**RCoA Research, Education & Travel Grants 2014**

Award: The Ernest Leach Fund

Applicant: Dr Simon Lambden

Project Title: The effect of acute hypoxia on the endogenous regulation of Nitric Oxide production and the pulmonary circulation in healthy human subjects

**Project Description:**

Importance: Hypoxia is a common feature of critical illness. This is associated with an increase in the pulmonary vascular resistance which in turn leads to dysfunction of the right heart and contributes to organ failure and dealth in critical illness. Treatment strategies for hypoxaemia are limited and not without severe adverse consequences. It is essential to explore potential mechanisms for the organ dysfunction associated with hypoxia.

Background: Nitric Oxide(NO) regulates vascular tone in both the systemic and pulmonary circulations. Nitric oxide production by Nitric Oxide Synthase(NOS) is endogenously regulated primarily by Asymmetric Dimethyl Arginine(ADMA). ADMA is metabolised by dimethylarginine dimethylaminohydrolase (DDAH).

We have shown that when exposed to a hypoxic environment, mice display an increase in pulmonary vascular resistance. This is directly related to an increase in ADMA level mediated by a decrease in DDAH in the pulmonary vasculature. This reduction is caused by an increase in levels of the micro RNA MiR-21, this occurs within hours of hypoxia onset. Inhibition of MiR-21 has been shown to inhibit DDAH mediated pulmonary hypertension in animal models.

Aims: We propose to study for the first time the effects of acute hypoxia in humans in both resting and post exertion conditions on Nitric Oxide regulated pulmonary vascular responses. Using non-invasive assessment of NO production and right heart function in conjunction with bloods samples we propose to determine whether the findings observed in our animal model are reproduced in healthy human volunteers. This would further our understanding of the role NO regulation plays in the pathogenesis of hypoxia induced organ dysfunction in humans and guide progression to further studies in critically ill patients.

Methodology: 15 healthy volunteer subjects will be recruited.

Nomoxia (21% oxygen) vs. Hypoxia(12% oxygen)

Each participant will undergo investigations whist breathing 21% Oxygen, and then have the same investigations repeated following ten hours exposure to 12% Oxygen. Exposure will be in a purpose built hypoxic chamber designed for training elite athletes.

Investigations:

1) Exercise testing: a simple stepping exercise will be performed to stimulate the physiological exercise response and non invasive tests repeated before and after exertion

2) Blood sampling

3) Lung function and exhaled nitric oxide concentration

4) Trans-thoracic echocardiographic assessment of right heart function and pulmonary arterial pressure.

Timescale: The study will take place over the course of 4 consecutive months at the Institute for Sports, Exercise and Health at UCL

Ethics: This project has been approved by the UCL ethics review board (ref: 2416/001).

Justification of funding:The two main costs of this project are compensation of healthy volunteers for time spent in the hypoxic chamber and disposable equipment costs. Volunteers will spend 10 hours in the hypoxic chamber – a considerable investment of time and limitation of activity. Recruitment will be challenging without the ability to compensate participants for their time. Availability of suitable disposables for the conduct of sample collection is essential for robust data collection.

Co-investigators:

Dr James Leiper. Chair, Nitric Oxide signalling group,MRC

Prof M Mythen, Smiths Medical Professor of intensive care,UCL

Dr Dan Martin, Senior Lecturer, UCL and Consultant in Intensive care,Royal Free Hospital