RCoA Research, Education & Travel Grants 2016

Award: The Ernest Leach Research Fund

Applicant: Dr Matthew Charlton

Project Title: *Establishing normal ranges of microcirculatory function as determined by CytoCam-IDF imaging*

Project Description:

Microcirculatory dysfunction plays a significant role in the pathophysiology of severe sepsis and septic shock.[1] Studies of microcirculatory dysfunction in patients with sepsis have shown better outcomes when microcirculatory function improves in response to early resuscitation, and worse outcomes when it does not.[2–4]

Despite recognition of its importance in sepsis, the microcirculation is not monitored routinely, partly because it is difficult to measure in clinical practice. Video microscopic techniques provide *in-vivo* visualisation of the microcirculation, allowing direct measurement of capillary density, perfusion and flow dynamics. Until recently these techniques have been challenging, because the available devices are bulky, operator-dependant and require time-consuming offline analysis.

A third-generation handheld microscope has recently been developed (CytoCam-IDF, Braedius Medical, NL), comprising a user-friendly, clinically applicable system. Crucially, the CytoCam is equipped with bespoke software allowing images to be stored and analysed automatically at the point of acquisition, opening up this monitoring modality to clinical practice. However, there are no validated normal ranges for the automatically measured variables generated by the Cytocam in health or disease states, with existing measures visualising fewer micro-vessels in a smaller field of view. [5]

Rationale

We propose that identifying the normal ranges for the automatically determined measurements derived by the CytoCam system will allow us to gain a better understanding of the function of the microcirculation as determined by this device in healthy individuals of different ages. This proposal is the first of a series of planned studies aimed at the early identification of patients with microcirculatory dysfunction (as is found in sepsis). Understanding normal ranges, intra- and inter-individual variability will inform future planned research, and possibly advise bedside microcirculatory monitoring in ICU.

Primary study objective

To identify the variability and normal ranges for automatically measured microcirculatory variables as determined by the CytoCam system.

Study design/methodology
Single observational cohort study in healthy (not acutely unwell) volunteers. A maximum of 150 participants will be recruited in to three groups based on age over a period of 6 months.

- ≤ 34 years
- 35-54 years
- ≥ 55 years

On advice of our departmental Medical Statistician (Dr Mintu Nath), 30 participants will be initially recruited in to each group. An interim analysis will be performed allowing determination of population distribution, mean and standard deviations of the measured variables. A further 20 volunteers will be recruited to each group if required.

Following written informed consent, patient characteristics will be recorded to include age, sex, smoking status, weight, height, past medical history and current prescribed medications. Baseline physiological measurements including non-invasive blood pressure, heart rate and oxygen saturation will be recorded.
Microvascular measurements will be obtained using the CytoCam system as per the manufacturer's guidance.

Following preliminary data analysis and assessment of data distribution patterns, reference ranges will be established using appropriate methodologies. Associations between baseline characteristics, physiological measurements and microcirculatory measures will be analysed.

Justification for funding
We have already purchased the CytoCam system, but require additional funding to purchase the disposables required for its use; specifically, single-participant-use disposable lens caps and ongoing calibration costs.

References:
[1] Sharawy N, Lehmann C. New directions for sepsis and septic shock research. J Surg Res 2014;.

[2] Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are
associated with organ failure and death in patients with septic shock. Crit Care Med 2004; 32(9): 1825-31.

[3] Trzeciak S, Dellinger RP, Parrillo JE, et al. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: Relationship to hemodynamics, oxygen transport, and survival. Ann Emerg Med 2007; 49(1): 88, 98, 98.e1-2.

[4] Trzeciak S, McCoy JV, Phillip Dellinger R, et al. Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med 2008; 34(12): 2210-7.

[5] Aykut G, Veenstra G, Scorcella C, Ince C, Boerma C. Cytocam-IDF (incident dark field illumination)
imaging for bedside monitoring of the microcirculation. Intensive Care Med Exp 2015; 3(1): 40,015-0040-7. Epub 2015 Jan 31.