RCoA Research, Education & Travel Grants 2018

Award: Ernest Leach Fund

Applicant: Dr Thomas H Craven

Project Title: *In vitro effects of Lidocaine on neutrophils from patients with sepsis*

Project Description:

Hypothesis: Lidocaine reduces activation of neutrophils in septic patients.

Aims:

- Does Lidocaine ameliorate the activation phenotype?
- Are neutrophils from patients with sepsis capable of further activation?
  - Does Lidocaine prevent further neutrophil activation?
- Does lidocaine reduce soluble inflammatory markers?

Sepsis is defined as "a life-threatening organ dysfunction caused by a dysregulated host response to infection." It is common and serious. The underlying biological mechanisms are complex, but the neutrophil plays a key role as the main host cell of acute inflammation. Neutrophils normally circulate harmlessly poised to react to a noxious stimulus. Upon activation, a wide range of phenotypic changes takes place and the formerly quiescent cell becomes destructive and harmful. This change destroys invading pathogens but brings about host tissue damage, thought to contribute to the adverse clinical sequelae.

Lidocaine, a widely used amide local anaesthetic, is given increasingly commonly by infusion for perioperative pain. Its pain relief action is primarily achieved through sodium channel blockade. However, it has been shown to have anti-inflammatory properties, including those affecting neutrophil function: reducing their adherence to surfaces, reducing superoxide species production [11] and re-balancing pro- and anti-inflammatory mediators, among others. However, current research fails to demonstrate the effects of lidocaine on neutrophil activation. Recognising the potential therapeutic opportunity of reassigning an already trialled drug, this project will explore the effects of lidocaine on neutrophil activity in sepsis.

Methods:

Patients with sepsis requiring admission to critical care will be recruited to provide a single whole blood sample. Provisional ethical approval has been obtained (REC: 18/NW/0556, final approval pending). Age and gender matched controls will be recruited through a separate protocol (AMREC 15-HV-013). Blood samples will be incubated with lidocaine +- further activation stimuli (Cytochalasin B/fMLP). Flow cytometry will be used to assess the functional responses, like calcium mobilisation, quantification of surface adhesion molecules, apoptosis and superoxide anion

generation, activation of NADPH oxidase enzyme system. We will also measure circulating inflammatory markers, namely TNF-alfa, IL-6 and IL-8, in plasma that act as potent priming agents of neutrophil activity. The project is schedules to run from 01 January 2019 for 4 months.