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ESRF

Experiment Report Form

The double page inside this form is to be filled in by all users or groups of users who have had access to beam time for measurements at the ESRF.

Once completed, the report should be submitted electronically to the User Office using the **Electronic Report Submission Application:**

http://193.49.43.2:8080/smis/servlet/UserUtils?start

Reports supporting requests for additional beam time

Reports can now be submitted independently of new proposals – it is necessary simply to indicate the number of the report(s) supporting a new proposal on the proposal form.

The Review Committees reserve the right to reject new proposals from groups who have not reported on the use of beam time allocated previously.

Reports on experiments relating to long term projects

Proposers awarded beam time for a long term project are required to submit an interim report at the end of each year, irrespective of the number of shifts of beam time they have used.

Published papers

All users must give proper credit to ESRF staff members and proper mention to ESRF facilities which were essential for the results described in any ensuing publication. Further, they are obliged to send to the Joint ESRF/ ILL library the complete reference and the abstract of all papers appearing in print, and resulting from the use of the ESRF.

Should you wish to make more general comments on the experiment, please note them on the User Evaluation Form, and send both the Report and the Evaluation Form to the User Office.

Deadlines for submission of Experimental Reports

- 1st March for experiments carried out up until June of the previous year;
- 1st September for experiments carried out up until January of the same year.

Instructions for preparing your Report

- fill in a separate form for each project or series of measurements.
- type your report, in English.
- include the reference number of the proposal to which the report refers.
- make sure that the text, tables and figures fit into the space available.
- if your work is published or is in press, you may prefer to paste in the abstract, and add full reference details. If the abstract is in a language other than English, please include an English translation.

ESRF	**Experiment title:** Functional imaging of the effects of inhaled drugs and air pollution particles on regional ventilation in healthy and asthmatic animals	**Experiment number**: MD429
Beamline: ID17	**Date of experiment**: from: I/2010 to: I/2010	**Date of report**: 31.1.2011
Shifts: 15	**Local contact(s)**: Christian Nemoz	*Received at ESRF:*

Names and affiliations of applicants (* indicates experimentalists):

Anssi Sovijärvi	Helsinki University Central Hospital, Finland
*** Sam Bayat**	University of Amiens, France
Skander Layachi	**-"-**
*** Liisa Porra**	University of Helsinki, Finland
Pyry Sipilä	
*** Satu Strengell**	**-"-**
*** Heikki Suhonen**	**-"-**
Pekka Suortti	**-"-**
Walid Habre	Geneva University Central Hospital, Switzerland
Tibor Janosi	**-"-**
*** Gergely Fodor**	
Zoltan Hantos	University of Szeged, Hungary
Ferenc Petak	**-"-**
*** Gergely Albu**	**-"-**

Report:

This report is the year 2010 report of Long Term Projects MD238 and its extension MD429. The proposal MD238 was accepted originally for the beamtime allocation periods 2006/II – 2008/I. Due to reconstruction of ID17, the use of beamtime was interrupted for one year. Extension MD429 for third year and 30 shifts was accepted in 2009.

Beamline	Shifts		Start Date	Finish Date	Local Contact
ID17	15	MD238/1	07 December 2006	12 December 2006	Dr. Christian NEMOZ
ID17	15	MD238/2	05 February 2007	12 February 2007	Dr. Christian NEMOZ
ID17	17	MD238/3	11 July 2007	16 July 2007	Dr. Christian NEMOZ
ID17	15	MD238/4	04 December 2008	09 December 2008	Dr. Christian NEMOZ
ID17	15	MD238/5	07 May 2009	12 May 2009	Dr. Christian NEMOZ
ID17	15	MD238/6	10 December 2009	15 December 2009	Dr. Christian NEMOZ
ID17	**15**	**MD429/1**	**6 May 2010**	**11 May 2010**	**Dr. Christian NEMOZ**

Background and aim of the project:

Traditional measurements of lung function such as spirometry can at best provide overall assessments and do not give any insight into the localization and heterogeneity of airway response. We have introduced a novel CT imaging technique that uses synchrotron radiation to quantitatively image inhaled stable xenon gas within the airways with a high spatial resolution (Bayat et al 2006). Using this method, regional lung volume, ventilation, and airway luminal diameters down to 2 mm can be measured. The spatial resolution of this technique is the best available for regional ventilation imaging in small animals, and the structure of the lungs can be studied simultaneously.

K-edge subtraction (KES) imaging and Forced Oscillation Technique (FOT) were combined in all MD238 experiments. KES provides high-resolution images of lung structure and ventilation distributions, and the frequency-dependent impedance of lung, as measured by FOT, provides physiological parameters of lung biomechanics. Simultaneous observations by KES and FOT yield a comprehensive picture of lung function.

Milestones in the LTP project plan

In the LTP proposal following schedule was planned:

Year	**Shifts**	**Planned experiments**
Year 1	30	Ventilation distributions in normal and sensitized animals without drug challenge
	15	Effects of histamine challenge in normal and sensitized animals (pilot experiments)
Year 2	30	Effects of different drug and air impurity doses on ventilation in normal and sensitized animals
	15	Controls of the previous studies with respect to the results of mathematical modeling of ventilation distributions
Year 3	30	Effects of medication on asthmatic animals
	15	Controls of the preceding experiments

Following the outline of the LTP for the first 2 years, the 3 first experiments concentrated on acute response of healthy and chronically ill animals to drugs and air impurities, and to method developments. In order to open up possibilities to use various experimental models of diseases, 4th and 5th experiment were used to develop high-resolution imaging setup. 6th experiment was devoted to understand the effect of Positive End Expiratory Pressure (PEEP), which is used to improve ventilation uniformity in asthmatic patients or in respiratory distress patients under mechanical ventilation. Last experiment (MD429/1) was used to aerosol distribution in the lungs. The studies and results are summarized below.

Methacholine challenge (Mch) is routinely used as non-specific challenge to diagnose bronchial hyper-reactivity, although its effect in the lungs and main airways as compared to a specific allergen challenge are not precisely known. Mch provocation was used instead of the histamine since it produces similar responses in the lung function and can be administered both as inhaled aerosol and intravenous solution. Mch provocation was studied in the first 2 experiments of the LTP project MD238/1 and 2. The aim of these studies was to use new asthma model using sensitized rabbits, and compare images obtained with synchrotron radiation with results on overall lung mechanics obtained with the forced oscillation technique (FOT) (Petak et al, 2006). This animal model was used to study first the effect of Mch in the lungs, and compare the results to the effects of allergen provocation. The results were compared to those of healthy animals (Bayat et al, 2009).

Tobacco smoke is an increasing health problem in the world, and more information about the acute effects of tobacco smoke in the lungs is needed. The effect of acute tobacco smoke was studied in the third experiment MD238/3, where the effects of previous smoke provocation on the subsequent Mch provocation were studied (Porra et al, 2010). Smoke induced some dilatation in large bronchi and attenuated the bronchoconstrictive effect of McH.

Studies of small animals are important lines of future research and opens up possibilities to use various experimental disease models in small animals. For example, development of whole-lung and 3D imaging,

and studies of transgenic mice are important for separation of expressions of hereditary and induced diseases. The methods of mechanical ventilation and physiological monitoring in KES+FOT experiments were developed for rabbits, and first trials of applying the methods in rats and mice have been carried out in the 4th and 5th experiment MD238/4 and /5. More detailed summary can be found in second report of MD238 (2008).

Positive end-expiratory pressure (PEEP) is used clinically to improve ventilation and gas exchange in mechanically ventilated patients with severe asthma or respiratory distress syndrome (ARDS). Previously, we have shown that PEEP improves the ventilation uniformity and opens collapsed lung zones (Porra et al. 2011). Broncho-alveolar lavage (BAL) removes surfactant from the alveoli and causes collapse. It is an experimental model of respiratory distress in premature neonates. This pathologic condition often requires mechanical ventilation after birth and knowing the effect of PEEP on ventilation is key issue when planning treatment. Effect of PEEP on lung function was studied before and after BAL in the 6th experiment of the project MD238. Publication is in preparation (Bayat et al. 2011). More detailed summary can be found in MD238 yearly report (2009)

Experiment MD429/1:

The distribution of aerosol in the lungs plays a great role both in provocation studies and in asthma drug delivery. We have shown previously that after aerosol provocation with histamine or methacholine , the distribution of ventilation becomes heterogenous. In this experiment we used KES imaging at iodine K-edge to image iodine containing aerosol distribution in the lungs, and compared the results with the distribution of ventilation imaged by xenon as contrast agent. Figure 1 shows the distribution of iodine in the lungs. Results will be fully analyzed and published later.

References:

Bayat S, Porra L, Suhonen H, Nemoz C, Suortti P, Sovijärvi AR. Differences in the time course of proximal and distal airway response to inhaled histamine studied by synchrotron radiation CT. *J Appl Physiol*. 2006 Jun;100(6):1964-73.

Peták F, Hantos Z, Adamicza A, Gálity H, Habre W. Development of bronchoconstriction after administration of muscle relaxants in rabbits with normal or hyperreactive airways. *Anesth Analg*. 2006 Jul;103(1):103-9.

Bayat S, Strengell S, Porra L, Janosi T, Petak F, Suhonen H, Suortti P, Hantos Z, Sovijärvi A, and Habre W. Metchacholine and ovalbumin challenges assessed by forced oscillations and synchrotron lung imaging. *Am J Respir Crit Care Med.* 2009 Aug 15;180(4):296-303.

Porra, L., Petak, F., Strengell, S., Neitola, K., Janosi, T. Z., Suhonen, H., Suortti, P., Sovijarvi, A. R. A., Habre, W. and Bayat, S. Acute cigarette smoke inhalation blunts lung responsiveness to methacholine and allergen in rabbit: differentiation of central and peripheral effects. *American Journal of Physiology: Lung Cellular and Molecular Physiology.* 2010; 299: 242-251.

Porra L. Suhonen H, Suortti P, Sovijärvi ARA, Bayat S. Effect of PEEP on regional ventilation distribution following airway constriction in rabbit studied by synchrotron radiation imaging. Submitted to *Critical Care Medicine*, 2011.

Bayat S, Porra L. Albu G, Suhonen H, Strengell S, Suortti P, Sovijärvi A, Petak F and Habre W. The value of combined analysis of lung volume, respiratory mechanics and synchrotron radiation images to distinguish overdistension and recruitment following PEEP elevation in a model of acute lung injury. In preparation 2011.

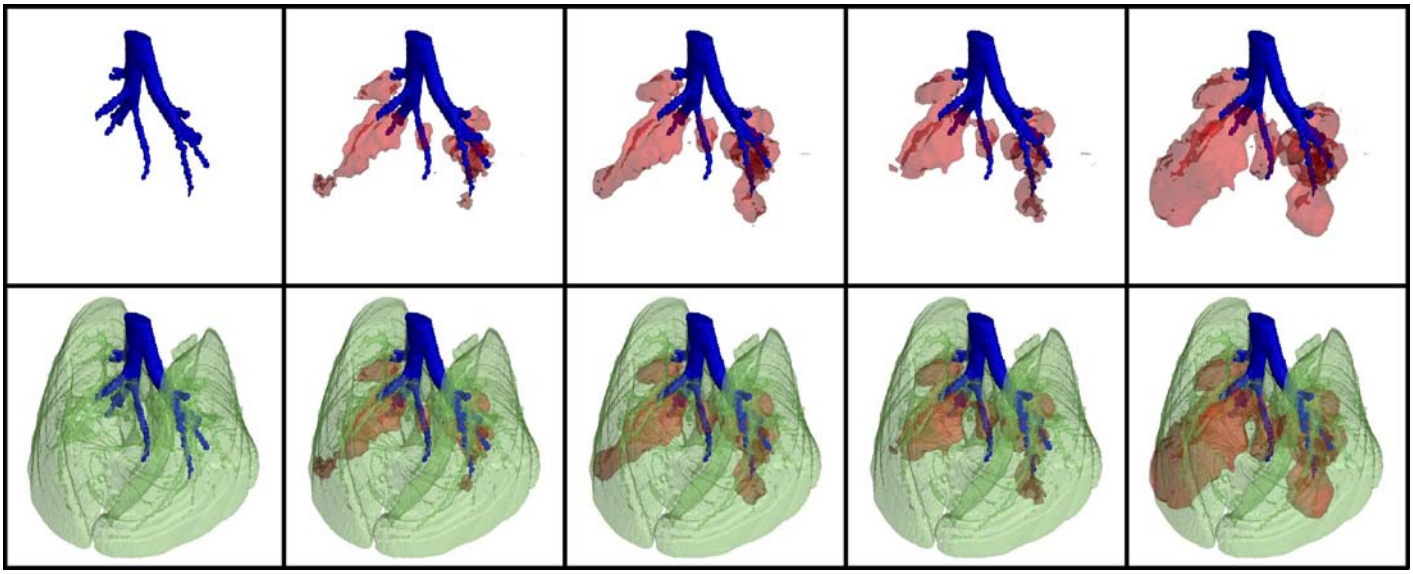

Figure 1: Time series of iodine aerosol distribution in rabbit lungs. Blue: Airways. Red: Iodine aerosol. Green: Lung tissue.

Publications 2010:

1. Porra, L., Petak, F., Strengell, S., Neitola, K., Janosi, T. Z., Suhonen, H., Suortti, P., Sovijarvi, A. R. A., Habre, W. and Bayat, S. Acute cigarette smoke inhalation blunts lung responsiveness to methacholine and allergen in rabbit: differentiation of central and peripheral effects. American Journal of Physiology: Lung Cellular and Molecular Physiology. **2010**; 299: 242-251.

Conference presentations 2010:

1. Anssi Sovijärvi. Biomedical beamline in ESRF- Quantitative airway and pulmonary function imaging with high spatial resolution. **Workshop on Nordic Biomedical Beamline at MAX-IV.** 15.11.2010, Lund, Sweden. Presentation
2. S. Strengell, L. Porra, P. Suortti, ARA. Sovijarvi. Effect of positive end expiration pressure on ventilation heterogeneity after bronchoalveolar lavage. **Finnish Respiratory Society Progress Report 2010**, 12.11.2010, Helsinki, Finland. Presentation.
3. ARA Sovijärvi. New method for lung function studies – subtraction imaging with Synchrotron radiation. **Workshop of the Finnish Clinical Physiology Society**. 4.11. 2010, Tampere, Finland. Presentation.
4. S. Bayat, L. Porra, G. Albu, H. Suhonen, S. Strengell, P. Suortti, A. Sovijärvi, W. Habre. Moderate PEEP improves ventilation heterogeneity with minimal overdistension in lavage-induced surfactant depletion in rabbits: a synchrotron imaging study. **European Respiratory Society annual congress 2010**, 18-22.9.2010, Barcelona, Spain. Poster.
5. G. Albu, L. Porra, F. Petak, H. Suhonen, S. Strengell, A. Sovijärvi, P. Suortti, S. Bayat, W. Habre. Changes in lung volume with PEEP following surfactant depletion in rabbits assessed by helium wash-out technique and synchrotron imaging. **European Respiratory Society annual congress 2010**, 18-22.9.2010, Barcelona, Spain. Poster.
6. Dept. of clinical physiology and nuclear medicine, Helsinki University Hospital. Regional lung function in experimental asthma studied by synchrotron radiation imaging (SRI) and forced oscillation technique (FOT). **Scientific Symposium,** 24.8.2010, Helsinki, Finland. Several presentations.
7. S. Bayat, L. Porra, G. Albu, S. Layachi, F. Petàk, P. Suortti, Z. Hantos3, A.R.A. Sovijärvi, W. Habre. Airway Response to Inhaled Allergen Assessed by High-Resolution Synchrotron Imaging and Forced Oscillation Technique in Sensitized Brown Norway Rat. **American Thoracic Society international conference 2010**, 14-19.5.2010, New Orleans, USA. Poster
8. L. Porra, S. Layachi, A.R.A. Sovijärvi, P. Suortti, S. Bayat. High-resolution in-vivo synchrotron imaging of lung structure and regional ventilation in rat using the K-edge subtraction technique. **American Thoracic Society international conference 2010**, 14-19.5.2010, New Orleans, USA. Presentation (#2896).
9. L. Porra, S. Bayat, S. Strengell, S. Layachi, ARA. Sovijärvi, P. Suortti. High-resolution *in-vivo* imaging of lung structure and function using K-edge subtraction technique. **Medical Applications of Synchrotron Radiation 2010**, 15-18.2.2010, Melbourne, Australia. Presentation (abstract #124).