EUROPEAN SYNCHROTRON RADIATION FACILITY

INSTALLATION EUROPEENNE DE RAYONNEMENT SYNCHROTRON

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 via the User Portal:

https://wwws.esrf.fr/misapps/SMISWebClient/protected/welcome.do

Reports supporting requests for additional beam time

Reports can 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 effects of a rapidly acting beta-2-agonist on proximal and distal airways in rabbits with asthmatic bronchoconstriction.	**Experiment number**: MD580
Beamline: ID17	**Date of experiment**: from: 29 April 2011 to: 04 May 2011	**Date of report**: 29.2.2012
Shifts: 15	**Local contact(s)**: Christian Nemoz	*Received at ESRF:*

Names and affiliations of applicants (* indicates experimentalists):

Prof. Anssi Sovijärvi	Helsinki University Central Hospital, Finland
* Dr. Sam Bayat	University of Amiens, France
* MSc. Mathieu Guilbart	-,,-
Dr. Walid Habre	Geneva Children's Hospital, Switzerland
* MSc. Eniko Lele	-,,-
Prof. Pekka Suortti	University of Helsinki, Finland
* Dr. Liisa Porra	-,,-
* MSc. Satu Strengell	-,,-
Prof. Zoltan Hantos	University of Szeged, Hungary
Dr. Ferenc Petak	-,,-
* MSc. Dorottya Czovek	-,,-

Report:

The experiment was the continuation of the Long Term Project (LTP) for the period February 2006 to February 2011. The background of the project are described in detail in an earlier report (experiment series number MD238 and MD429).

Background and aim of the study

Airway narrowing is the hallmark of obstructive lung diseases such as asthma and COPD (Chronic Obstructive Pulmonary Disease), leading to regional abnormalities in lung ventilation. Histamine, an inflammatory mediator involved in the pathologic mechanism of airway narrowing, and methacholine, a cholinergic agonist with similar effects, are routinely administered as an aerosol in patients as a diagnostic test for asthma. Traditional measurements of lung function such as spirometry can at best provide overall assessments and do not give any insight into the heterogeneity of airway narrowing, nor to the determinants of this heterogeneity.

We recently 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 (1). Using this method, regional lung volume (2), ventilation (3), and airway luminal diameters down to 1 mm can be measured. The same method can be used to image local blood volumes in the lungs successively using iodine infusion as contrast agent (4). The spatial resolution of this technique is the best available for regional ventilation imaging, allowing quantitative measurements of regional lung function in small animal models. Imaging results can be compared with overall lung function measurements obtained with Forced Oscillation Technique (FOT).

We have found that histamine aerosol bronchial provocation induces patchy abnormalities of regional lung ventilation (5), the severity of this phenomenon being itself unequal depending on the anatomic location within the lungs, but highly reproducible. The local heterogeneity in lung ventilation and perfusion is of major importance in the pathophysiology of asthma since it induces hypoxia through the mismatch of ventilation and perfusion, and since it is a significant challenge to get drugs administered as an aerosol to the most constricted lung zones. Currently, it is not known how salbutamol, one of the most frequently used medication in asthma relaxing directly the airway smooth muscle – differentially acts on the proximal vs. smaller-caliber distal airways and particularly in the context of severely heterogeneous lung ventilation.

The goal of the present experiment was to find out how salbutamol can differentially relax the airways and its impact on regional lung ventilation in heterogeneously vs. uniformly constricted airways. The results of this experiment may help to explain why salbutamol causes a worsening in gas exchange (hypoxaemia) in some patients with acute asthma exacerbations (6).

Experiments

We have used KES imaging technique for imaging regional ventilation ($\dot{V}$) and blood volume (V_B) successively after Mch aerosol inhalation and after salbutamol aerosol treatment. Experiments were performed in anaesthetized and mechanically ventilated healthy New Zealand rabbits (n=5). Regional ($\dot{V}$) and V_B were imaged before and after Mch aerosol inhalation. Regional heterogeneity was estimated as the coefficient of variation (CV) of all parameters. Lung mechanics were studied with FOT measurements.

Results

Images of $\dot{V}$ and V_B and their ratio ($\dot{V}/V_B$) are shown at baseline and after Mch and salbutamol in one rabbit (Figure). Changes in measured parameters are shown in the table. Values are means ±SD, (*) shows significant change (P<0.05, paired student's T-test) compared to the baseline, and (#) shows significant difference between Mch and salbutamol.

	$\dot{V}$	V_B	CV of $\dot{V}$	CV of V_B	CV of $\dot{V}/V_B$
Methacholine	* 75.7±24.2%	*# 69.4±12.7%	* 334.2±185.9%	* 140.4±21.4%	*# 180.1±49.9%
Salbutamol	* 65.2±20.2%	# 88.7±20.5%	* 407.3±202.8%	* 138.9±26.3%	*# 227.6±65.8%

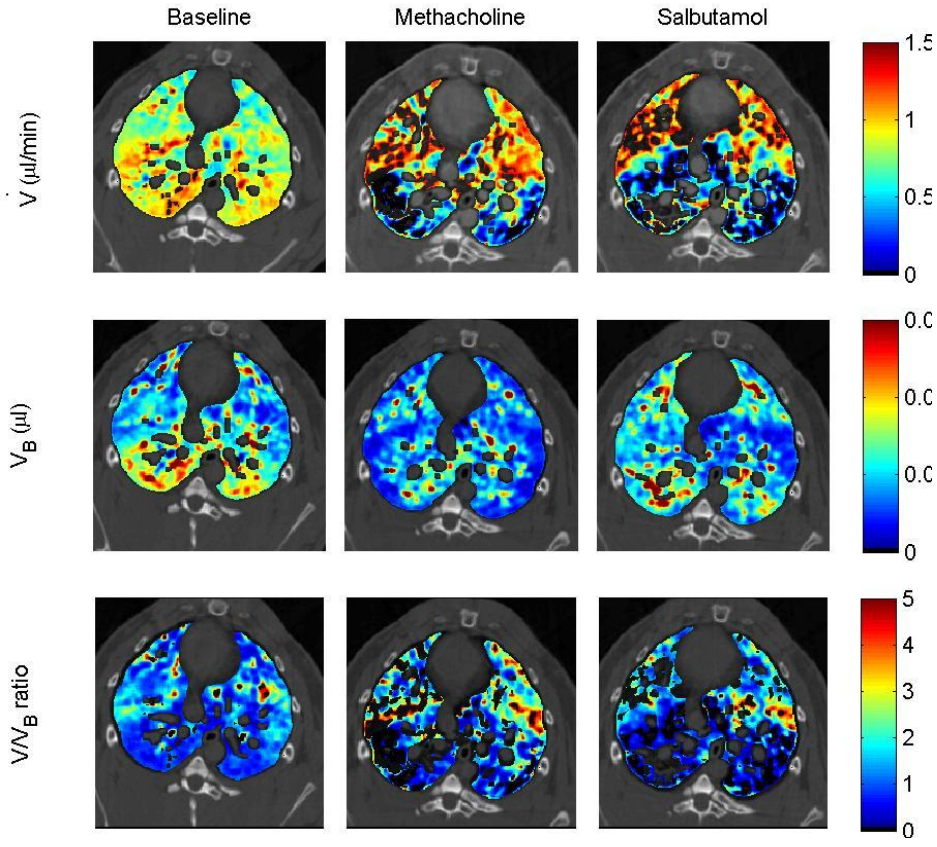

Figure 1. Images of ($\dot{V}$) and V_B in one representative rabbit. Mch increases markedly heterogeneity in $\dot{V}$ and V_B. Salbutamol does not improve the heterogeneity of $\dot{V}$ but causes an increase in mean V_B and increases further the mismatch between $\dot{V}$ and V_B.

Conclusions

Inhalation of Mch aerosol induced significant heterogeneity of ventilation and blood volume. Salbutamol aerosol worsened the heterogeneity of ventilation, but the distribution of pulmonary blood volume became more uniform, thus worsening the ventilation/perfusion mismatch. This phenomenon can explain hypoxaemia after acute salbutamol inhalation in asthma. This study will be fully analyzed and published later (7).

Conference abstracts

1. **M. Guilbart, L. Porra, S. Strengell, A. Sovijärvi, P. Suortti, S. Bayat.** Quasi-simultaneous *in-vivo* synchrotron imaging of regional ventilation and blood volume distributions after methacholine provocation in rabbit. *Physiologie Pharmacologie et Thérapeutique*. 4-6.4.2012, Dijon, France. Abstract 18-P110.
2. **L. Porra, S. Bayat, S. Strengell, P. Suortti, A. Sovijärvi.** *In-vivo* synchrotron imaging of regional ventilation and blood volume after methacholine provocation in rabbit. *American Thoracic Society International Conference* 2012. 18-23.5.2012, San Francisco, USA. Abstract 27677, oral presentation.
3. **L. Porra, M. Guilbart, S. Strengell, P. Suortti, A. Sovijärvi, S. Bayat.** Synchrotron imaging of regional ventilation and blood volume after methacholine provocation in rabbit. *European Respiratory Society annual Congress* 2012. 1-5.9.2012, Vienna, Austria. Abstract 851746.

References

1. **Bayat S, Le Duc G, Fiedler S, Berruyer G, Nemoz C, Thomlinson W, Porra L, Suortti P, Grimbert F, Standertskjöld-Nordenstam CG, Sovijärvi ARA.** Quantitative functional lung imaging by synchrotron radiation using stable xenon gas as contrast agent. *Phys Med Biol*. 2001 ; 46 :3287–3299.
2. **Monfraix S, Bayat S, Porra L, Berruyer G, Nemoz C, Thomlinson W, Suortti P, Standertskjöld-Nordenstam CG, Sovijärvi ARA.** Measurement of Absolute Regional Lung Volume Using Spiral Synchrotron Radiation Computed Tomography. *Phys Med Biol.* 2005; 50 :1 - 11.
3. **Porra L, Monfraix S, Berruyer G, Nemoz C, Thomlinson W, Suortti P, Sovijärvi ARA, Bayat S.** Effect of tidal volume on ventilation distribution in rabbits; High resolution quantitative assessment with synchrotron radiation computed tomography. *J Appl Physiol.* 2004; 96: 1899–1908.
4. **Suhonen H, Porra L, Bayat S, Sovijärvi ARA and Suortti P.** Simultaneous in vivo synchrotron radiation computed tomography of regional ventilation and blood volume in rabbit lung using combined k-edge and temporal subtraction. *Phys Med Biol* 2008 53: 775-791.
5. **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.
6. **Connett G, Lenney W**. Prolonged hypoxaemia after nebulised salbutamol. *Thorax* 1993;48:574-5.
7. **Porra L et al.** *In-vivo* synchrotron imaging of regional ventilation and blood volume after methacholine and salbutamol provocation in rabbit. Manuscript in preparation.