Final Report

Author: Dr Felix Ng
Qualification: MBBS, PhD, MPH
Institution: Royal Melbourne Hospital
Date: 1st December 2021

Title of Project: Beyond Revascularisation: Maximizing Acute Stroke Treatment Outcome Post-reperfusion

Summary:
Stroke is the most frequent cause of permanent disability in adults and a major cause of death worldwide. Despite timely reperfusion, residual disability is common and may be due to established irreversible injury prior to revascularisation or post-reperfusion secondary injury. This project consists of several studies that aimed to characterise post-reperfusion pathophysiology using advanced follow-up imaging in ischemic stroke patients who had thrombectomy for acute large vessel occlusion from a prospective neuroimaging study and a pooled clinical trial dataset. Specifically, we aimed to explore the topographic characteristic of ischemic tissue injury, the temporal response of ischemic cerebral tissue, and the role of blood-brain barrier on post-reperfusion complications.

Firstly, we evaluated the degree of variability in microstructural injury within and adjacent to regions identified as infarcted tissue using Diffusion Tensor Imaging (DTI) in a prospective longitudinal study of 18 patients presenting with 12hours of ischemic stroke evaluated with baseline CT-perfusion and follow-up MRI at one month. Lower FA and higher MD values were observed within both the infarct lesion and the peri-infarct tissue compared with their homologous contralateral brain regions (all comparisons $p \leq 0.01$). No difference was observed in FA and MD between remote non-hypoperfused tissue and its contralateral homologous region (FA $p=0.42$, MD $p \geq 0.99$). The magnitude of asymmetry (ipsilateral/contralateral ratios) of FA and MD was greater with increasing severity of hypoperfusion in a dose-response pattern. Asymmetry greatest in the area of infarction with severe hypoperfusion, followed by infarction with moderate hypoperfusion, the peri-infarct hypoperfused tissue and lastly the remote non-hypoperfused normal tissue (median on clustered quantile regression $p \leq 0.01$). We conclude that a gradient of microstructural injury corresponding to the severity of ischemic insult is present within and beyond conventionally-defined infarct boundaries. The traditional dichotomized notion of infarcted versus non-infarcted tissue widely adopted in clinical research and in practice warrants re-examination.

Secondly, we evaluated the temporal evolution of ischemic tissue as assessed by diffusion weighted imaging (DWI) and diffusion kurtosis imaging (DKI) in 60 patients

recruited at the Royal Melbourne Hospital. Both modalities are used to assess tissue microstructural properties (of water molecules as a marker of cellular pathology). DWI and DKI increased in size between 12 and 72hours after reperfusion treatment by thrombectomy. For the DWI and DKI lesions at <12hours after reperfusion, the DKI lesion volume was not significantly different (p=.172) than DWI lesion volume. When compared to the 3-month FLAIR outcome lesion, the FLAIR lesion was significantly larger (p=0.045) than the DKI lesion but similar to the DWI lesion. (p =.708). For the DWI and DKI lesions obtained on the 24-72hours MRI, DKI volume was significantly smaller (p <0.001) than DWI volume. The 3-month FLAIR lesion volume was similar (p =.057) to the DKI volume, but significantly smaller than the DWI volumes (p <.001). This suggest DKI obtained in the acute period is more accurate than DWI in reflecting final (3-month) ischemic lesion volume, possibly by reflecting the most severely injured tissue while the DWI lesion may comprise reversibly injured tissue that will normalise at 3-months.

Thirdly we investigated the relationships between BBB integrity and space-occupying cerebral edema in 238 patients who received acute reperfusion therapy in pooled analysis of recent international thrombectomy trials. We found increased BBB permeability was independently associated with more edema (measure by midline shift and relatively hemispheric volume) after adjusting for age, occlusion location, reperfusion, parenchymal hematoma and thrombolytic agent used (Midline shift cOR=1.12,95%CI 1.03-1.20, p=0.005; relative Hemispheric Volume ß=0.39,95%CI 0.24-0.55,p<0.0001).

These studies thesis has collectively showed the importance of pathophysiological changes in the post-reperfusion period of ischemic stroke characterized by a heterogenous and evolving response to reperfusion that is (1) variable in regional topography and (2) underpinned by downstream microvascular dysfunction. We also show that advanced imaging performed after treatment may help identify novel markers of treatment response or therapeutic targets to enhance patient selection for treatment. These studies will inform future studies using neuroimaging to study post-reperfusion pathology in ischemic stroke which will help understand the biology of post-reperfusion injury and, ultimately, avenues to reverse these pathologies.