Perfusion imaging in acute and evolving brain ischemia

By
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Submitted in total fulfilment of the requirements for the degree of Doctor of Philosophy

Submitted
10 July 2012
Declarations

STATEMENT OF ORIGINALITY

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

Andrew Bivard

5 July 2012
ACKNOWLEDGEMENT OF AUTHORSHIP

I hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

Andrew Bivard

5 July 2012
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I, Dr Neil Spratt, attest that Research Higher Degree candidate Andrew Bivard contributed significantly to the data collection analysis and writing of the publications entitled:


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Presented at the International Stroke conference 2010 in San Antonio, Texas

2. Andrew Bivard, Patrick McElduff, Neil Spratt, Christopher Levi, Mark Parsons University of Newcastle (Newcastle, Australia) Validating Perfusion-Computed Tomography in Defining Extent of Brain Ischemia; Circulation 2010;122;e16: O304

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Presented at the World Cardiology Congress 2011 in Beijing, China

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### Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIF</td>
<td>Arterial Input Function</td>
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<tr>
<td>AIS</td>
<td>Acute Ischemic Stroke</td>
</tr>
<tr>
<td>ASL</td>
<td>Arterial Spin Labeling</td>
</tr>
<tr>
<td>BCD</td>
<td>Block Circulant Deconvolution</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral Blood Flow</td>
</tr>
<tr>
<td>CBV</td>
<td>Cerebral Blood Volume</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>CTA</td>
<td>Computed Tomography Angiography</td>
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<tr>
<td>CTP</td>
<td>Computed Tomography Perfusion</td>
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<tr>
<td>ddSVD</td>
<td>Delay and dispersion corrected Single Value Deconvolution</td>
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<tr>
<td>DT</td>
<td>Delay Time</td>
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<tr>
<td>DWI</td>
<td>Diffusion Weighted Imaging</td>
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<tr>
<td>EPI</td>
<td>Echo Planner Imaging</td>
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<tr>
<td>FT</td>
<td>Fourier Transform</td>
</tr>
<tr>
<td>ICH</td>
<td>Intracranial Haemorrhage</td>
</tr>
<tr>
<td>INR</td>
<td>International normalized ratio</td>
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<tr>
<td>IRF</td>
<td>Input residue function</td>
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<tr>
<td>MRA</td>
<td>Magnetic Resonance Angiography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MTT</td>
<td>Mean Transit Time</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PWI</td>
<td>Perfusion weighted imaging</td>
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<tr>
<td>rTPA</td>
<td>Recombinant tissue plasminogen activator</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single-photon emission computed tomography</td>
</tr>
<tr>
<td>SVD</td>
<td>Single value deconvolution</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>TTP</td>
<td>Time to peak</td>
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<tr>
<td>VOF</td>
<td>Venous out flow</td>
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Thesis Abstract

Background: Established acute stroke treatment protocols require further investigation to identify patients who are most likely to respond to treatment. The aim of hyper-acute ischemic stroke treatment is to salvage hypoperfused tissue that would infarct soon (penumbra), thus preserving brain tissue and allowing better functional recovery of an individual patient. Penumbral salvage is achieved by removal of a cerebrovascular occlusion in the cerebral circulatory system through the use of intravenous thrombolytic therapy (iv rtPA), or mechanical intra-arterial thrombus retrieval. However, the current clinical guidelines for the treatment of ischemic stroke totally fail to measure the volume of the treatable penumbra. This thesis aims to provide the technical ability to measure the acute penumbra and infarct core, using readily available clinical imaging techniques. Furthermore, this thesis also aims to provide the clinical relevance of measures of the acute infarct core and penumbra, when compared to current treatment guidelines.

Objectives: This thesis investigated clinically accessible perfusion imaging techniques, such as Computed Tomography Perfusion, as well as Magnetic resonance perfusion weighted imaging and arterial spin labelling, for their utility in acute ischemic stroke. The specific aims of this thesis were:

1) Determine a method by which to investigate perfusion imaging as compared to current gold standard measurements of tissue pathophysiology.

2) Investigate the threshold cut offs to determine the acute critical tissue pathophysiology measurements of the acute penumbra and infarct core.

3) Optimise the measures of the acute penumbra and infarct core.
4) Standardise the measure of the acute penumbra and infarct core, or failing standardisation, determine the optimal thresholds for the acute infarct core and penumbra for all software post processing algorithms available.

5) Determine the clinical importance of measures of the acute penumbra and infarct core.

6) Finally, compare various perfusion techniques to one another to determine cross compatibility of different measures.

Methods: A cohort of 320 acute ischemic stroke patients who were admitted to the John Hunter hospital were enrolled in the studies for this PhD. These patients underwent an acute CTP with a 24 hour follow-up MR sequence. Sixty seven patients also underwent an additional acute MR, with perfusion and diffusion imaging.

Clinical assessments were performed on all patients acutely, at 24 hours and at 90 days post stroke by a certified neurologist or neurology registrar. Clinical assessments included the National Institutes of Health Stroke Scale (NIHSS), and a modified Rankin Score.

All perfusion images underwent post processing using MiStar, a commercially available software package. MiStar generates the perfusion maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak.

Once imaging was processed and ready for analysis, a broad range of statistical tests were used. Statistical tests included summery statistics such as linear regression, or specific statistical methods such as a receiver operator characteristic curve analysis.

Results: Acute CTP imaging was able to readily identify the volumes of the acute infarct core and penumbra. Analysis of different post processing algorithms revealed
there were obvious themes for detecting the acute tissue pathophysiology. A Time To Peak measures (or its variants of Tmax and Delay Time) were always optimal to define the acute perfusion lesion, and a CBF measure was optimal to define the acute infarct core. However, each post processing algorithm used, required a different threshold to define the acute tissue pathophysiology. Additionally, by defining the acute infarct core within the acute perfusion lesion, through restricting the volume of the infarct core, a greater level of accuracy was always achieved.

Next, the MR sequence, Arterial Spin Labelling was the only perfusion technique that is clinically available, that was able to show hyperperfusion. Hyperperfusion at 24 hours was associated with reperfusion and penumbra salvage. Therefore if a patient showed hyperperfusion in their stroke region (previously hypoperfused tissue), they ultimately had a much better clinical outcome compared to patients that did not reperfuse or hyper-perfuse.

**Conclusions:** This thesis demonstrated that it was possible to define acute ischemic tissue pathophysiology using CTP. Moreover, it was shown that measures of the acute penumbra and infarct core were directly related to clinical outcome, and likelihood of treatment success. The threshold measures of the acute infarct core and penumbra provided by this thesis can be applied to all acute clinical CTP scanning platforms in order to provide treatment relevant information. This underlines the importance of perfusion imaging in the acute clinical setting to guide treatment based decision making.