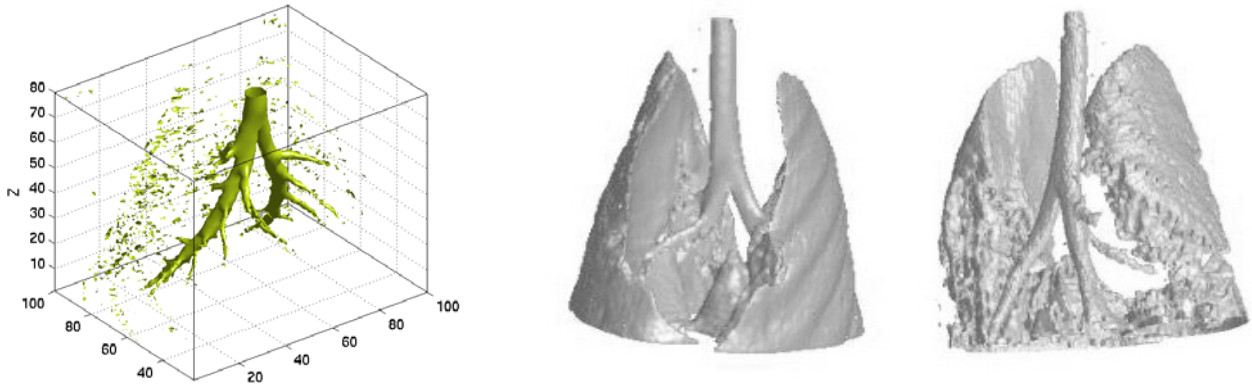

Fig. 3. *Left:* Bronchial tree imaged by the KES method using reconstruction from multi-slice CT. *Middle:* 3-dimensional image of Xe filled normal lung. *Right:* Same image of lung after a simulated asthma attack (histamine-induced bronchoconstriction).

4. An asthma-type broncho-constriction was induced by inhaled histamine aerosol [6,7]. 2-dimensional maps of specific ventilation were derived at apical (top), middle, and basal (bottom) levels of the lungs. Following effects of broncho-constriction were observed when the animals were constantly mechanically ventilated (metabolic normoventilation): (a) ventilatory gas exchange becomes very non-uniform, specific ventilation is very low in some regions, but is compensated by recruitment of other parts of the lung, so that the distribution of specific ventilation becomes bi-modal, (b) there are dynamical changes during broncho-constriction and even reversals of well and poorly ventilated areas, and these effects are presumably due to delayed effects in the lumens of the bronchi, which are different in large and small bronchi, (c) the acute effects of inhaled salbutamol on quantitative ventilatory variables are mixed, leading to more uniform distributions in most cases, but sometimes causing increased non-uniformity. This is the first time that the effects of asthma-like broncho-constriction have been described quantitatively with good spatial resolution. Some of the results are unexpected, and they are significant for understanding spontaneous recovery after an asthma attack, the effects of medication, and its optimal administration.

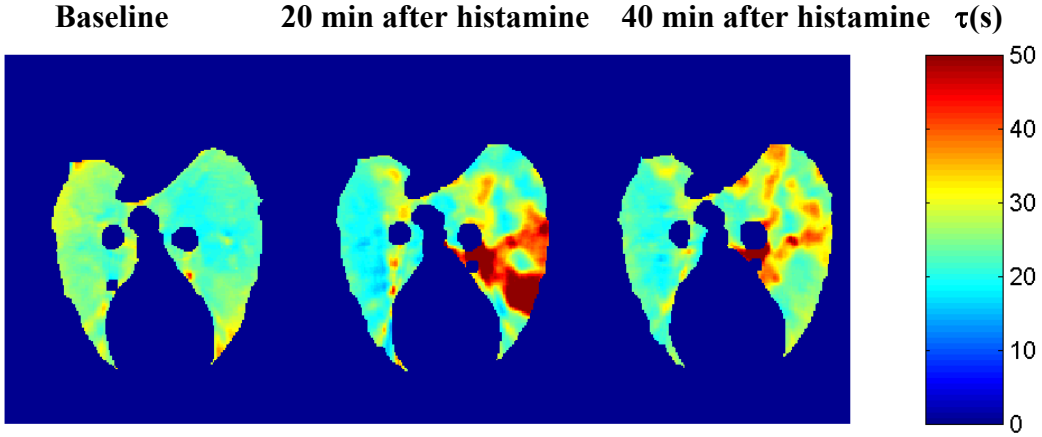

Fig. 4. Maps of time constant τ at different levels for normal lung (baseline) and for a lung where an asthma attack has been simulated by inhaled histamine aerosol.

Physical modeling

A close analysis of the ventilation distributions at different tidal volumes revealed that the distributions of the time constant τ follow the log-normal shape, i.e. the distributions are normal in the log (τ) scale. Furthermore, the width of the distribution for each lung level is almost independent of the tidal volume VT. This indicates that the response of the lung to an increase in VT is uniform, so that on the relative scale the ventilation distributions are unchanged during mechanical volume controlled ventilation. This seems to be characteristic to a normal lung, which is an important benchmark for studies of diseased lungs and the effects

of simulated asthma attacks. The airways form a fractal-like structure, and it can be simulated by engineering models based on finite element analysis which are used for design studies of gas and liquid flow. The model parameters may be derived from the reconstructed bronchial tree.

Development of human studies protocol

In the course of experiments it has become evident that a human studies protocol must be based technically on the coronary angiography protocol, which has been used at the ESRF successfully during the past 3 years. KES-imaging of human patients at the iodine K-edge can be adapted to imaging at the xenon K-edge, and the animal experiments show that sufficient contrast is achieved for imaging small airways (1-2 mm in diameter) within acceptable dose limits (skin entry dose less than 30 mGy per projection). The success with the rabbit model suggests that the intermediate step involving large animals (pigs, dogs) may not be necessary before human studies.

The protocol for human studies must be approved by an ethical committee, which evaluates the direct benefits to the patient and the indirect benefits obtained by a better understanding of diseases and the effects of medication. Therefore, the suggested protocol is adapted from the clinical protocols that are used in studies and diagnosis of diseases such as asthma and COPD. Acceptance of a human studies protocol is a long process, which has not been initiated yet. Human studies require much manpower and technical support from the ESRF and contribution of Grenoble University Hospital, and these resources must be ensured before presenting a protocol for bronchography of human patients.

Summary

The essential goals of the Long Term Project have been achieved. The project has been modified at some points, as new possibilities have surfaced, and some of the original ideas have been discarded. In general, the emphasis has shifted from imaging of the airways to functional studies of ventilation. This is achieved by development of CT imaging, which provides high-resolution maps of specific ventilation. The 3-dimensional distribution of the contrast gas in the steady state gives a detailed quantitative picture of active regions of the lung. These new techniques have been applied in studies of the normal lung, and in studies of the effects of drugs and medication. A rabbit model has been developed for these studies, and the results of the experiments show that this line should be pursued actively. A new field of biomedical imaging has been opened by development of a method which provides absolute ventilation distributions with good spatial and temporal resolution.

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