**University of Leicester**

**Cardiovascular Sciences PhD**

* This project is open to overseas applicants who can fund their own study or have their own PhD sponsor. There is no University of Leicester funding available.
* Fees for this project will be £32,100 per year of study
* Eligibility: International applicants only

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**Section 2 – *Project Information***

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| **Project Title** | Impairment of cerebral blood flow regulatory mechanisms in stroke: the influence of stroke sub-type, severity and location |
| **Project Summary** | |
| The Cerebral Haemodynamics in Ageing and Stroke Medicine (CHiASM) Research Group of the Department of Cardiovascular Sciences has an international reputation for leading research on cerebral haemodynamic alterations resulting from ischaemic and/or haemorrhagic stroke. The group’s reputation has been the result of a focused MD/PhD programme in the last 25 years, as well as several intercalated BSc and MSc projects.  The PhD project will investigate the impairment of cerebral blood flow (CBF) regulatory mechanisms in patients with stroke. In particular, the new student will be carrying out a more detailed analysis of the longitudinal evolution of cerebral haemodynamic impairment in patients with haemorrhagic stroke. One key finding from our group (Salinet et al *Cerebrovasc Dis Extra* 2014;4:186-197), that was subsequently confirmed by other international centres, was that the impairment in CBF regulation following ischaemic stroke has a characteristic time-course that needs to be taken into account in the care plan of these patients. We have reported alterations in the cerebral haemodynamics of patients with haemorrhagic stroke, but detailed description of its temporal evolution remains to be investigated and this key feature of the response of the brain circulation to the haemorrhagic insult should be a priority target in future investigations. The main reason why we have not been able to address this topic in the past, has been the lack of adequate human and technical resources. However, with the recent expansion of our team (to include Clinical Research Vascular Scientist) and duplication of data collection equipment, suitably designed as a ward-friendly mobile unit, we are ready to face this challenge and are likely to be the first international group to report on this highly relevant facet of haemorrhagic stroke.  **Hypothesis:**  Specific hypotheses would apply to the sub-studies of the project, but the overarching hypothesis is that the impairment of CBF regulatory mechanisms following haemorrhagic stroke has a temporal course that is different from what has been reported in ischaemic stroke, and it is dependent on the location and volume of the haematoma.  **Research Plan:**  The research plan for this project follows similar strategy adopted for previous PhD students to provide suitable training in research methods and to acquire in-depth knowledge of the topic to enable independent problem-solving and original, internationally leading results at the later stages of their research. In summary, the resulting dissertation should involve the following chapters:   1. Introduction – problem identification, state-of-the art knowledge and research proposal. 2. Systematic Review of the literature on the longitudinal changes in cerebral haemodynamics in haemorrhagic stroke (peer-reviewed publication expected). To be registered in PROSPERO. 3. Multivariate modelling study of the CBF regulation response to changes in arterial blood pressure and PaCO2. This will test the hypothesis that a combined hypercapnic-hypocapnic manoeuvre can allow simultaneous extraction of metrics defining both the dynamic cerebral autoregulation and CO2 reactivity in healthy subjects. This sub-study will not require a new ethics committee approval since it will be based on data recently added to the historial CHiASM database of physiological recordings. This sub-study should lead to one or more peer-reviewed publications. 4. Development of suitable respiratory manoeuvres for identification of CO2 reactivity in haemorrhagic stroke patients. In his project, Abdulaziz Alshehri (current PhD student) has demonstrated that a combined hypercapnic-hypocapnic manoeuvre could be an optimal approach for identification of CO2 reactivity, combined with dynamic cerebral autoregulation in healthy subjects. However, the use of 5% CO2, followed by hyperventilation, are not suitable for use in critically ill patients and for this reason alternatives need to be found. In the first sub-study, also to be performed in healthy subjects, alternative manouevres, such as the use of different breathing frequencies and expiratory resistances, will be tested and compared to the original hypercapnic-hypocapnic manoeuvre, that will be used as reference. The sub-study will require Ethics Committee approval that will be sought through the University of Leicester new Infonetica system. This sub-study should lead to at least one peer-reviewed publication. 5. Intra-subject variability of CBF regulatory parameters identified from breathing manoeuvres. In this sub-study, the manoeuvre identified as best to replace the reference hypercapnic-hypocapnic manoeuvre, will be adopted in a longitudinal study in 12 healthy subjects, to identify the reliability of four repeated measurements, with a similar design of the study performed by Brodie et al (*Clin Sci* 2009;116:513-520) but using multivariate modelling, instead of only the metric for dynamic cerebral autoregulation. In addition to the manoeuvre, measurements will also be performed at rest to allow similar modelling based on spontaneous fluctuations in end-tidal CO2, regarded as a sub-optimal approach to extract the relevant parameters. This sub-study will require Ethical Committee approval through the University of Leicester and will provide key information to interpret the findings of the main study (Chapter 7). This sub-study should lead to at least one peer-reviewed publication. 6. Validation of suitable respiratory manoeuvres for identification of CO2 reactivity in haemorrhagic stroke (ICH) patients. In the second sub-study, the manoeuvre that best approximates the results of the reference hypercapnic-hypocapnic manouevre, identified in Chapter 4, will be adapted to be reproduced as a brief modification of ventilator parameters. This will be validated in a sub-group of 12 ICH patients, taking into consideration its safety, feasibility, acceptance, and reliability of estimated parameters. The sub-study will require Ethical Committee approval that will be sought with an IRAS application. This sub-study should lead to at least one peer-reviewed publication. 7. Identification of the longitudinal evolution of CBF regulatory mechanisms in ICH. This main study of the project will follow up patients with ICH with four repeated measurements during the three month period after hospital admission. The study will recruit a minimum of 36 patients, formed of three sub-groups of 12 patients each with distinct combinations of haematoma location and volume. The sub-study will require Ethical Committee approval that will be sought with an IRAS application. In the eventuality of lack of acceptability of the new respiratory manoeuvre, as tested in the previous sub-study (Chapter 6), estimates of CO2 reactivity will be based on spontaneous fluctuations of end-tidal CO2 as demonstated previously (Panerai et al *Am J Physiol Heart Circ Physiol* 2012;302:H459-H466). In either case, the corresponding information about the intra-subject variability of derived CBF regulatory metrics will be provided by the sub-study in Chapter 5. This sub-study should lead to at least two peer-reviewed publications. 8. Conclusions – Project main findings, interpretation, limitations and proposals for future work. | |
| **References** | |
| Simpson DM, Payne SJ, Panerai RB. The INfoMATAS project: Methods for assessing cerebral autoregulation in stroke. *J Cereb Blood Flow Metab*. 2022;42(3):411-429.  Minhas JS, Panerai RB, Swienton D, Robinson TG 2019 Feasibility of improving cerebral autoregulation in acute intracerebral hemorrhage (BREATH-ICH) study: Results from an experimental interventional study. *Int J Stroke* 15:627-637.  Intharakham K, Beishon L, Panerai RB, Haunton VJ, Robinson TG 2019 Assessment of cerebral autoregulation in stroke: A systematic review and meta-analysis of studies at rest. *J Cereb Blood Flow Metab* 39(11):2105-2116.  Minhas JS, Kennedy C, Robinson TG,Panerai RB2019 Different strategies to initiate and maintain hyperventilation: their effect on continuous estimates of dynamic cerebral autoregulation. *Physiol Meas*. 2019; 23;40(1):015003.  Minhas JS, Panerai RB, Robinson TG 2018 Modelling the cerebral haemodynamic response in the physiological range of PaCO2. *Physiological Measurement* 39:(11pp):065001.  Minhas JS, Panerai RB, Robinson TG 2018 Feasibility of improving cerebral autoregulation in acute intracerebral haemorrhage (BREATHE-ICH) study: a protocol for an experimental interventional study. *BMJ Open* 2018;8:e020758 doi:10.1136/bmjopen-2017-020758.  Salinet ASM, Panerai RB, Robinson TG. 2014 The Longitudinal Evolution of Cerebral Blood Flow Regulation after Acute Ischaemic Stroke. *Cerebrovasc Dis Extra* 4:186-197.  Panerai RB, Salinet AS, Robinson TG 2012 Contribution of arterial blood pressure and PaCO2 to the cerebrovascular responses to motor stimulation. *Am J Physiol Heart Circ Physiol* 302:H459-H466. Brodie FG, Atkins ER, Robinson TG, Panerai RB 2009 Reliability of dynamic cerebral autoregulation measurement using spontaneous fluctuations in blood pressure. *Clinical Science* 116:513-520*.* | |