Pathophysiology of
Normal Pressure Hydrocephalus

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Thesis
Doctor of Philosophy

2004
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Statement of Authenticity

This thesis contains a record of original research performed by the author at the Academic Neurosurgery Unit, Addenbrooke’s Hospital, Cambridge, United Kingdom, the Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, United Kingdom, the Department of Neurosurgery, Royal Prince Alfred Hospital, Sydney Australia and the Department of Surgery, University of Sydney, Sydney, Australia.

In all sections of the thesis, the author was primarily responsible for the conduct and direction of the research, study design and the analysis of results. This work has not been submitted for consideration of an award, diploma or degree at any institution previously.

Research was conducted with approval of the Cambridge Regional Ethics Committee when applicable in accordance with the Declaration of Helsinki as amended in September, 2000.
Acknowledgements

I would like to express my gratitude for the advice, guidance and supervision of Professor John D. Pickard, Associate Professor Michael Besser and Dr. Ian Johnston.

Drs. Zofia and Marek Czosnyka designed and developed the computerised CSF infusion and collaborated in its application to the studies of this thesis. Dr. Alonso Péna designed and performed the finite element modelling during CSF infusion studies. Dr. Shahan Momjian collaborated in performing the cerebral blood flow studies. The staff of Wolfson Brain Imaging Centre assisted in the development and analysis of the experimental data. These researchers include Dr. Neil Harris, Dr Piotr Smielewski, Dr. Tim Fryer, Mr. Tim Donovan and Dr. Adrian Carpenter. I would like to thank my colleagues in Cambridge for their friendship.

I was supported by the Sydney University Medical Foundation Woods Grant and the Madeline Foundation for Neurosurgical Research. I would like to express my appreciation for the support of these two organisations. The work contained in this thesis was also funded by an MRC Programme Grant (No. G42,00005).

My gratitude and appreciation goes to my family and my partner Tara for their understanding and sacrifice that allow me to pursue my career and academic interests.
Publications arising from thesis material

Publications in Peer Reviewed Journals


Abstracts in Conference Proceedings


pressure hydrocephalus using diffusion tensor imaging. World Congress of Neurological Surgeons. Sydney, Australia.


**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>Autoregulation</td>
</tr>
<tr>
<td>AMP&lt;sub&gt;beg&lt;/sub&gt;</td>
<td>CSF pulse amplitude - baseline</td>
</tr>
<tr>
<td>AMP&lt;sub&gt;end&lt;/sub&gt;</td>
<td>CSF pulse amplitude - equilibrium</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CC</td>
<td>Corpus callosum</td>
</tr>
<tr>
<td>CCx</td>
<td>Calcarine cortex</td>
</tr>
<tr>
<td>CO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CPP</td>
<td>Cerebral perfusion pressure</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CVR</td>
<td>Cerebrovascular reactivity</td>
</tr>
<tr>
<td>D</td>
<td>Mean diffusion</td>
</tr>
<tr>
<td>DAT</td>
<td>Dementia of the Alzheimer’s type</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion tensor imaging</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion weighted imaging</td>
</tr>
<tr>
<td>EAM</td>
<td>External acoustic meatus</td>
</tr>
<tr>
<td>El</td>
<td>Elastance</td>
</tr>
<tr>
<td>EPI</td>
<td>Echo planar imaging</td>
</tr>
<tr>
<td>FA</td>
<td>Fractional anisotropy</td>
</tr>
<tr>
<td>gCBF</td>
<td>Global cerebral blood flow</td>
</tr>
<tr>
<td>GE</td>
<td>Gradient echo</td>
</tr>
<tr>
<td>IC</td>
<td>Internal capsule</td>
</tr>
<tr>
<td>ICP</td>
<td>Intracranial pressure</td>
</tr>
<tr>
<td>ICP&lt;sub&gt;beg&lt;/sub&gt;</td>
<td>Intracranial pressure - baseline</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>ICP&lt;sub&gt;end&lt;/sub&gt;</td>
<td>Intracranial pressure - equilibrium</td>
</tr>
<tr>
<td>i.v.</td>
<td>Intravenous</td>
</tr>
<tr>
<td>mmHg</td>
<td>Millimetres of mercury</td>
</tr>
<tr>
<td>mmHg/ml/min</td>
<td>Millimetres of mercury per millilitre per minute</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NPH</td>
<td>Normal pressure hydrocephalus</td>
</tr>
<tr>
<td>OER</td>
<td>Oxygen extraction rate</td>
</tr>
<tr>
<td>P</td>
<td>Isotropic component of diffusion tensor</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PVI</td>
<td>Pressure-volume index</td>
</tr>
<tr>
<td>PVL</td>
<td>Periventricular lucency</td>
</tr>
<tr>
<td>Q</td>
<td>Deviatoric component of diffusion tensor</td>
</tr>
<tr>
<td>RA</td>
<td>Relative anisotropy</td>
</tr>
<tr>
<td>rCBF</td>
<td>Regional cerebral blood flow</td>
</tr>
<tr>
<td>R&lt;sub&gt;csf&lt;/sub&gt;</td>
<td>Resistance to CSF absorption</td>
</tr>
<tr>
<td>RF</td>
<td>Radiofrequency</td>
</tr>
<tr>
<td>sAR</td>
<td>Static Autoregulation parameter</td>
</tr>
<tr>
<td>sARi</td>
<td>Static Autoregulation index</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
</tr>
<tr>
<td>TE</td>
<td>Echo time</td>
</tr>
<tr>
<td>Xe</td>
<td>Xenon</td>
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</table>
Summary

Normal pressure hydrocephalus (NPH), a CSF circulation disorder, is important as a reversible cause of gait and cognitive disturbance in an aging population. The inconsistent response to CSF shunting is usually attributed to difficulties in differential diagnosis or co-morbidity. Improving outcome depends on an increased understanding of the pathophysiology of NPH. Specifically, this thesis examines the contribution of, and inter-relationship between, the brain parenchyma and CSF circulation in the pathophysiology of NPH.

Of the four core studies of the thesis, the first quantifies the characteristics of the CSF circulation and parenchyma in NPH using CSF infusion studies to measure the resistance to CSF absorption and brain compliance. The second study assesses cerebral blood flow (CBF) was using O\(^{15}\)-labelled positron emission tomography (PET) with MR co-registration. By performing CSF infusion studies in the PET scanner, CBF at baseline CSF pressure and at a higher equilibrium pressure is measured. Regional changes and autoregulatory capacity are assessed. The final study examines the microstructural integrity of the parenchyma using MR diffusion tensor imaging.

These studies confirm the importance of the inter-relationship of the brain parenchyma and CSF circulation. NPH symptomatology and its relationship to the observed regional CBF reductions in the basal ganglia and thalamus are discussed. Regional CBF reductions with increased CSF pressure and the implications for autoregulatory capacity in NPH are considered. The reduction in CBF when CSF was increased was most striking in the periventricular regions. In addition, periventricular
structures demonstrated increased diffusivity and decreased anisotropy. The relationship between these changes and mechanisms such as transependymal CSF passage are reviewed.

The findings of this thesis support a role of both the CSF circulation and the brain parenchyma in the pathophysiology of NPH. The results have implications for the approach to the management of patients with NPH.