

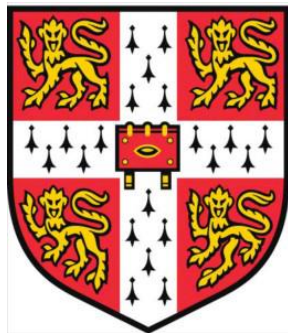
Dynamics of cerebral fluids in patients suffering from hydrocephalus and pseudotumour cerebri

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This dissertation is submitted for the degree of Doctor of Philosophy

Preface

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text.

This dissertation is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text.

This dissertation does not exceed the word limit of 60,000 words.

“...Καλά πια καταλαβαίνεις πως αυτή είναι η αξία του ανθρώπου: να ζητά και να ξέρει πως
ζητά το αδύνατο, και να είναι σίγουρος πως θα το φτάσει...”

(...Now you understand well, how the ultimate value of man is as follows: to strive, and
to know that you are striving, for the impossible; and to be certain that you shall
achieve it...)

N. Kazantzakis, Captain Michalis

SUMMARY

Dynamics of cerebral fluids in patients suffering from hydrocephalus and pseudotumour cerebri

Despoina Afroditi Lalou

This dissertation is devoted to dynamics of brain liquids in patients with altered CSF circulation and pressure-volume compensation. Since the introduction of intracranial pressure (ICP) monitoring, the studies of CSF dynamics have revealed unique information about the intracranial circulation and opened new opportunities for diagnosis and treatment of hydrocephalus and pseudotumour cerebri. The adaptation of infusion tests in clinical practice over 45 years ago has introduced a practical tool to benefit both patients and research into altered CSF dynamics. Objective testing of intracranial circulation in patients with clinical symptoms constitutes a unique situation, where the discovery of new patterns and reasons for disturbed intracranial circulation can be quantified. Such macroscopic yet practical quantifications can easily be translated to clinically useful information, and back, in real time or alternative past and future synchronicities.

The aim of this dissertation is to demonstrate the value of testing CSF dynamics *in vivo* and how it could provide pathophysiological and clinical insights into hydrocephalus and pseudotumour cerebri syndrome (PTCS). My intention was to describe and reflect the main themes involved in the study of CSF dynamics: a) their role in diagnosis and treatment, b) their use in understanding shunts and shunt malfunction c) the need to optimise our understanding of the contents of ICP, meaning that long-term ICP monitoring or dynamic tests are required in CSF disorders, not snapshot ICP measurements and finally d) the mapping and quantification of the interaction between CSF circulation and cerebral blood flow (CBF).

As the above foundations and results of my work lead to the formation of a required, albeit expected, long doctoral treatise, I have structured the later in 9

chapters containing a comprehensive literature review of the Resistance to CSF outflow as well as a systematic literature review of the CBF and autoregulation of the CBF in NPH. I have also dedicated a methods chapter, Chapter 3, into introducing and explaining the variable tested during a CSF infusion test, such as the fundamental amplitude of ICP and the compensatory reserve indices. Following this is the presentation of the data and clinical material used for my original projects. Specifically, my results contain the following:

I) Autoregulation of cerebral blood flow in hydrocephalus

CSF infusion tests provide a unique setting where both ICP and cerebral blood flow and autoregulation can be measured in ambulatory patients utilising many different methods. Autoregulation has been studied by quantifying the interaction between the CSF and cerebral blood circulation has revealed diagnostic and outcome implications that could perhaps describe the natural course of a CSF disorder, or differentiate between a CSF disorder and a vascular disorder, or the coexistence of the two, opening new chapters to the comprehension of shunt responsive NPH. I have explored the state of global autoregulation in patients undergoing infusion tests, in an attempt to set out a reference for investigations related to NPH, Resistance, autoregulation and their clinical implications.

In the 5th chapter, I have:

- Described the relationship between Rout, cerebral autoregulation and arterial blood pressure. Rout demonstrates a negative linear relationship with global autoregulation. When I combined these parameters and accounted for the patients' age, I was able to show a good correlation with outcome, much improved compared to Rout alone.

II) CSF dynamics in normal pressure hydrocephalus and pseudotumour cerebri.

CSF dynamics in different conditions have shown that parameters such as the Resistance to CSF outflow in NPH and ICP at baseline combined with compensatory reserve indices in PTCS, could provide important diagnostic and management

information. This could be a valuable addition of objective evidence to imaging and clinical examination.

Using large cohorts of patients, I have explored the Resistance to CSF outflow (R_{out}) in NPH in the context of different aetiologies of NPH, its relationship with age as well as its overall correlation with outcome after shunting. I have also explored these relationships in relevance to clinical practice. In PTCS, I have described the findings from infusion tests in both adult and paediatric patients and have highlighted the differences with hydrocephalus.

In chapter 6, , I have described the following:

- Davson's equation in NPH: The so-called Davson's equation describes the relationship between ICP, R_{out} , CSF formation rate and sagittal sinus pressure under physiological circumstances. I have validated the existence of such a linear relationship in NPH.
- CSF dynamics in post-traumatic hydrocephalus: Traumatic brain injury, as a cause of secondary NPH, shows some differences in R_{out} and ICP amplitude compared to idiopathic NPH. I have also described the effect of decompressive craniectomy and of cranioplasty on CSF dynamics.

In chapter 7, I have explored the CSF dynamics of PTCS and in particular:

- The coupling between CSF pressure and Sagittal sinus pressure (SSp) in PTCS patients at baseline and during infusion tests. I have also shown how this relates to Davson's equation under an unstable SSp and the possible pathophysiological consequences of this finding.
- The CSF dynamics of paediatric patients with PTCS. Those included all patients assessed in Cambridge and classified as definite, probable and not PTCS.

III) Shunt testing in vivo.

Shunts are currently the mainstay for the management of hydrocephalus, as well as an important part of the management of PTCS. They change CSF dynamic parameters in a way that is easily assessed with shunt infusion tests. The knowledge

of the post-shunting CSF circulation contains crucial information on the state of the shunt function, as well as the adequate restoration of the patients' intracranial circulation. I have described how objective knowledge from shunt testing in vivo impacts clinical practice and patients' outcomes.

In chapter 8, I have presented two studies about testing shunt function in-vivo:

- Shunt testing in vivo using infusion tests is important in avoiding unnecessary revisions of patent shunts and allows patients to be managed conservatively, with good outcomes. This also translates to financial benefits for healthcare systems.
- In paediatric hydrocephalus, shunt infusion studies are an accurate and useful tool for investigating insidious shunt obstruction.

IV) Slow waves of Intracranial Pressure.

Reliable, long-term overnight monitoring is the gold standard in monitoring and analysing ICP and its contents. Slow waves, compensatory reserve and relationship with the venous circulation contain reliable information that are again correlated to clinical practice and can be compared and incorporated into the shorter-term infusion test. I have explored the behaviour of slow waves in anaesthetized patients

In chapter 9, I have investigated the influence of general anaesthesia on slow waves of ICP in NPH and traumatic brain injury (TBI) patients.

Conclusion: Infusion tests are a practical tool for research and possibly diagnosis and treatment in patients with PTCS and NPH. CSF dynamics provide a quantitative description of cerebral pathophysiology in CSF disorders, both for CSF and potentially for cerebral blood flow. After shunting, infusion tests are a reliable and cost-effective tool for identifying or excluding shunt malfunction. Further studies are needed to verify the clinical implications of CSF infusion tests and cerebral blood flow and autoregulation in those patients.

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LIST OF PAPERS PUBLISHED/UNDER REVIEW

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Lalou AD, Czosnyka M, Donnelly J, Lavinio A, Pickard JD, Garnett M, Czosnyka Z. Are Slow Waves of Intracranial Pressure Suppressed by General Anaesthesia? *Acta Neurochir Suppl.* 2018;126:129-132.

Lalou AD, Czosnyka M, Donnelly J, Pickard JD, Nabbanja E, Keong NC, Garnett M, Czosnyka ZH. Cerebral autoregulation, cerebrospinal fluid outflow resistance, and outcome following cerebrospinal fluid diversion in normal pressure hydrocephalus. *J Neurosurg.* 2018 Mar 1:1-9.

Lalou AD*, Levrini V*, Garnett M, Nabbanja E, Kim DJ, Gergele L, Bjornson A, Czosnyka Z, Czosnyka M. Validation of Davson's equation in patients suffering from idiopathic normal pressure hydrocephalus *Acta Neurochir (Wien)*. 2018 May;160(5):1097-1103

Dias-Fernandes S*, Lalou AD*, Spang R, Haas-Lude K, Garnett M, Fernandez H, Czosnyka M, Schuhmann M, Czosnyka Z. Value of computerized Shunt-Infusion-Study in assessment of paediatric hydrocephalus shunt function – a two centre observational study. *Childs Nerv Syst.* 2020;36(1):59-71

Lalou AD, McTaggart J, Czosnyka Z, Krishnakumar D, Czosnyka M. Cerebrospinal fluid dynamics in paediatric pseudotumour cerebri syndrome. *Childs Nerv Syst.* 2020;36(1):73-86

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Lalou AD, Czosnyka M, Petrella G, Garnett M, Nabbanja E, Czosnyka Z, Pickard JD Outcome and financial implications of shunt infusion tests. [*Acta Neurochir \(Wien\)*](#). 2020 Feb 20. doi: 10.1007/s00701-020-04212-0. [Epub ahead of print]

Lalou AD*, Levrini V*, Gergele L, Koliass A, Hutchinson PJ, Czosnyka M, Czosnyka Z. CSF dynamics in non-acute post-traumatic ventriculomegaly. In press, *Fluids and Barriers of the CNS*.

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Co-authored publications

1. Bjornson A, Tapply I, Nabbanja E, Lalou AD et al. Ventriculo-peritoneal shunting is a safe and effective treatment for idiopathic intracranial hypertension. *Br J Neurosurg*. 2019;0(0):1-9.
2. Nabbanja E, Pickard JD, Lalou AD, Czosnyka ZH. Use of CSF infusion studies to unblock occluded hydrocephalus ventricular shunt catheters: a preliminary report of two patients. *BMJ Case Rep*. 2018;2018. doi:10.1136/bcr-2017-223861.
3. Nabbanja E, Czosnyka M, Keong NC, Garnett M, Pickard JD, Lalou DA, Czosnyka Z: Is There a Link Between ICP-Derived Infusion Test Parameters and Outcome After Shunting in Normal Pressure Hydrocephalus? *Acta Neurochir Suppl*. 2018;126:229-232. doi: 10.1007/978-3-319-65798-1_46.
4. Kaczmarska K^{1,2}, Kasprowicz M³, Grzanka A⁴, Zabolotny W⁴, Smielewski P⁵, Lalou DA⁵, Varsos G⁵, Czosnyka M^{4,5}, Czosnyka Z⁵ Critical Closing Pressure During a Controlled Increase in Intracranial Pressure.. *Acta Neurochir Suppl*. 2018;126:133-137. doi: 10.1007/978-3-319-65798-1_28.
5. Puppo, C., Kasprowicz, M., Steiner, L. A., Yelicich, B., Lalou, D.A., Smielewski, P., & Czosnyka, M. (2019). Hypocapnia after traumatic brain injury: how does it affect the time constant of the cerebral circulation? *J Clin Monit Comput*. 2019 Jun 7

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Lalou AD, Czosnyka M, Donnelly J, Pickard JD, Nabbanja E, Keong NC, Garnett M, Czosnyka ZH. Global cerebral autoregulation, cerebrospinal fluid outflow resistance, and outcome following cerebrospinal fluid diversion in normal pressure hydrocephalus. Hydrocephalus 2017, Kobe, Japan

Lalou AD, Czosnyka M, Nabbanja E, Petrella G, Garnett M, Pickard JD, Czosnyka ZH. Outcome and financial implications of shunt testing in vivo Hydrocephalus 2017, Kobe, Japan

Lalou AD, Czosnyka M, Nabbanja E, Petrella G, Garnett M, Pickard JD, Czosnyka ZH. Outcome and financial implications of CSF shunt infusion tests Society of British Neurological Surgeons Spring meeting 2018, Torquay, UK

Lalou AD, Czosnyka M, Donnelly J, Pickard JD, Nabbanja E, Keong NC, Garnett M, Czosnyka ZH. Predictive value of PRx and cerebrospinal fluid outflow resistance on outcome following cerebrospinal fluid diversion in normal pressure hydrocephalus. Cerebral Autoregulation Network 2018, Oxford, UK

Lalou AD, Czosnyka M, Czosnyka Z, Krishnakumar D, Pickard JD, Higgins JN: Coupling of CSF and sagittal sinus pressure in adult pseudotumour cerebri. Hydrocephalus 2018, Bologna, Italy.

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LIST OF ABBREVIATIONS

MAPMAPMAP

ACZ, Acetazolamide

AMP, fundamental amplitude of ICP

AMP-P, amplitude-pressure regression line or its slope

AUC, area under the curve

BMI, **body-mass index**

CA, cerebral autoregulation

CaBV, cerebral arterial blood volume

CBF, cerebral blood flow

CI, confidence interval

CO₂, carbon dioxide

CPP, cerebral perfusion pressure

CrCP, critical closing pressure

CSF, cerebrospinal fluid

CSFp, cerebrospinal fluid pressure (refers to the pressure measured via the lumbar space)

CT, computed tomography

CVR, cerebrovascular reactivity

ETCO₂, end-tidal carbon dioxide concentration

FFT, fast Fourier transformation

FV, **cerebral blood flow velocity**

GCS, **Glasgow coma scale**

HR, **heart rate**

ICP, **intracranial pressure**

IIH, idiopathic intracranial hypertension

INPH, idiopathic normal pressure hydrocephalus

LP, **lumbar puncture**

MAP, mean arterial blood pressure

MCA, middle cerebral artery

MRI, magnetic resonance imaging

Mx, mean flow cerebral autoregulation index based on cerebral perfusion pressure

NA, **not available**

NCCU, **Neurosciences Critical Care Unit**

nICP, non-invasive intracranial pressure

NM, **not measured**

NPH, normal pressure hydrocephalus

NPV, negative predictive value

NS, **not significant**

ONSD, optic nerve sheath diameter

OR, **odds ratio**

PaCO₂, partial pressure of carbon dioxide

PET, Positron emission tomography

PTH, Post-traumatic hydrocephalus

PI, **pulsatility index**

PPV, positive predictive value

PRx, pressure reactivity index

PTCS, pseudotumour cerebri syndrome

R, **correlation coefficient**

RAP, correlation coefficient of AMP and pressure as index of compensatory reserve
ROC, receiver operating characteristic
R_{out}, resistance to cerebrospinal fluid outflow
SAH, subarachnoid haemorrhage
SCA, state of cerebral autoregulation
SD, standard deviation
SDE, standard deviation of the error
SJ_{O2}, jugular bulb venous blood oxygen saturation
SSp, sagittal sinus pressure
TBI, traumatic brain injury
TCD, transcranial Doppler ultrasonography

CHAPTER 1

INTRODUCTION

1.1 Intracranial Pressure and Cerebrospinal Fluid dynamics

Since the total volume of the brain has been established to be around 1,500 mL and the volume of CSF around 150 mL, the commonly described role of CSF as a “buoyant” means for the brain is a gross misconception and dismissal of Archimedes’ actual law of buoyancy. It is hence impossible for such a large volume of brain to float in a volume of fluid equating to less than a drinking glass. Based on such a misconception, one could understand perhaps how many difficulties there have been in studying and describing CSF and its roles throughout the years.

Modern understanding of CSF dynamics through mathematical modelling has given us a thorough representation of the intracranial circulation. The Marmarou model(1) (Figure 1.1), presented as a simple electrical circuit, was based on the classical experimental findings and includes CSF formation, circulation through R_{out} , storage and absorption through the venous compartment. Knowledge of which component is disturbed could provide us with important diagnostic and treatment options in different disorders.

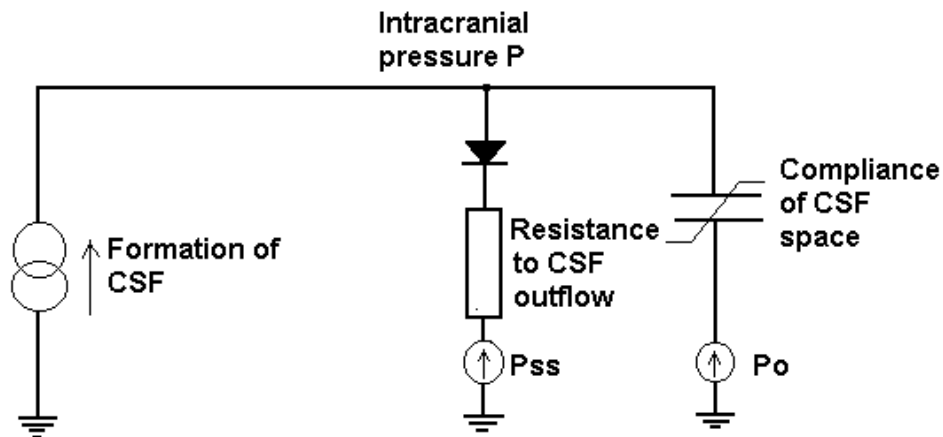


Figure 1.1: CSF dynamics as an electrical circuit: CSF formation represents the current source, with the resistor being the R_{out} , created from a pressure gradient between sagittal sinus pressure (SSp) and ICP. The compensatory space in the brain and spine constitutes the capacitor. From Marmarou A: A theoretical model and experimental evaluation of the cerebrospinal fluid system. Thesis, Drexel University, Philadelphia, PA, 1973(2)

1.2 Normal Pressure Hydrocephalus and Pseudotumour Cerebri Syndrome

1.2.1 Normal Pressure Hydrocephalus

Hydrocephalus, from the Greek words hydro (ὕδωρ-water) + cephalus (κεφαλή/κέφαλος -head), involves a very heterogenous range of disease in all age groups with a disturbance in their CSF circulation(3,4). NPH is a rare condition in the adult population (2.2/million new cases /year, frequency in the general population still uncertain and potentially significantly higher with increasing age, with prevalence of described around 2% in >65s but around 5% in >80s)(5–10). Albeit rare, it is the only reversible dementia so far, and is possibly underdiagnosed. This is highlighted by studies unravelling NPH in around 6% of total dementias, but this was as high as 14 - 22% in nursing home residents with severe dementia of unclear diagnosis and no response to other treatments(11). It is traditionally classified into idiopathic (iNPH) and secondary, with the majority of the cases (c. 2/3) being idiopathic, whereas rarely a cause such as traumatic brain injury (TBI), subarachnoid haemorrhage (SAH), aqueductal stenosis etc is known and identified(11,12). With neurosurgical treatment [insertion of a shunt or endoscopic third ventriculostomy (ETV), when there is a recognised obstructive cause], symptoms can be completely reversible, but without neurosurgical treatment it leads to severe dementia and death after progressive loss of the ability to walk & control ones' bodily functions(13).

Since its first description, now over 50 years ago, there has been significant progress and research on testing for, imaging and researching NPH, however there are many significant, unanswered questions holding back progress in understanding and managing NPH. Firstly, although described as consisting of the clinical triad of gait disturbance, dementia and urinary incontinence as well as radiological hydrocephalus and normal baseline CSF pressure, its very definition remains controversia(14–16)1. In addition, no definitive criteria and methods have been established to differentiate NPH from the current common vascular dementias and neurodegenerative diseases of the elderly, such as Parkinson's plus syndromes, and even Alzheimer's disease(16–20). It is a disorder of CSF circulation, as analysis of CSF pressure recordings and

infusion studies demonstrate an increased resistance to CSF outflow and an increased frequency of pathological waves of ICP(21–25). However, it has recently been demonstrated that increased Rout or frequent/pathological ICP waves are not satisfactorily predictive of outcome after shunting, raising a lot of questions related to Rout and iNPH management(26,27). Lastly, neurosurgical intervention as well as long-term shunt implantation carry significant risks for elderly patients and only 40-80% of patients respond to shunting(4,26,28). From poor understanding of definition, spanning to challenging diagnosis, doubtful prognostication and no objective evidence of why improvement after shunting often fails to occur, NPH constitutes a very complex syndrome in the modern era, often underestimated and neglected. Given the limitations that clinical, subjective and semi-quantitative investigations have in advancing our understanding for NPH, prioritising objective testing of those patients could provide some solutions to all above issues.

1.2.2 Pseudotumour cerebri syndrome

Pseudotumour cerebri syndrome (PTCS) has been principally described as a disease of post-pubertal females with raised BMI and its accurate diagnosis is particularly challenging in the paediatric population(29). The current intracranial pressure (ICP) thresholds in the paediatric spectrum of the disease (28cm CSF for obese and/or sedated children, 25cm CSF for normal weight and non-sedated children for definite PTCS), have been established epidemiologically, being set at the 90th percentile level of ICP measurements obtained in a single, ‘normal’ paediatric population(29,30). There are no adequately powered, randomised studies to reliably confirm that the thresholds are clinically relevant. Furthermore, current diagnostic criteria and guidelines, although thorough, are not able to explain patients’ symptoms, disease burden, or direct successful diagnosis and pharmacological or neurosurgical management(29,31).

Despite uncertainty on its probable cause, its underlying mechanism has been shown to be abnormalities of the venous system leading to impaired CSF drainage, therefore classifying the condition as a syndrome, the Pseudotumour Cerebri Syndrome(32–35).

This complex syndrome's venous pathophysiology includes known, secondary causes from venous sinus lesions such as cerebral venous thrombosis and stenosis, that are potentially treatable with resolution of the resulting venous sinus obstruction. In idiopathic intracranial hypertension (IIH) however, raised cerebral venous pressures had generally been considered the result of raised intracranial pressure or raised central venous pressure, until early MR and CT venographies suggested stenosis with a gradient between CSFp and sagittal sinus pressure (SSp) as a common mechanism. This led to the use of stenting as a management option in IIH, particularly for those cases where the venous sinus stenosis appears primarily localised in the venous system and is demonstrated not to be amenable to CSF drainage(33,35,36). Nonetheless, the causes, as well as a standardised practice and investigating PTCS patients in order to clarify whether raised venous pressures are a cause or effect of the disease process remain uninvestigated. Moreover, even as venous sinus pathology is generally accepted as one of the main pathophysiological mechanisms in PTCS, there is still some evidence of alternative or co-existing mechanisms, such as cerebral oedema, increased cerebral arterial blood volume (CaBV) and impaired CSF absorption(37–39). Due to the high variability of the disease's symptoms and manifestations, this evidence is sparse and conflicting, yet revealing a large spectrum of possibilities and subcategories within the same syndrome. Despite limited knowledge of the disease pathophysiology, a large armamentarium of old and new management options, have eliminated the interest in investigating CSF dynamics and therefore it has been one of the main goals of this dissertation to achieve this and to link the dynamics with further understanding and clinical implications of the syndrome.

1.3 Shunts

In order to understand the management of hydrocephalus and the reasons behind its success, failure and complications, it is important to possess in-depth knowledge and information on the hydrodynamic properties of shunts and how they alter CSF dynamics.

Shunts are pressure-passive and are characterised by an operating pressure, which is the pressure at which the valve opens and CSF drainage begins; a critical pressure, representing the maximum pressure the shunt allows, and a resistance, which is usually low ($<6 \text{ mmHg} \cdot \text{min/ml}$, with a few exceptions) and fixed, with very few having variable resistance (mainly the Polaris and Orbis-Sigma valves)(40–44). There are several overdrainage prevention mechanisms, nowadays either included in the shunt and valve system, or implanted separately. Examples of the first include the Strata valve, that contains an integrated siphon control device, or the Pro-GAV valve, that also consists of a shunt assistant(44–47). Fundamentally, the selection and implantation of a shunt on a patient with disturbed CSF dynamics should aim at: 1) altering the CSF dynamics so as to reverse the initial disturbance (e.g. lowering the high R_{out} in NPH) and 2) preventing overdrainage, and therefore preventing its consequences as well as future shunt revisions.

To approximate this, the integration of a shunt in the electrical circuit in Figure 1.1 represents how, when a shunt is open, alters the operating pressure and R_{out} (**Figure 1.2**). As a result, the investigation and management of CSF disorders does not stop at the initial assessment and implantation of the shunt, but continues and binds together the state of the pressure, resistance, and overall CSF dynamics electrical circuit before shunting with what happens after shunting, together with troubleshooting and diagnosis of shunt malfunction(1,42,48).

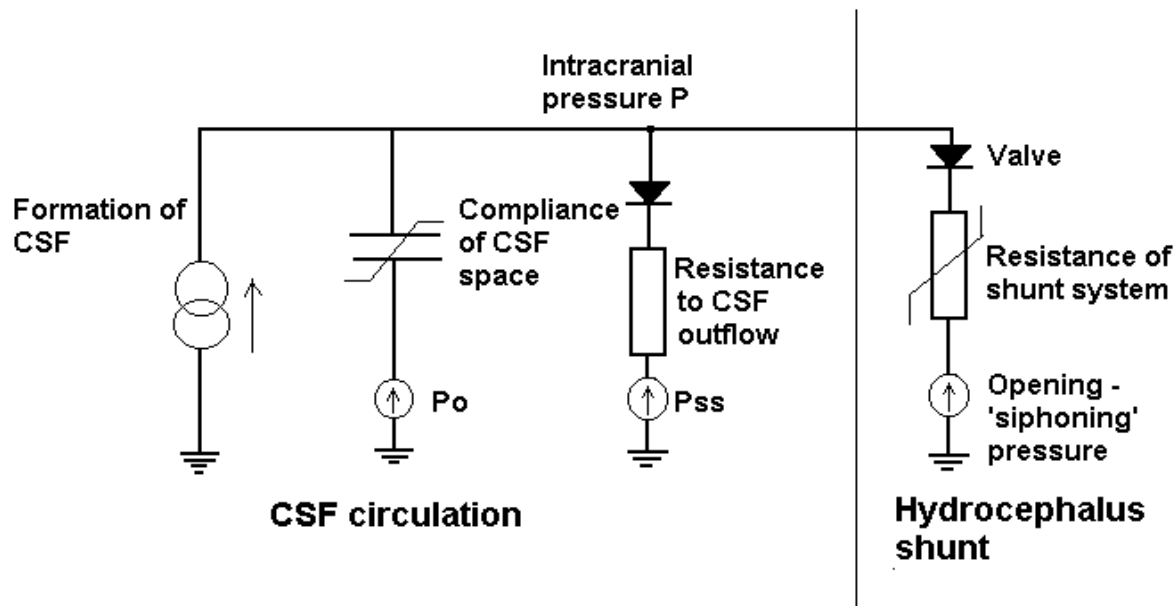


Figure 1.2: Extension of the previous model in Figure 2.1, where the hydrodynamic consequence of shunting is shown: when the second diode (valve) is open, the previous resistor is replaced with the R_{out} of the implanted shunt. From Marmarou A: A theoretical model and experimental evaluation of the cerebrospinal fluid system. Thesis, Drexel University, Philadelphia, PA, 1973 (2)

1.4 CSF infusion studies and overnight ICP monitoring

Overnight ICP monitoring via an intraparenchymal bolt remains the gold standard in studying ICP and its contents(49–51). Due to the dynamic nature of ICP, long-term monitoring allows us to calculate components such as slow waves and pathological plateau waves or spikes of ICP that are frequent and/or above the expected limit. Slow waves, also known as b-waves, are rhythmic oscillations of ICP at a frequency of 0.3-3 cycles/minute, most likely vasogenic in origin and have been described both in normal as well as individuals with disturbed CSF dynamics, particularly in NPH. Furthermore, the assessment of compensatory reserve with the use of the RAP index becomes more reliable with overnight monitoring, as well as intracranial hypotension and/or shunt overdrainage, especially posture-related overdrainage(52–54).

Aims & Goals of infusion tests

Infusion studies have been used experimentally and clinically for CSF disorder for over three decades.

Overall, the scientific, patient outcome and financial benefits of infusion studies can be summarised in 4 main points:

- 1) Reliable, longer-term baseline ICP**
- 2) Assessment, recording & storage of dynamic changes**
- 3) Post-shunting outcome implications**

1) Reliably measuring and monitoring ICP

There is a growing body of evidence accentuating the importance of proper, long-term ICP monitoring against single “snapshot” measurements(50,52,55,56). This is because it is well-known that standard LP measurements can be affected by posture, movement, emotion, volume loss, anaesthetic agents and hypercapnia, which can lead to unreliable estimation of ICP. Most importantly though, ICP levels are dynamic, so a ‘normal’ recorded ICP at a single time-point may not be a representative value. In adults and children, the assessment of average ICP over more than 20 minutes (‘steady state’), is reported to be more reliable than a single opening pressure measurement(50,52,56). Therefore, using LP manometry to diagnose, classify and treat CSF disorders is a methodological error, that unfortunately has shaped part of the universal clinical practice and will continue to do so unless we generate the appropriate clinical evidence to disprove that. It is also an inadequate tool for scientific standards, due to lack of recording and objective evidence when reporting data for reproducible and transparent purposes.

2) Investigation and assessment of CSF dynamics

Although it is important to estimate ICP more reliably, baseline ICP as a number cannot provide a full assessment for the diagnosis and understanding of the CSF circulatory disorders. This is because it is the production, circulation or reabsorption of CSF that make ICP dynamic and are likely to be deranged in PTCS. Historically, only around 30% of these disturbances have been shown to be reflected on steady-state ICP values(50,55,57). For these reasons, monitoring of ICP in conjunction with CSF dynamics has long been established in the field.

In many centres around the world, patients are shunted on the basis of clinical examination and radiological findings. Nowadays, it is known that almost 70-80% of those selected from such rudimentary investigations respond to shunting(26,58,59). However, this improvement rate, based on recent randomised trials has also come into question, unmasking two recurring issues in NPH research and clinical practice: a) there is significant variation in the improvement rate reporting between centres, as well as the methodology of outcome assessment(26,28,60–63), and b) blind shunting deprives these patients of the opportunity to understand why they did not improve, as well as getting a different diagnosis and treatment that could slow down their degenerative process, instead of worsening it. Lastly, this approach deprives us from the knowledge of the state of the cerebral circulation before shunting and a better description of the disorder, as well as what its effects are on the blood flow, facts that have got important implications for shunting as well as understanding how shunting works, whether it has restored the CSF and the cerebral blood circulations and how to best select for shunting, including timing of shunting.

Resistance to CSF outflow in NPH

NPH is a heterogeneous disease characterized radiologically by enlarged ventricles and clinically by Hakim's triad: gait disturbance, urinary incontinence, and dementia. Since its first description in 1965, the works of Marmarou and the development of the lumbar infusion test by Katzman set the path for studying the CSF dynamics of the patients presenting with this clinical syndrome(2,12,64). Early trials such as those from Borgensen et al and the Dutch normal pressure hydrocephalus study, demonstrated that increased R_{out} (>12 mmHg*min/ml and >18 mmHg*min/ml respectively) was characteristic of NPH and strongly predictive of outcome after shunting(12,64–67). Unfortunately, more and more modern centres, despite guidelines, clinical and paraclinical test, discovered shunting responders varied from 40-80%, with the latter being the most frequent on modern, specialised centres. Moreover, new studies and trials failed to demonstrate the initially described as very high prognostic value of R_{out} for shunting(26,68,69). From the data available in Cambridge, one of the main modern centres to utilise infusion tests in NPH, we can

begin to understand the problems with Rout by comparing it to the results of trials from the other centres in **Table 1.1**. **Figure 1.3** illustrates the differences among centres in the reporting of the prognostic value of Rout.

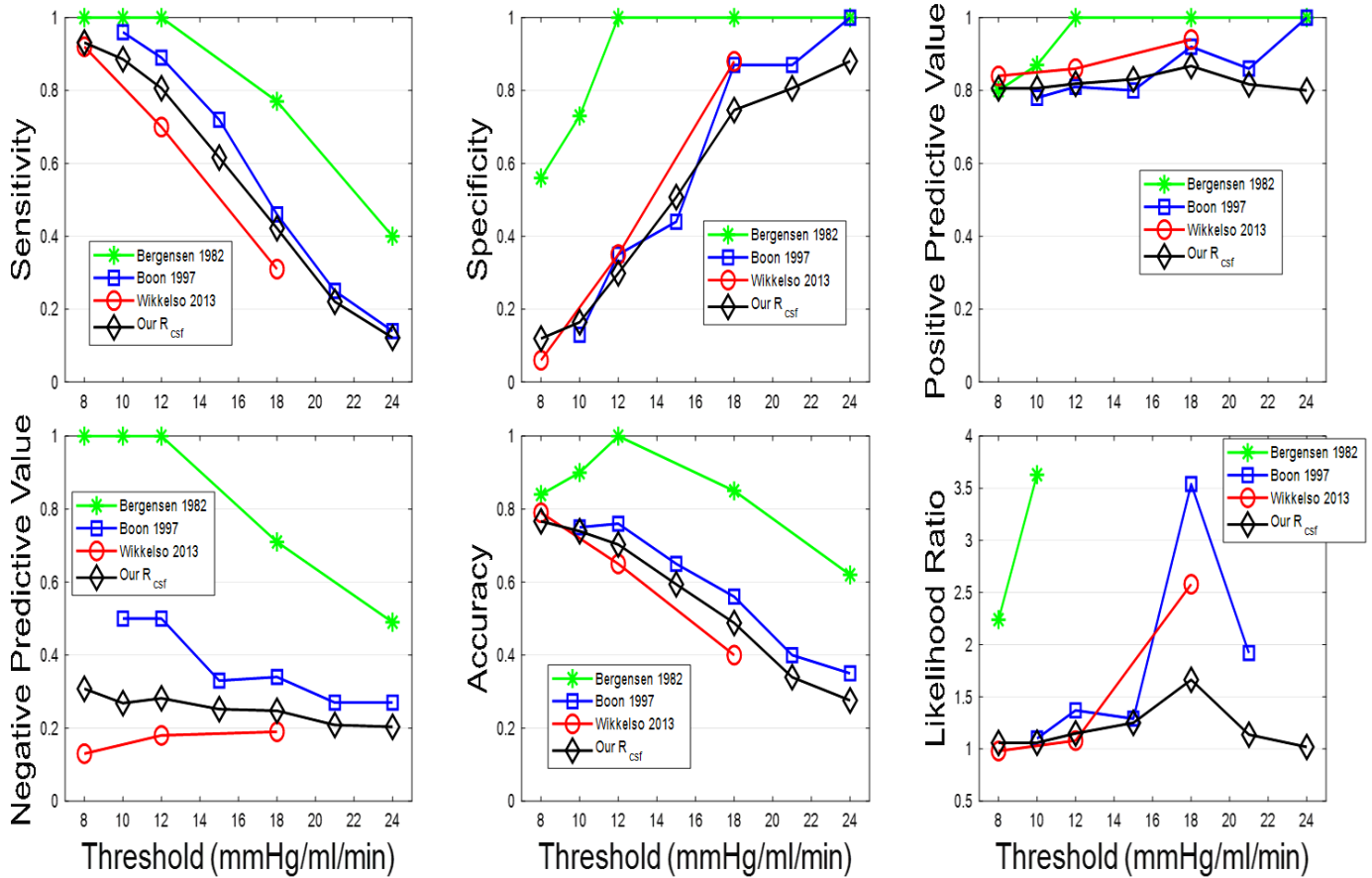


Figure 1.3 (Modified from Lalou AD, Asgari S, Czosnyka M et al *The role of CSF dynamics in Normal Pressure Hydrocephalus Diagnosis and Shunt Prognostication*; In press, *Acta Neurochir Suppl*): Comparison of centre-reported predictive values of Rout(26,62,63,66,67). All studies presented are single-centred except for the multi-centre trial of European iNPH by Wikkelse et al(26). The different Rout thresholds reported in each study are plotted against the absolute values for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy, as well as overall Rout likelihood ratio. Studies varied in numbers and aetiology of NPH, with overall the Borgensen and Dutch studies yielding the most optimistic PPV, likelihood ratio (LR) and sensitivity, and the European iNPH the most pessimistic, with a LR close to 1 for all Rout thresholds except 18mmHg*min.ml, signifying that Rout between 8 and 18 is barely related to outcome after shunting.

A summary of all studies and trials on Rout and outcome is shown in **Table 1.1**.

Table 1.1 (Modified)(70) Studies of Resistance to CSF outflow (Rout) in NPH: prediction of outcome after shunting.

Reference	NPH	Aetiology	Rout	PPV	NPV	Other main Findings
Borgensen et al (1982)(67)	80	mixed	≥ 12	96-100%	>95%	NA
Borgensen et al (1989)(66)	183	mixed	≥ 12	NA	100%	NA
Boon et al (1997)(63)	101	iNPH	≥ 12 & ≥ 18	80% & 92%	34%	Highest LR of 3.5 for Rout 18
Kahlon et al (2002)(71)	68	iNPH	≥ 14	80%	NA	Strong correlation of Rout with Outcome
Wikkelso et al (2013)(26)	115	iNPH	≥ 12 & ≥ 18	86% & 94%	18% & 18%	No correlation of Rout with Outcome
Nabbanja et al (2016)(62)	310	mixed	≥ 13 & ≥ 18	NA	NA	Rout correlated with outcome. Kruskal- Wallis Value >6.5 and >6.

Despite criticism, CSF circulation is still one of the main pathophysiological hypotheses of NPH and studies related to the resistance and other components of the intracranial compartment are essential until the complex puzzle of NPH is unravelled. Furthermore, shunting, with its hydrodynamic implications as shown in Figure 1.2 of this introduction, remains the mainstay of management of hydrocephalus, via drainage and reduction of Rout.

Whether other elements of the circulation or metabolism, such as the regulatory mechanisms of CBF are disturbed cannot be concluded based on previous studies(72,73). With an unknown state of cerebral haemodynamics, combined with a persistently unknown state of CSF dynamics, a need for direction on rigorous research, with detailed knowledge of these aspects and improved sample sizes emerges.

Furthermore, in 2005, the NPH guidelines study group concluded that a single standard for shunt prognostication in iNPH was lacking(4). New guidelines are yet to be developed, therefore despite the current clear definition, even the label of NPH remains uncertain, the concept of NPH as a whole recently coming to question. Among the burning questions in NPH are the behaviour of the resistance related to age and the aetiology of NPH (idiopathic, secondary and all causes under secondary), as well as its differentiation with cerebrovascular disease, questions that are extremely difficult to address, given the relative rarity of disease and the complexity of the ageing population. Some of these questions will be addressed in parts of this dissertation.

3) Understanding the cerebral circulation post shunting

When a pre-operative infusion has been performed, we are able to understand whether the shunt has made any difference in the patient's circulation by comparing the measured parameters pre and post shunting. In cases of no improvement, there is a margin to understand why some patients are probably getting more drainage than they require, or less, even none, in cases where the shunt is set at an inappropriate setting. Shunt infusion tests simply allow is to "look inside" a brain with an implanted shunt, describe the ICP and its parameters, assess the flow through the shunt and prevent excessive drainage before it causes unwanted effects.

A shunt, as a mechanical device, often malfunctions and fails. It is not easy to diagnose shunt malfunction in clinical practice, especially at an elderly brain. Shunt infusion studies provide objective and detailed information on the functioning status of a shunt(42,43,48,74,75).

1.5 Cerebral blood flow and autoregulation in CSF disorders

Intracranial hypertension is often linked to a vascular problem, either in the arterial or the venous compartment. It is known that ICP and cerebral blood flow (CBF) interact; the constructed Cerebral Perfusion Pressure [CPP; equal to mean arterial blood pressure (MAPMAP) - ICP] influences how cerebral vessels physiologically react

to changes in its value in order to maintain a constant CBF in the very well-described and well-known concept of cerebral autoregulation (CA). A simple model of the cerebral circulation inside a rigid skull (represented as a box), describes the interactions the cerebral blood and the CSF circulation from arterial blood inflow to CSF formation and venous outflow (**Figure 1.3**).

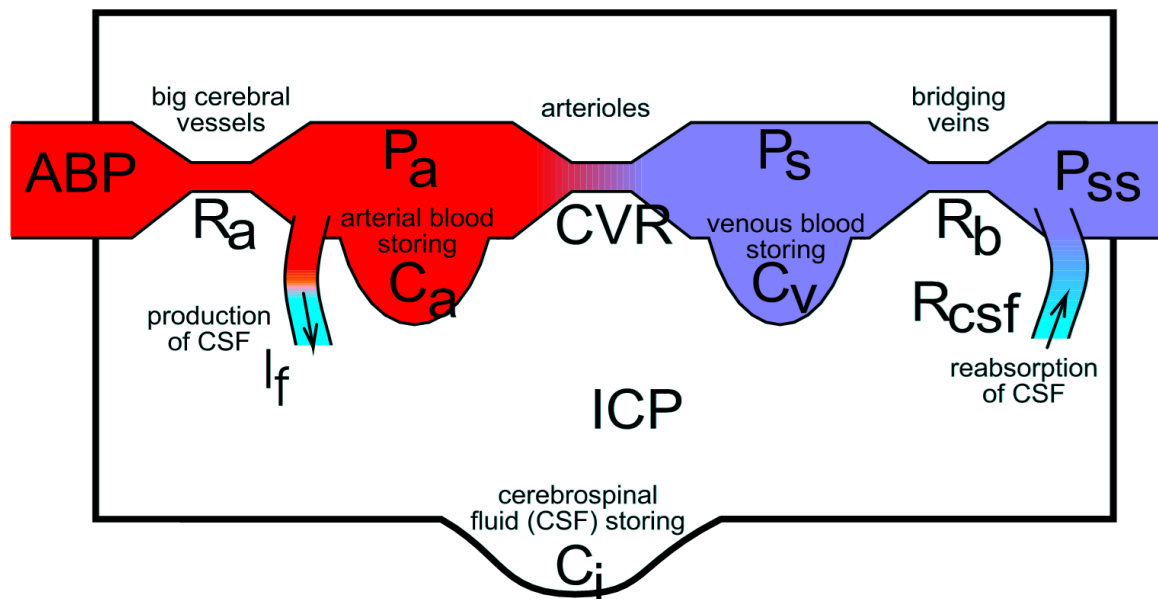


Figure 1.3 Global Model of Cerebral Blood Flow and Circulation of Cerebrospinal Fluid. The outer box represents the skull. C_i : CSF storing associated with the compliant dural sac within the lumbar channel. At the start of the pathway, arterial blood flows through the high resistance of large intracranial arteries (R_a) to the high-pressure arterial compartment (P_a); C_a =arterial compliance. CBF through the cerebrovascular resistance (CVR) vessels is influenced by autoregulation. Finally, venous blood (P_s : Pressure in the venous compartment + C_v : venous compliance) comes across the Resistance of venous outflow (bridging veins, R_b) and flows out to the sagittal sinus. In parallel, CSF undergoes formation, storage and reabsorption. Pathophysiological changes in any of the compartments and their interaction creates different disequilibria in flows and pressures. MAP: Arterial Blood Pressure, ICP: Intracranial Pressure, R_{csf} : Resistance to CSF outflow. From: Czosnyka M, Piechnik S, Richards HK, Kirkpatrick P, Smielewski P, Pickard JD. Contribution of mathematical modelling to the bedside tests of cerebrovascular autoregulation. *Journal of Neurology, Neurosurgery, and Psychiatry* 1997; 63:721-731(76).

The influence of vascular factors into the development and progress of NPH has been investigated over the last four decades, and a clear relationship between disturbed CBF/CA and NPH is suspected(15,73,77–79). Whether it is vascular factors driving the CSF circulation disturbance though, or vice versa, is not yet known and remains to be elucidated. Furthermore, a standardised method to quantify the two circulations and their interactions is yet to be demonstrated and the clinical implications of such a relationship are also yet to be specified.

Efforts to understand autoregulation in NPH should ideally be focused on understanding both circulations combined and separately, as much of the complexity in NPH is not only on the state of the CBF and CA, but also on its very definition, description and natural or pathological progression. The meaning of disturbed CSF circulation has come in contrast with the progression of the disease, the presence of atrophy (or even lowered CBF), as well as outcome after shunting(80). It is often difficult to investigate a CSF disorder diagnosis, early versus late disease and diagnosis versus shunting outcome in a logical and evidence-based time continuum. As such, mapping pathological intracranial circulation in all its complexity could contribute to elucidating some of the main unanswered questions in NPH, vascular disease and the ageing brain.

Alzheimer's disease and cerebrovascular disease (degeneration of the cerebral vessels due to chronic damage from hypertension and other vascular factors) are thought to be a lot more common in the elderly than NPH. This means that a) these conditions could often be coexisting with NPH, making their differentiation and characterization quite challenging b) part of those diagnosed with these disorders could instead be suffering with hydrocephalus(81–86), and since proper testing of the CSF circulation is not common in clinical practice, a misdiagnosis would have condemned them to inevitable decline and death, as highlighted above from its high prevalence in nursing homes.

Using a quantitative test such as the infusion tests, which could mark their CSF circulation parameters, as well as describe their cerebral blood flow, could therefore be of significant value in investigating and treating those patients.

CHAPTER 2

AIMS AND HYPOTHESES

Even though CSF dynamics studies have been consistently performed since over 40 years now, the clinical significance and utility of their derived information are still under scrutiny. Since brain physics laboratory in Cambridge exclusively acquires data from the bedside, I have focused on laying the foundations for reliably applying our results and interpretations back to the bedside.

My main thesis is very broad, reflecting the importance of understanding and treating CSF disorders as a continuum, both before and after shunting, and that clinical testing of the CSF circulation, ideally together with autoregulation, should be performed as an adjunct in all neurosurgical patients when clinically possible.

Hypotheses

In the course of my main thesis supporting projects, I formulated and subsequently tested the following hypotheses:

Hypothesis I: CSF dynamics in NPH requires investigation and assists in definition, diagnosis and appropriate management.

NPH has been traditionally known as a disorder of increased Resistance to CSF outflow (R_{out}). Despite evidence that questions the clinical validity and predictive value of R_{out} , an alternative explanation of the pathophysiology of the condition could not be described, to the best of our knowledge. Therefore, as derived from Davson's equation, it is the R_{out} that is increased and not the CSF production or the sagittal sinus pressure. Any interaction that disturbs the cerebral blood flow and its regulation in the brain could be reversed by lowering R_{out} through shunting. Other elements that compose the dynamic nature of ICP, such as compensatory reserve, could provide more insights as to why R_{out} does not always correlate with the clinical presentation and outcome after shunting.

Hypothesis II: PTCS is a disorder with characteristic CSF dynamics, resulting from venous outflow abnormalities.

Contrary to NPH, it is not the Rout but the venous pressure that are increased, and as a result of impaired venous absorption and high venous pressures, the excessive fluid produces characteristic patterns of depleted compensatory reserve and variation but generally increased CSFp and SSp. The pathophysiology likely is the same in both adult and paediatric patients. PTCS could be diagnosed and/or managed through careful exploitation of its pathophysiological CSF dynamics properties

Hypothesis III: Shunt testing in vivo with infusion tests is a highly accurate method for assessing shunt function that could improve the management of shunted hydrocephalus and PTCS patients.

Shunt testing in vivo has been utilised clinically for many decades. It is possible because of previous testing of shunts in vitro and knowledge of their properties and how they alter CSF dynamics. I aimed to show how the adaptation from the laboratory to patients works with high accuracy and how this changes the way a lot of shunted patients are managed.

Hypothesis IV: Detection of slow waves needs standardisation before it could reveal clinically useful information

There have been different methods reported in the calculation of slow waves in hydrocephalus, as well as optimistic and pessimistic clinical correlates. I aimed to explore the limitations and benefits of different algorithms, in order to conclude what the most accurate method could be and what the clinical significance of the magnitude of slow waves could be in larger cohorts of patients.

Hypothesis V: The CSF circulation and regulation of CBF interact in hydrocephalus, with diagnostic and outcome implications.

It is known that CSF and CBF interact, however exactly how dependent one is on the other and what this correlation means is not known. I have hypothesised that there

is a quantifiable dependence of the Rout and autoregulation and that the results of the quantified interaction could help in predicting outcome after shunting and mark degrees of cerebrovascular disease that either point away from NPH or make it irreversible.

CHAPTER 3

MATERIAL AND METHODS: THE CSF INFUSION TEST

My dissertation has mainly been built on retrospective studies, using material from the Brain Physics Laboratory. In all 8 of my original works, I have used this retrospective material, and on occasions and where necessary to increase the external validity of my findings, have supplemented it with some infusion tests collected prospectively. Those included infusion tests on non-shunted patients (via LP or Ommaya reservoir) or shunted patients.

Analytically, chapters and sections 5, 6.1, 7.1, 7.2 and 8 consist only of retrospective material. Section 7.2 has paediatric PTCS patients whose clinical data had been entered prospectively, with some infusion tests having been collected retrospectively but a few performed in 2016, at the beginning of my PhD. Chapter 5 also contains data with CSF infusion tests and arterial blood pressure monitoring, where the patients had been monitored before 2016, but some were followed-up after the infusion test during 2016.

3.1 Material

3.1.1 Infusion test database

Brain Physics Laboratory through the years has formed a database with over 7,000 infusion tests and overnight ICP monitorings of hydrocephalus and PTCS patients. Some of these patients date back to 1992, however most patients had been recruited after 2003, whereby ICM+ was launched and replaced its older version, ICM (4194 between 2003 and 2017, of whom 3533 had investigations for hydrocephalus of all aetiologies and 661 for PTCS). The monitoring modalities included ICP, with non-invasive MAP occasionally monitored via Finapres®(87–90).

Clinical information and reporting of radiological findings are also stored in the infusion database. Information includes symptoms, reasons for referral, general medical history, demographical details and report of CT/MRI as per expert neuroradiologist. All patients tested for NPH in Cambridge University Hospital have

documented and reported radiological evidence of ventriculomegaly on CT and/or on MRI scans, without significant and disproportionate to age atrophy, baseline CSF and at least two of or a complete Hakim & Adams triad (gait disturbance, cognitive impairment, urinary incontinence), including gait disturbance plus one or more of these features. When the documented details were not adequate to meet the objectives of a study, the documentation from their assessment at the Hydrocephalus Clinic was used. Until 2013, dementia was diagnosed by neuropsychologists and gait was assessed by physiotherapists. Detailed tests were performed, as part of research as well as clinical purposes. After 2013, cognitive and gait impairment were assessed by routine clinical tests. It has not been my purpose to assess those tests or link them with my current findings, therefore I have used the diagnosis provided by the consultant neurosurgeons, who make the final decisions on diagnosing and shunting. There is some data overlap with previous publications, with patients recruited from the same database in overlapping time periods.

Limitations of using infusion tests in Cambridge for NPH prognostication

Cambridge University Hospital has a nearly three-decade long history now of performing infusion tests for hydrocephalus (for PTCS it is slightly more recent(25,62,91–94)). Rout has been and remains one of the main parameters our neurosurgeons use in order to support and formulate their clinical decisions. Therefore, in addition to limitations related to the retrospective nature of my studies, it is likely that a lot of the results are at high risk of selection bias (mainly allocation bias).

3.1.2 Ethical approval

Health Research Authority approval was sought and granted when required and, in line with this approval and the protocol in the Cambridge University Hospitals NHS Trust, all the retrospective studies were conducted without separate approval from

an ethics committee. This applies to all the following studies performed using infusion tests including in my dissertation from now on (Total of 8 studies, Chapters 5-9).

All patients were investigated with infusion test within the clinical neurosciences department, or other paediatric departments in collaboration with clinical neurosciences as a part of routine clinical assessment. They (themselves or next of kin) all consented for these studies.

All 8 studies performed were registered and approved as clinically oriented service evaluations/quality improvement projects, with local trust approval. No additional information and consent for research project participation is required under those condition to include patient data in the below analyses and to access their medical records as a result.

Patient recruitment period was between 2003-2017 for all projects, except for a few additional patients between 1995 and 2002 for Chapter 5 and a few up to March 2018 for Chapter 6.2. These were before the Data Protection Act implementing the General Data Protection Regulation (GDPR) came into effect in the UK in May 2018.

3.2 Methods

3.2.1 Data acquisition

Data were recorded, safely stored, processed and analysed using ICM+ software (Cambridge Enterprise, UK, <https://icmplus.neurosurg.cam.ac.uk>). MAP and ICP waveforms were sampled at 30 - 50 Hz and amplified and digitalised to 100 Hz. ADL and MC (authors) independently searched and extracted articles. The disagreements that emerged regarding the final data synthesis were settled with JDP (third reviewer) who also lead and facilitated a relevant discussion.

A flowchart of patients recruited for each project of this dissertation is shown in **Figure 3.1**

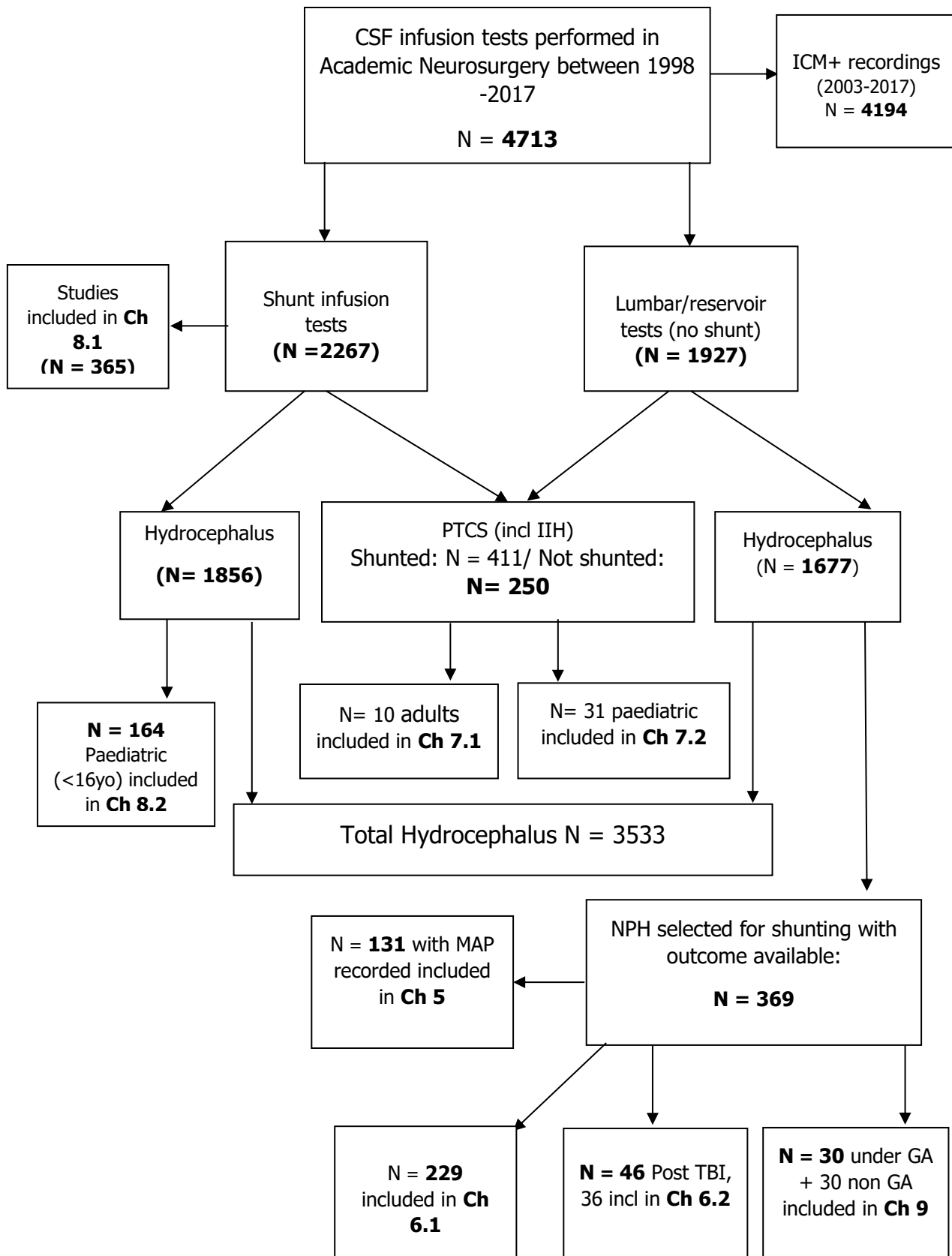


Figure 3.1: Flowchart of patients selection from all CSF infusion tests in the Brain Physics lab database for each of the projects included

3.2.2 Infusion test parameters and analysis

Infusion test procedure

There are different infusion techniques developed during the 1970s. Constant-rate infusion is the standard in Cambridge, as initially described by Katzman et al(64) for the lumbar test and adapted to its modern, computerised version. This constant-rate technique, after shunt testing in vitro, was applied for shunt testing in vivo to assess shunt function(42,48,75,95).

There are not very strict criteria for selecting a patient for infusion and they can vary from independent consultants. Criteria involve signs and symptoms of raised ICP (headaches, vomiting, developmental delay, attention deficits, behavioural issues etc) without changes in ventricular size, and are requested in order to assess the need for a shunt revision or safety for reassurance and transfer of care to a different specialty. Even at the presence of clear clinical and radiological signs, investigating the shunt in order to receive an accurate diagnosis of the shunt issue and the possible site of obstruction gives supporting information for planning treatment (e.g. locating the site of the obstruction so that only part of the shunt gets revised(44,96)).

ICP is assessed when the infusion set-up is connected to a line with direct access to the ventricles (shunt or Ommaya reservoir). When access to the CSF is gained via LP, then the pressure is referred to from now on as CSFpressure (CSFp). Although preliminarily a high correlation between these two pressures has been shown, there is no evidence that correlates them in either PTCS or NPH.

The procedure takes place as follows: A lumbar puncture is performed by the duty doctor with an 18-gauge Quincke needle after infiltrative local anaesthesia. Two 25-gauge orange butterfly needles are inserted when a pre-implanted Ommaya reservoir/shunt is in situ. In the first instance, the patient is lying on a left lateral decubitus position, whereas if an Ommaya is present, they are able to lay flat in the supine position. The edge of the needle is then attached to fluid filled manometer lines with a pressure transducer (Edwards LifesciencesTM) and pressure amplifier

(Spiegelberg or Philips) and ICP (or CSFp) waveform detected digitally in real-time using ICM+(95,97,98).

Once the expected waveform has been confirmed, CSFp is then recorded continuously and stored at a frequency of 30-100Hz. Baseline measurements were taken for 10 minutes, followed by infusion of Hartmann's solution at 1.5ml/min until the ICP had stabilised for 5-10minutes (plateau). As a safety measure, if ICP increased to 40mmHg or above the infusion was stopped. The total duration of the infusion tests was approximately 30 to 45 minutes. Once the infusion test was concluded, a tap test withdrawal of 30 – 50 mls of CSF is carried out prior to removal of LP needle and the patient was kept in hospital for observation for 4 hours. A representative example of an infusion test recording and analysis can be found in **Figure 3.2 (in next page)**.

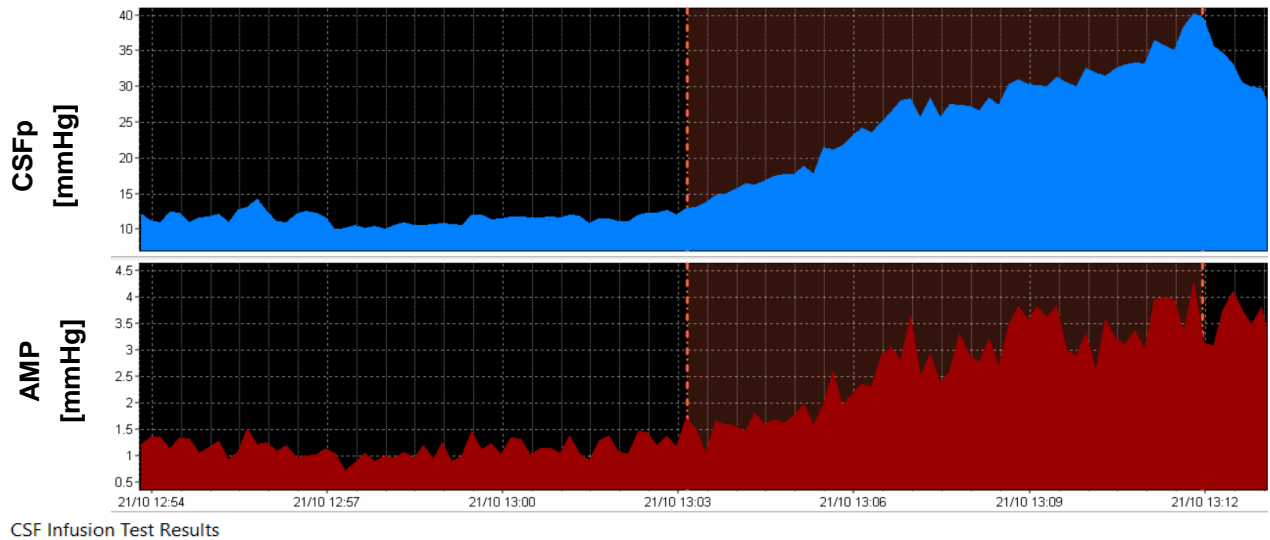


Figure 3.2: Representative example of a CSF infusion study recording and analysis of the test results.
Upper panel: Example of a lumbar infusion test recording of a patient with possible iNPH. CSFp (upper area) is monitored at baseline for 5-10 minutes and is gradually increased by Hartmann's infusion until a stable plateau. AMP (fundamental amplitude of ICP – dark red area) typically follows the increase of CSFp. **Lower panel;** CSF infusion test analysis using theoretical models integrated in ICM+ to optimise calculation of Rout and other parameters calculated during infusion test. Right curve: the solid, red line represents the theoretical model representing the response of CSFp to infusion at each time -baseline, during infusion and plateau. The fitted blue line represents the calculations performed by the interpreter of the CSF test and which should optimally fit the theoretical mode. Left curve: The solid, light blue line represents a similar model, where the calculations of the user (blue dotted line) should fit the Pressure – Volume curve as proposed by Marmarou (1974) and integrated in ICM+.

AMP

Pulse amplitude usually refers to the peak-to-peak amplitude of the ICP waveform, i.e. the difference between the systolic and diastolic peak of the wave (Figure 3.3 upper panel). However, in most of my work, unless referred to otherwise, AMP is automatically calculated through ICM+ as the fundamental amplitude of the first harmonic of the ICP pulse waveform (Figure 3.3 lower panel)(25,99–102).

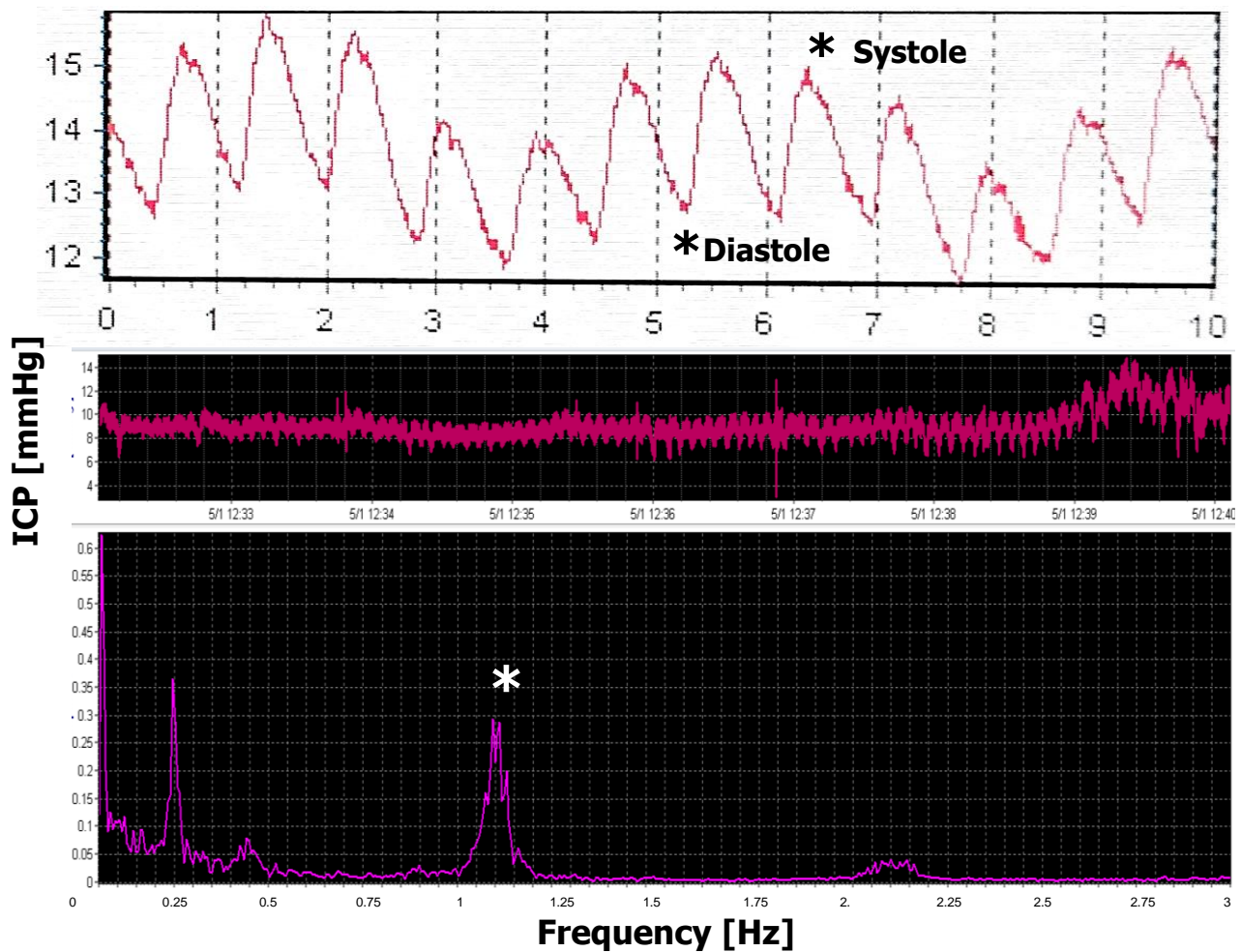


Figure 3.3 Peak-to-peak amplitude and fundamental amplitude of ICP. Upper panel: Pulse waveform of ICP. The difference between the systolic and diastolic peak represent the classic peak-to-peak amplitude. Lower panel: Time plot and spectral analysis of ICP, showing the fundamental amplitude of AMP marked with an asterisk. The rest of the peaks in the graph, from left to right, represent an initial spike that is produced by the rise in ICP, the slow waves, and last before AMP, the respiratory wave.

RAP

RAP is calculated as the moving correlation coefficient between ICP and AMP. The pre-configured infusion test profile in ICM+ automatically displays RAP through this moving 4-minute window that updates every 10 seconds(75,100,103).

RAP is generally more reliable when calculated from continuous ICP monitoring in TBI and overnight ICP monitoring in hydrocephalus(50,100,104–106). However, with a proper, artefact-free baseline of over 10 minutes, it is possible to calculate a reliable RAP,

although this has not been validated against overnight ICP monitoring. **Figure 3.3A** (upper panel) demonstrates an example where baseline RAP could not be calculated during an infusion test, versus the lower panel, where a longer, stable baseline allowed for a reliable RAP value to be generated.

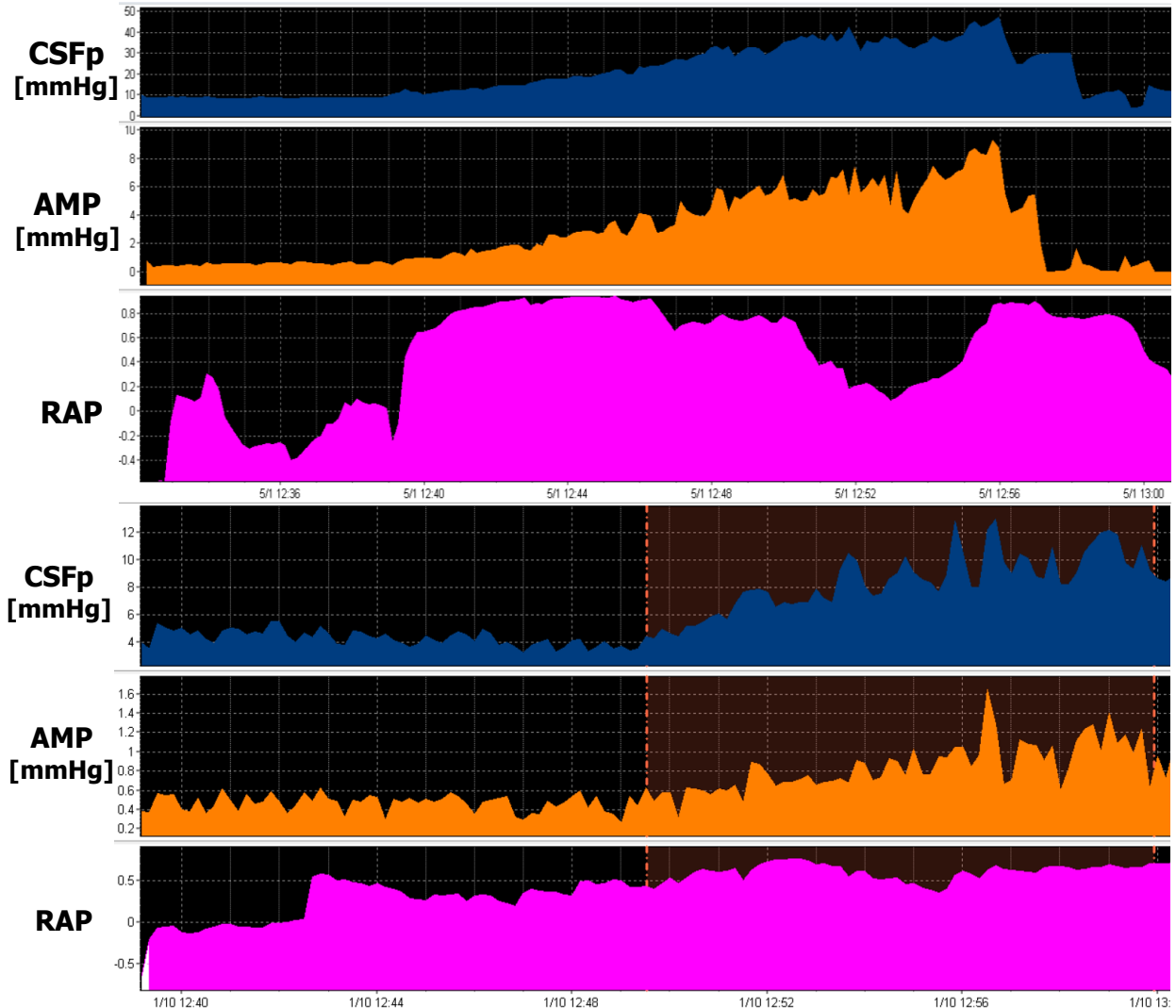


Figure 3.4 Baseline RAP calculation via CSF infusion test. Upper panel: ICP and AMP monitored at baseline, however RAP not calculated properly, as the monitoring period was short (4 minutes), which is also portrayed in the noisy recording of RAP. In all such cases, RAP is considered as NaN. Lower panel: Longer-term monitoring of ICP without artefacts allowed for a more reliable calculation of RAP after the first 4 minutes of monitoring. RAP baseline >0.6 is an indicator of depleted pressure-volume compensation.

AMP-P slope

AMP and ICP show a strong, linear correlation during infusion. Sometimes, a strong linear relationship is present at baseline, without any breakpoints of the regression

line (Figure 3.5 upper panel). Frequently, there is a breakpoint present, after which the relationship gains its stronger linear characteristic. This is referred to as the lower breakpoint of the AMP-P line (Figure 3.5 lower panel). The slope of the AMP-P line is strongly correlated to elasticity, as a steeper slope reflects the increase in pulsatility caused by decreased compliance(107,108).

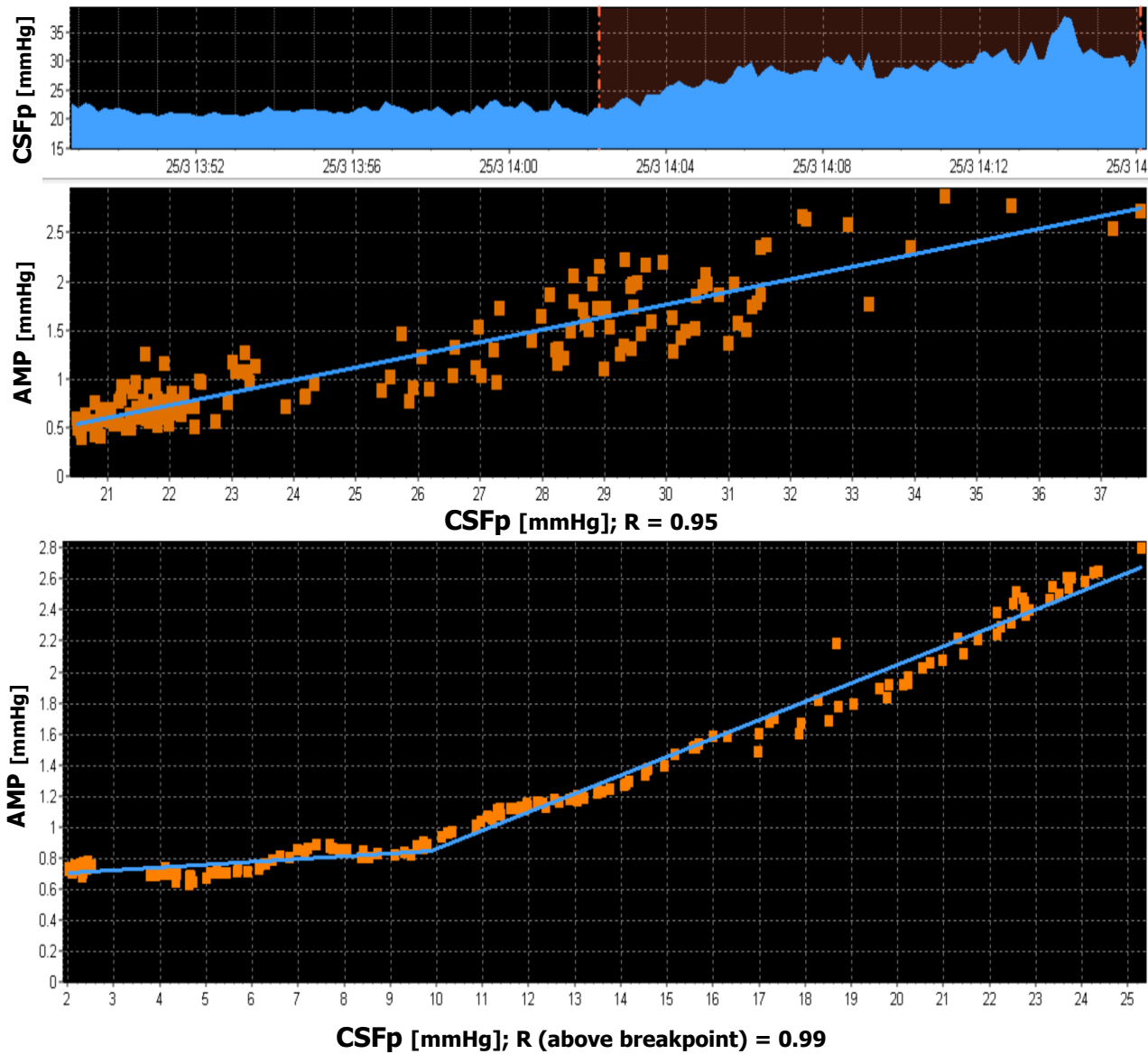


Figure 3.5 Slope and lower breakpoint of the AMP-P line. Upper panel: ICP and AMP correlate strongly, without a lower breakpoint. Lower panel: Lower breakpoint of the AMP-P regression line, whereby above the breakpoint the addition of volume during infusion causes steeper rise in pulsatility and pressure, as compliance decreases.

Elasticity

Elasticity is calculated automatically through ICM+ using the mathematical formula $Elasticity = 1/[C * (ICP - P_0)]$, where C is compliance (109–112) (**Figure 3.6**). P_0 is usually neglected or assumed to be similar to the Sagittal Sinus pressure (SSp). In ICM+ calculations, P_0 is estimated as the intercept of the amplitude-pressure line with the pressure axis. Nonetheless, Elasticity is not dependent on ICP, and a value <0.18 describes a compliant system, whereas a value >0.18 indicates depletion of pressure-volume compensation.

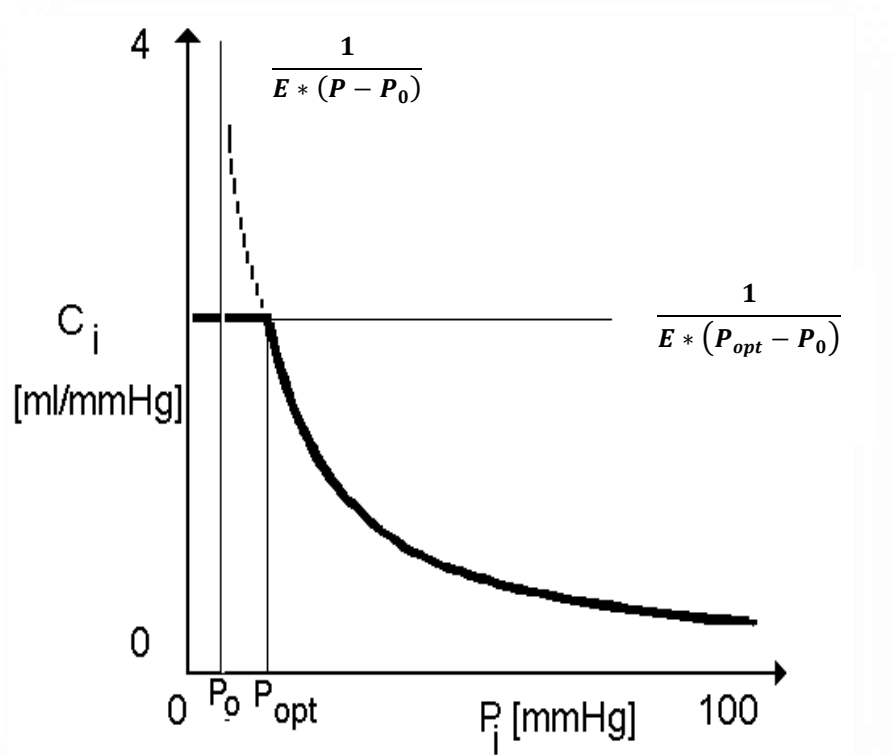


Figure 3.6 Relationship between compliance and ICP. Compliance (C_i) is dependent on ICP (P_i) via the formula at the top left: $C_i = 1/E*(P-P_0)$. P_0 has been reported as either insignificant compared to P and therefore could be omitted, or equal to Sagittal Sinus Pressure. In ICM+ calculations, P_0 is estimated as the intercept of the amplitude-pressure line with the pressure axis. Elasticity, or Elastance coefficient E , is constant and when increased, compliance is significantly decreased, therefore causing sharp increases in P_i .

Rout

Rout is calculated using Davson's equation ($ICP = Rout * If + SSp$). Since the infusion test consists of a steady-state ICP after infusion (ICP plateau) and a steady-state ICP before infusion (ICP baseline), the Rout calculated during an infusion test in non-shunted patients is derived by subtracting ICP_{plateau} and ICP_{baseline} from the Davson's equation formula. Therefore, the static formula for Rout is $(ICP_{plateau} - ICP_{baseline}) / If$, whilst If during infusion is the infusion rate used (1ml/min or 1,5 ml/min)(1,97,113–115). Rout estimation can be optimised by fitting the infusion test calculations to the in-software mathematical model.

In shunted patients, provided that the proximal end is patent and the shunt valve open, according to **Figure 1.2**, the Rout measured during infusion should be the Rout of the shunt, unless there is a distal obstruction, which increases this Rout.

Sedation, general anaesthesia and paediatric infusion tests

Sedation is strictly avoided in adults, due to possible and unconfirmed effects on intracranial circulation and difficulty in close monitoring of patients during the procedure. If adults cannot comply with the procedure, this will be attempted in operating theatres after general anaesthesia (GA) with close monitoring. We routinely perform lumbar and reservoir infusion tests in children under investigation for PTCS and hydrocephalus, as well as those already diagnosed or shunted. All children unable to cooperate in the fully alert state are studied under GA. Occasionally, mild sedation [chloral hydrate but mainly Entonox (nitrous oxide/oxygen mixture 50%/50%) inhalation during needle insertion] is given and, when feasible, children are studied fully conscious with parent (s) and play activities at the bedside. The procedure then takes place in the exact same way as in adults.

Complications associated with infusion tests

i) Lumbar infusion tests

I have not explored infections associated with lumbar infusion tests. From data of a previous internal audit (unpublished), our lumbar infusion tests infection rate has been shown to be quite low (<1%) and our aseptic technique quite effective. The overall tolerability of the invasive test, which uses a larger needle (18g) for a long period of time, and includes infusion as well as withdrawal, appears quite good. From a series of 562 patients reported in multiple centres from Sweden and one centre in Denmark, headaches and back pain 24hrs after infusion tests occurred in about 15% of patients, however were short lasting and disappeared within the next days(116). From our experience, we hardly ever see serious headaches or back pain post lumbar infusions, and only 1-2 patients/year will require hospitalisation for severe headaches after the procedure (from an average of 150 tests/year).

ii) Reservoir/shunt infusion tests

Similar to lumbar tests, reservoir/shunt test infection rate has been audited and shown to be quite low (<0.5%, unpublished data). I have also investigated the infection rate in the cohort studied in chapter 8.1

CHAPTER 4

CEREBRAL BLOOD FLOW AND AUTOREGULATION IN NPH: A SYSTEMATIC REVIEW

4.1 Introduction

Normal Pressure Hydrocephalus: pathophysiology

NPH remains, to the best of our current knowledge, the only reversible dementia. Its potential reversibility, combined with the suboptimal clinical understanding and limited shunt responsiveness, form a demand for elucidating its pathophysiology. Guidelines and best-practice recommendations have existed for a while and continue to be updated. Over 50 years since the Hakim and Adam description of the clinical syndrome, there is no good modern definition of NPH, nor better description of its underlying mechanisms. Few studies have sought to interpret imaging findings in the context of theories of NPH pathogenesis.(14,117,118) Furthermore, the division between idiopathic NPH (iNPH) and secondary NPH, is also based on a consensus and there exist barely any quantitative, adequately powered studies that have investigated the differences in pathophysiological sequelae between the two(119,120). Physiologically, it is known that the CSF and the cerebral blood circulation interact, hence many historical and current reports have focused on vascular factors -expressed in studies of Cerebral Blood Flow (CBF), including cerebral autoregulation (CA) in NPH. The interaction between hydrocephalus and disturbed CBF has been studied increasingly since 2001, with the development of new imaging methods(73,121–123).

Cerebral Blood Flow and its Regulation

The difference between Mean Arterial blood pressure (MAP) and ICP represents the constructed concept of Cerebral Perfusion Pressure (CPP). Cerebral autoregulation refers to the physiological, adaptive vascular responses in the brain to changes in CPP that maintain CBF relative constant. As such, the paramount role of autoregulation in maintaining a healthy brain, protected from ischaemic and hyperaemic insults has prompted a

plethora of investigations into its underlying processes. Most of them have been summarised analytically but still remain to be deciphered and applied therapeutically (124–127).

Current knowledge on cerebral blood flow and autoregulation in NPH

While CA has been extensively studied in healthy individuals, as well as diseases such as brain injury and stroke(49,128–135), the state of CA in NPH is more complex and ambiguous, with scarce studies putting CBF/CA into the context of the CSF circulation. Furthermore, there are no gold standard tests for the assessment of CBF as a diagnostic or prognostic tool or current systematic review of the methods. We have not aimed to attempt this with the current review.

Owler et al(73) systematically reviewed in 2001 the past efforts on implicating CBF and a few CA measurements in NPH diagnosis and outcome predictions, including reviewing the methods available at the time. With this review, important foundations in reviewing and designing studies to further our discoveries in the topic have been laid. The reviewers also concluded that: 1) There remained abundant ground for investigation in this area, especially related to CA 2) It is important to obtain sufficient numbers of patients and well-defined patient subgroups, one of the most important challenges in NPH. Definition of “normal pressure” and even NPH are not yet homogeneous enough globally 3) More detailed studies on regional CBF(rCBF) could shed some important light 4) magnetic resonance (MR) perfusion could be a promising technique for NPH 5) Concomitant studies of cerebral metabolism are needed, since there are no reports of whether reduced CBF could reflect a correspondingly reduced metabolism in NPH and 6) Relative findings in the field need to be transferable to the bedside and signify something for patients’ outcomes. Additionally to updating the previous systematic review and methodology, we sought to review the new information available thanks to new imaging techniques, not only in perfusion, but also in structural, especially microstructural studies.

4.2 Methods

We used the PRISMA checklist and flowchart for quality in systematic review reporting(136). From March 4th up to 31 January 2018, we performed a detailed search on Scopus, Cochrane, PubMed, Scopus and Web of Knowledge, using the key phrases “autoregulation in hydrocephalus”, “cerebrovascular reactivity in hydrocephalus” and finally “autoregulation/cerebrovascular reactivity AND hydrocephalus”, in order to extend the search to all studies related to CBF, CVR and CA in NPH. Study participants had to be patients with idiopathic or secondary NPH, measurements of their CBF and/or CA/other CVR test, comparing baseline state with post-surgical state and also magnitude of the symptoms with CBF/CA.

Results were filtered in order to yield manuscripts after 2001 (date of completion of the Oowler et al review) and up until 31/01/18. The language in which papers were written did not matter, since we had access to a vast majority of the world languages. The articles had to be published, and conference/other abstracts without a corresponding paper, unpublished work or work under publication were not considered

We looked into a wide spectrum of the NPH vignette: pre-shunting assessment of CBF or autoregulation at baseline and/or after CSF drainage or shunting; this was because at each step, baseline, post-shunting, or prognostic value, the relative questions related to the state of CBF and/or CA have not yet been answered. We weighed and compared all papers for consistency of references, background, analytical reporting of methods according to guidelines and checklists. Reasoning and drawing of conclusion in an unbiased manner, taking into account NPH literature and its pathophysiological considerations was an important factor for discussion.

We extracted data from all the original articles using piloted data forms; the forms underwent some dynamic changes during the data extraction when new data or information arose. The RTI tool was used to assess bias in observational studies(137). The QUIPS tool was used for assessing risk of bias for study participation, prognostic factor measurement and outcome measurement(137).

The GRADE tool was used to classify the diagnostic and prognostic level of evidence as High, Moderate and Low(138). In order to assign higher level of evidence in current findings, the following criteria had to be met in defining and selecting the NPH group, as reported in Owler et al(73):

- 1) Full or incomplete clinical triad/primarily gait disorder;
- 2) ventricular dilatation on CT/MRI without significant atrophy;
- 3) absence of focal neurological deficit or focal pathology on CT;
- 4) normal ICP/CSF pressure (<15 mmHg) (ICP monitoring or infusion study(56,95,139,140));
- 5) objective, well documented follow-up.

This review design and protocol can be accessed in the PROSPERO register, with its registration number CRD42018090946.

4.3 Results

A total of 51 articles met our criteria for the final synthesis, from an initial total of 3,597 from all databases (2,996 when duplicates were removed and only 373 relevant to the topic searched for). Results from the search were synthesised into 4 main categories: 1) global CBF & rCBF 2) CA and CVR 3) CBF after temporary CSF withdrawal and 4) CBF and CA/CVR post-shunting (with or without baseline reference).

Analytical results, including main findings are represented in **Tables 4.1-4.4.**

Table 4.1 A (modified): Summary of previous evidence and newer studies on baseline global CBF after 2001: N = number of patients included. iNPH = aetiology of NPH (idiopathic vs secondary). PC MRI: phase contrast MRI, tCBF: total CBF, PVWM: periventricular white matter, DSC MRI: dynamic susceptibility contrast perfusion MRI. The * denotes that the marker study included results on rCBF as well as tCBF.

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Bateman et al (2008) (156)	32	iNPH	Comparison between iNPH and healthy control pre-shunting	PC MRI	Total blood inflow, sagittal sinus outflow, relative compliance ratio all significantly ↓ in the NPH group compared to controls.	
Takaya et al (2010) (157)	14	iNPH	Pre-shunting iNPH CBF assessment & association with clinical symptoms.	MRI & SPECT	Hypoperfusion developed in all brain regions before the appearance of symptoms & was not correlated with the degree of symptoms in iNPH	
El Sankari et al (2011) (85)	13	iNPH	tCBF in iNPH vs healthy volunteers, amnesic Mild Cognitive Impairment & Alzheimer's disease	PC MRI	tCBF lower in iNPH than in a-MCI and tended to be lower than AD, but no different to healthy volunteers	
Szczepański et al (2012) (196)	40	mixed	BFV & PI assessment in pre-shunted iNPH & changes during CSF infusion tests	infusion test & TCD	increase of the pulsatility indices of BFV may indicate preserved autoregulation	No changes of BFV during infusion
Ziegelitz et al (2013) (158)	21	iNPH	Preoperative assessment of CBF in iNPH	DSC MRI	Decreased preoperative CBF in the global parenchyma.	perfusion deficits in PVWM, lentiform nucleus & hippocampus, not in thalamus
Qvarlander et al (2017) (159)	16	iNPH	Comparison between iNPH & healthy controls	PC MRI	Total CBF not lower in NPH compared to healthy individuals.	

Table 4.1 B (modified): Summary of studies on baseline regional CBF (rCBF) after 2001: *pCASL: Pseudo-continuous arterial spin labeling, eZIS: easy Z-score Imaging System. The * again denotes these studies included results on pre & post-operative CBF. The paper of Momjan et al, denoted with 2 asterisks, is repeated on table 2A and contains measurements of rCBF at baseline, autoregulation at baseline as well as CBF pre& post-operatively.*

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Owler et al (2004) (140)	17	mixed	Pre-shunt rCBF in healthy controls vs iNPH & iNPH vs secondary NPH	H2O PET& 3T MRI	Decreased rCBF in the thalamus, putamen and cerebellum of NPH compared with controls	Decreased rCBF in the same regions in iNPH vs secondary NPH
Momjan et al(2004) (161)	12	iNPH	CBF+CA pre&post-shunting & clinical improvement measurement	H2O PET &MRI	Poorest autoregulation associated with proximity to the ventricles	Same area showed greater restoration of rCBF after shunting which correlates with clinical improvement
Owler et al (2004) (160)	17	iNPH	Assessment of pre-shunted iNPH with CSF dynamics measurements	PET&MRI&infusion test	Mean rCBF decreased in the thalamus and basal ganglia & white matter regions.	These reductions significantly correlated with changes in ICP and with proximity to the ventricles.
Sasaki et al (2007) (164)	30	iNPH	Assessment of iNPH vs controls pre-shunting & correlation with symptoms	SPECT	Significantly decreased rCBF areas in the iNPH group compared with the normal control group.	Genuine urge incontinence with reduced bladder filling sensation associated with a global decrease of the CBF
Takeuchi et al (2007) (14)	44	iNPH	iNPH rCBF investigation pre & post-shunting	SPECT	2 cerebral circulatory disorders in iNPH: 1)at the cerebral cortical region & 2)at the thalamus-basal ganglia	reduced CBF pre-shunting. Post-shunting improvement of CBF frontoparietally,
Kobayashi et al (2009) (193)	12	iNPH	Comparison of rCBF in non-shunted iNPH vs Alzheimer's Disease	SPECT	In iNPH, enhanced perfusion in areas surrounding the cingulate gyrus, while no AD cases showed these findings.	Two-layer appearance in SPECT using eZIS could be a means to detect iNPH.

Table 4.1 B(modified): continues from previous page

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Yoon et al (2009) (166)	10	iNPH	Comparison of pre-shunting iNPH rCBF & correlation with cognitive decline	SPECT	rCBF changes in prefrontal & subcortical areas, associated with frontal subcortical circuit; the latter may contribute to the cognitive decline in iNPH .	The reduction of rCBF and clinical cognitive impairment are closely connected in patients with iNPH.
Virhammar et al (2017) (163)	21	iNPH	rCBF measurement in iNPH vs healthy controls	pCASL MR	reduced PVWM, lentiform nucleus & thalamus CBF compared with controls	cognitive function correlated with CBF in PVWM, cerebellum and pons

Table 4.2 A(modified): Summary of studies on baseline cerebral autoregulation in NPH after 2001. *TCD: transcranial doppler. Asterisk denoting that this paper is repeated in able 1B as well as contains information on pre & post-operative CBF. Rcsf: Resistance to CSF outflow*

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Czosnyka et al (2002) (175)	35	mixed	Global autoregulation pre-shunt with parallel CSF dynamics measurements	TCD&CSF infusion test	Increased resistance to CSF outflow associated with preserved autoregulation	autoregulation tended to be worse in patients with ischaemic changes in MRI
Momjan et al (2004) (161)	12	iNPH	Assessment of pre-shunt iNPH, post-shunted iNPH & clinical improvement measurement	H2O PET and MRI T1&T2-weighted	Poorest autoregulation associated with proximity to the ventricles	Same area showed greater restoration of CBF after shunting which correlates with clinical improvement

Table 4.2 A (modified): continues from previous page

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Czosnyka et al (2005) ⁽¹⁷⁴⁾	68	mixed	Global CA with CSF dynamics measurements & association with outcome post-shunting	infusion test +photoplethysmography	Disturbed CSF dynamics associated with preserved autoregulation	autoregulation tended to associate with outcome; preserved autoregulation tended to be associated with improvement post-shunting
Haubrich et al (2016) ⁽¹⁷⁶⁾	23	mixed	Assessment preoperatively in parallel with CSF dynamics	CSF infusion tests &TCD	Dynamic autoregulation is dependent on pressure-volume compliance	
Haubrich et al (2016) ⁽¹⁷⁷⁾	20	mixed	Assessment preoperatively in parallel with CSF dynamics	CSF infusion tests &TCD	Exhaustion of CSF compensatory reserve can limit CBF regulation	

Table 4.2 B(modified): Summary of studies on baseline cerebrovascular reactivity in NPH after 2001. *ACZ: acetazolamide. ASL: arterial spin labelling perfusion MRI. The asterisk denotes that the article contains information on pre- & post-operative CBF, and if marked so more information from other sections.*

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Klinge et al (2002) ⁽¹⁵⁴⁾	60	iNPH	global cortical CBF & CVR before & after shunting & before & after ACZ & correlation with outcome	15-O-H2O PET	Lower CBF in responders vs non-responders pre-operatively. CVR not different. CVR increased post-operatively in responders vs decreased in in non-responders.	early individual increases in CVR after shunting

Table 4.2 B (modified): continues from previous page

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Klinge et al (2002) (190)	57	iNPH	CBF & CVR in "high risk" and "low risk" groups (based on vascular risk factors)	15-O-H2O PET	CBF in "high risk" group decreased pre-operatively. CVR increased post-operatively. CVR in "low-risk" group decreased in non- responders vs increased in responders.	CBF in "high-risk" lower in responders vs non-responders
Klinge et al (2002) (153)	27	iNPH	CBF & CVR using ACZ before & after surgery, compared with neuropsychology	15-O-H2O PET	CBF & CVR reduced in different cortical regions in responders vs non-responders. Gait improvement related to increased CVR, visual attention and verbal memory	no relationship between neuropsychological tests & haemodynamics pre-operatively
Jarus-Dziedzic et al (2005) (169)	13	mixed	BFV at baseline & CVR after ACZ; comparison between atrophy, NPH and healthy age-matched controls	TCD	BFV at baseline reduced in both atrophy and NPH but at the lower limit of normal compared to the healthy age-matched group. CVR reduced in atrophic vs control group	BFV not different between atrophy& NPH, however CA better in NPH vs atrophy and not significantly different in NPH vs control group.
Chen et al (2008) (171)	28	iNPH	Comparison of 3 CVR measurements with sustainment of shunt response	Xe-CT, MRI and MRSI	In patients with relatively better average rCBF and ACZ challenge, rCBF could have a higher probability of better outcome.	Preop rCBF reduced in all. If normal in ≥ 2 CVR parameters, improvement is likely& lasts for 3 years
Chang et al (2009) (168)	162	iNPH	CBF and CVR in patients with full or incomplete Hakim triad pre-& post-operatively	SPECT and Xe-CT	No significant difference in preoperative CBF between responders and nonresponders. Preoperative CVR significantly impaired in responders compared to controls, but not in non-responders	Responders w incomplete triad:lower preop CVR, but not CBF, than controls. Full triad:significantly lower preop CBF & CVR than with incomplete Postop CBF &CVR increased in responders

Table 4.2 B(modified): continues from previous page

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Ivkovic et al (2015) (170)	25	iNPH	CBF pre-& post long-term ACZ administration	ASL MRI	Increase in tCBF in ACZ responders, combined with decreased white matter hyperintensities	Non-relevant findings related to white matter hyperintensities post drainage without CBF measurement

Table 4.3 (modified): Results of studies focused on CBF before and after temporary CSF withdrawal. *pwMRI: perfusion-weighted MRI. ACZ: acetazolamide*

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Mori et al (2002) (181)	22	Mixed	Pre-& post CSF drainage CBF in shunt responders vs non-responders	CSF removal & SPECT	Baseline clinical characteristics & baseline CBF values not significantly different between responders & non-responders. Post-drainage CBF changes significantly higher in responders.	> 80% increase in CBF after CSF removal was predictive of response to shunt surgery with 77% accuracy
Hertel et al (2003) (179)	27	iNPH	Preoperative STT combined with CBF for shunt response prognostication	STT & pwMRI /SPECT	Optimal results in post-shunting outcome achieved with a combination of preoperative STT & SPECT/pwMRI	results of SPECT and pwMRI correlated in 92 % of the patients (11 of 12)
Dumarey et al (2005) (182)	40	iNPH	CBF & gait measurements pre-& post STT & identification of post-shunting CBF changes	SPECT	Gait improvement at the STT in NPH associated with an rCBF increase localized in the bilateral dorsolateral frontal and left mesiotemporal cortex.	No statistical difference between pre- and post-STT SPECT images

Table 4.3 (modified): continues from previous page

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Walter et al (2005) (180)	28	iNPH	CBF pre- & post STT vs clinical tests for shunt outcome prognostication	PW MRI	Improved brain perfusion after STT can assist predictions of the postoperative outcome, as opposed to using clinical examination alone	
Virhammar et al (2014) (162)	20	iNPH	CBF before & after STT & comparison with gait improvement after STT	pCASL	In patients with increased CBF in lateral and frontal white matter after the CSF STT, gait function improved more than it did in patients with decreased CBF in these regions.	No significant increase in CBF after CSF removal compared with baseline investigations.

Table 4.4 A(modified): Results of studies focused on CBF before & after shunting, its possible predictive role and its behaviour post-shunting.

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Bakker et al (2002) (351)	10	iNPH	BFV before & after surgery	TCD	Higher BFV before surgery is related to clinical improvement after surgery.	
Diez-Castro et al (2003) (155)	20		Comparison of pre- & post-shunting global & rCBF and correlation with improvement after shunting	SPECT	Reduced global CBF at baseline associated with post-surgical improvement	

Table 4.4 A (modified): continues from previous page

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Mataró et al (2003) (352)	15	iNPH	Comparison of pre- & post-shunting global & rCBF and correlation with improvement after shunting	SPECT	Significant rCBF increase of both frontal lobes & right parietal lobe. The 2 areas most related to clinical improvement were right medial prefrontal region and the frontal part of the left lobule of Reil insula.	Increased rCBF in left prefrontal dorsolateral areas, right frontal premotor area, right medial prefrontal region, right frontal white matter area, right basal ganglia and inferior parietal lobule.
Tullberg et al (2004) (187)	28	mixed	Association of wakefulness with pre-&post shunting CBF & outcome	SPECT	Impaired wakefulness associated with reduced rCBF in the anterior cingulate cortex. Improved wakefulness post-shunt corresponds to increments in frontal and hippocampal rCBF.	Impairment of wakefulness is an important prognostic symptom in NPH that should be assessed.
Piechnik et al (2005) (189)	13	mixed	Measurement of rCBF pre- & post-operatively & analysis of difference	SPECT	No significant changes in rCBF post-operatively	
Murakami et al (2007) (192)	24	iNPH	Pre-operative rCBF in shunt surgery responders vs non-responders	3D-SSP SPECT +MRI	lower rCBF in the basal frontal lobes & cingulate gyrus in responders than in non-responders.	reduced rCBF in the posterior part limits the efficacy of shunt
Bateman et al (2008) (156)	20	iNPH	Pre-operative rCBF in shunt responders vs non-responders	1.5T Tq-T2-w MRI	normal/increased CBF, improved more than in decreased CBF.	
Klinge et al (2008) (188)	65	iNPH	Local and global CBF pre-operatively in clinically improving vs non-improving patients	H2O PET	In shunt responders, local CBF compared to pre-op increased. Significantly decreased in the same areas in non-responders.	Global blood flow did not show any correlation with pre- & postop status based on the clinical score of gait and cognition

Table 4.4A (modified): continues from previous page

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Ishii et al (2011) (184)	84	iNPH	Recognition of CBF reduction patterns characteristic of NPH & shunt-responsive NPH	SPECT	3 different patterns of CBF reduction recognized.	No predictive value of CBF. could reflect the severity of the disease as measures by MMSE & rankin pre-shunting
Ziegelitz et al (2014) (158)	18	iNPH	CBF in shunt responders vs non-responders & in low vs high intensity of symptoms	CT-perf	No CBF difference between responders & non-responders. In responders, CBF recovered potop by 2.5-32%, but remained significantly decreased in the PVWM of non-responders.	The pre & postoperative CBF of cortical and subcortical regions correlated with the intensity of symptoms.
Ziegelitz et al (2015) (186)	32	iNPH	Measurement of pre & post-op CBF changes in shunt responders vs non-responders; measurement of CBF pre & post STT for shunt prognostication	CSC MRI	Post-operative rCBF correlated with clinical improvement and whole brain CBF changes in the responder group were significantly higher than in the nonresponder group	Increase of more than 80% in CBF after CSF removal was predictive of response to shunt surgery with 77% accuracy.
Tuniz et al (2017) (197)	23	iNPH	Perfusion measurement pre& post-operatively between selected vs non-selected for shunting	pw&dw MRI	increased perfusion post-operatively to selected for shunting (all improved) vs decrease in non-shunted.	perfusion & diffusion positively correlated in basal ganglia but negatively in PVWM

Table 4.4 B(modified): Results of studies focused on CVR before & after shunting. *Xe-CT: xenon-enhanced computed tomography. Asterisk denoting the article contains information on baseline CBF & CVR as well.*

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Klinge et al (2002) (167)	60	iNPH	global cortical CBF & CVR before & after shunting & before & after ACZ & correlation with outcome	15-O-H2O PET	Lower CBF in responders vs non-responders pre-operatively. CVR not different. CVR increased post-operatively in responders vs decreased in non-responders.	early individual increases in CVR after shunting
Klinge et al (2002) (168)	57	iNPH	CBF & CVR in "high risk" and "low risk" groups (based on vascular risk factors)	15-O-H2O PET	CBF in "high risk" group decreased pre-operatively. CVR increased post-operatively. CVR in "low-risk" group decreased in non-responders vs increased in responders.	CBF in "high-risk" lower in responders vs non-responders
Klinge et al (2002) (169)	27	iNPH	CBF & CVR using ACZ before & after surgery, compared with neuropsychological tests	15-O-H2O PET	CBF & CVR reduced in different cortical regions in responders vs non-responders. Gait improvement related to increased CVR, visual attention and verbal memory	no relationship between neuropsychological tests & haemodynamics pre-operatively
Chang et al (2003) (167)	48	SAH	Comparison of CBF & CVR measurement before & after shunting	tec99m HCMP & ACZ	lower CBF& CVR in 30 shunt responders compared to normals. Postop CBF&CVR increased significantly in 21 shunt responders but not in non-responders	reduced CVR but not CBF in asymptomatic ventriculomegaly compared to normals. 4 non-responders with reduced CBF but preserved CVR.
Chen et al (2008) (171)	28	iNPH	Comparison of 3 CVR measurements with sustainment of shunt response	Xe-CT, MRI and MRSI	In patients with relatively better average rCBF and ACZ challenge, rCBF could have a higher probability of better outcome.	Preoperative rCBF reduced. Normal results in >2 CVR parameters indicative of improvement with durability >3 years

Table 4.4B (modified): continues from previous page

Ref	N	iNPH	Study Design	Method	Main Findings	Other main Findings
Chang et al (2009) (147)	162	iNPH	Comparison of both CBF & CVR in full or incomplete Hakim triad pre- & post-operatively	SPECT and Xe-CT	No difference in preop CBF between responders and nonresponders. Preop CVR impaired in responders compared to controls, but not in non-responders	Responders w incomplete triad: lower preop CVR, but not CBF, than controls. Full triad: lower preop CBF & CVR than in incomplete. Postop CBF & CVR increased in responders
Yamada et al (2013) (165)	25	iNPH	Pre-operative CBF & ACZ, association with outcome & comparison with healthy individuals	SPECT + ACZ	<20% increase in preoperative ACZ SPECT predicted improvement of MMSE score with 100% sensitivity and 60% specificity. CBF & CVR reduced at baseline compared to normal.	Diffuse reduction in global CBF pre-shunting similar to patients with ventriculomegaly due to age. No postoperative increase in CBF.

4.4 Discussion

A) Methodologies

a) Assessment of Cerebral Blood Flow without Cerebral Autoregulation

As stated in the design of this review, it has not been our current objective to review the methodologies used in imaging/measuring or monitoring CBF. The different methods of imaging CBF have been previously reviewed(73), although since then several new methods have emerged, mainly perfusion MRIs. There are many fundamental questions in the subject of CBF/CA that need to be carefully reviewed besides methodology: The relationship between CA and age is not well established, however this is not the case for CBF, where many studies have addressed this question. A synthesis of the evidence related to CBF/rCBF also remains to be completed. SPECT, perfusion MRI and PET imaging initially lacked standardisation. After several new guidelines, consortiums and reviews of imaging methodology, a lot of recent papers have managed to achieve appropriate segmentation and number of voxels in defined regions of interest(140–143). However, most studies do not report in great detail how they achieved appropriate segmentation and how they avoided artefacts and influences of nearby structures. Therefore, a very rigorous review of these methodologies is required before assessing the pathophysiological value of these findings.

b) Cerebral autoregulation and cerebrovascular reactivity assessment methods

i) Reactivity to Acetazolamide (ACZ) and CO₂

Reactivity to ACZ and to CO₂ inhalation can be examined using imaging and TCD. Both CO₂ inhalation and IV ACZ, with their vasodilatory effect, are expected to cause an increase in CBF. These methods had been used more widely in the past for CVR assessment and had yielded some interesting results on the state of CVR pre and post-shunting (144,145).

ii) Cerebral Autoregulation & CSF dynamics assessed using infusion tests

The CSF infusion test, despite the short time-frame of recording (~45 minutes), provide a unique method for measurement of CA/CVR using primarily a static method and even dynamic ones if combined with a TCD and any other CBF, CVR and CA assessment methods. It is important to remember that reliable ICP monitoring, as provided mainly by overnight ICP monitoring or CSF infusion studies is almost a requirement when assessing NPH patients, especially when assessing CA in NPH at a research if not at a clinical setting in what is so far the most reliable methodology(76,79,124,125,146).

The global autoregulation index, PRx, is thus calculated as the correlation coefficient between ICP and MAP, reflecting the reactivity of the vascular bed to changes in MAP (50,87,131,147–149). CPP significantly decreases during infusion, mainly because MAP stays almost constant and ICP is artificially increased. It is useful to assess CBF during infusion studies or other estimates that could reflect ischaemia and the reaction of the vascular bed to spontaneous, intermittent ICP increases(140,150).

B) Discussion of results

1) Baseline global and regional Cerebral blood flow

The previous review of the evidence suggested a possible reduction in tCBF at baseline in NPH(73,77,78,121,151). Isolated CBF measurements appear to have overall produced contradictory evidence and remain difficult to interpret, not only due to the variety of imaging techniques but also due to highly contradictory reports. The previous(152–155)s review also directed towards more evidence on rCBF patterns in NPH compared to normal ageing and Alzheimer's, shifting priorities towards this direction. Some of the rCBF reduction patterns reported already before 2001 were the frontal cortex and subcortex and thalamus. We identified 29 studies in total, investigating the state of global CBF in NPH at baseline. Most of these studies (17/29), were focused on identifying a specific pattern of CBF reduction instead of searching for a global reduction of CBF. There were 4 studies(85,156–158) that reproduced

previous findings of global cerebral hypoperfusion, however recent original papers agree that either CBF is not globally reduced or the degree of reduction is associated with clinical severity and vascular factors(140,159–162). Momjian et al (161)investigated the white matter regional CBF in 12 iNPH patients using H₂(15)-O PET and discovered a pattern of increasing reduction from distally in the white matter to proximally in the lateral ventricles. Owler et al reported hypoperfusion in the thalamus, putamen and cerebellum at baseline, as well as no difference in these patterns between idiopathic and secondary NPH patients(140,160). Other groups agreed(14,163,164), and different patterns included the thalamus and basal ganglia region, as well as the hippocampus and the cerebral cortex ; a few studies did not find these expected regions to be hypoperfused. (158,162,165,166) Notably, detailed ICP or other CSF dynamics monitoring was utilized only in the Momjian and Owler studies.

2) Baseline cerebral autoregulation and cerebrovascular reactivity in NPH

Already in 1998, the first study on regional CVR had been attempted, with other CVR studies around this time adding towards a possibly reduced response to ACZ and CO₂ preoperatively. Overall, very few studies resort to testing CVR anymore. No one attempted to use CO₂ as a reactivity test in NPH patients, with the 5 studies in total testing reactivity to ACZ. 3 of the studies tended to consistently agree that CVR was reduced in NPH compared to normal controls, however 2 out of the 3 involved post-SAH NPH patients, and the results cannot be applied to iNPH(165,167,168). The remaining 2 studies indicating preserved baseline CVR involved iNPH and mixed iNPH with secondary NPH; furthermore, the iNPH study involved long-term administration of ACZ with CBF testing afterwards(169,170). Therefore, results remain contradictory and with different aetiologies needing to be studied separately. Furthermore, none of the studies report a power analysis, even though they used normal controls and there was already similar evidence in the literature that could serve as reference(76).

Unlike CVR, testing of CA required ICP. Concomitant studies of CSF circulation and cerebral metabolism has been shown to be crucial in NPH patients, due to the interactions between CSF dynamics, CBF and CBO (131,171–173). Since CSF diversion is the main treatment strategy for these patients, it is impossible to ignore the CSF dynamics investigations in any effort to produce viable, applicable to the bedside methods of CBF/CA investigations.

To the contrary, the studies that have attempted measuring either global or regional CA are sparse. There have only been 5 studies since 2001 investigating autoregulation in NPH, all derived from the same centre in Cambridge, UK(161,174–177). CA and CVR in NPH probably form pieces of a complex puzzle, as derived by different studies showing different patterns of autoregulation depending on the presence of white matter lesions, exhausted compensatory reserve, Resistance to CSF outflow and other known factors. Adding to this the not very well-explored flow-metabolism coupling, the field is still under development and will require more multidisciplinary, combined investigations and patient stratification in the future.

3) CVR & CBF as measured by imaging in response to temporary CSF withdrawal

a) CBF before & after Spinal Tap Test

Previously, the STT, which consists of removal of 10-60 mls of CSF, was most commonly used in order to diagnose and select NPH patients for shunting (11,178). 9 such older studies had produced conflicting evidence on CBF before&after CSF withdrawal, reporting various degrees of increase and even decrease of CBF post STT. Differences in the imaging techniques as well as the timing of performing extra tests to assess the CBF response were and remain extremely variable among subjects and more importantly, the methods and the patterns of CBF reduction/alteration in NPH were still not standardised and unknown in many cases. The combination of STT and perfusion- weighted MRI or other perfusion imaging methods could have shown promise, but the results were inconclusive (179,180). Therefore, these studies inclined towards the fact that the change in CBF after CSF removal was not useful in

predicting outcome. The study of CBF after 30-50 ml of CSF removal does not appear to have clinical utility(181,182) .

b) CBF before & after Extended Lumbar Drainage

ELD has recently been implemented as the preferred predictive tool for shunt response in NPH, giving rise to new studies being designed around this clinical investigation. A study used MRI in iNPH patients following oral ACZ and ELD and mainly concluded that white matter hyper intensities decreased in ACZ & ELD responders to a significantly higher degree than in non-responders. While it is useful to quantitatively measure response to all these tests, the literature on the correct approach appears to be sparse, and sustainable, bedside-oriented approaches appear to lack (162,181). ELD remains to be evaluated in clinical practice, and perfusion scans concomitantly to ELD have not been performed, most likely due to questionable cost-effectiveness of all these implementations.

c) CBF & metabolism

The reversibility of NPH and possible restoration of CBF/CA could depend on the cerebral metabolism. Speculations around NPH involve that it is not a metabolism, but a flow disorder and it would be interesting to study this in the context of immediate CBF restoration, if it exists, after temporary CSF withdrawal, or shortly after shunting. Notably, we found no such published studies and there was only one paper that measured both rCBF and metabolism in NPH patients, claiming a significant correlation between the two pre-operatively(172). It is generally reported that the metabolism, on top of CBF, is reduced in NPH and the above finding should prompt more investigations of the flow-metabolism coupling in NPH, as well as its behaviour pre- and postoperatively(161,172,183).

4) Predictive role of CBF pre-operatively

As mentioned earlier, none of the studies trying to look into the predictive role of pre-shunting CBF were designed or powered in a systematic way to conclude with some degree of certainty on the predictive role of CBF in shunt response. 4 studies correlated decreased global baseline CBF with better clinical outcome(152–155),

whereas 3 concluded that there is no role of pre-CBF in shunt response(168,184,185). 12 studies [Table 4.4A accordingly] were able to identify different rCBF patterns where reduction was correlated to clinical improvement post-shunting, however there was no unified agreement between the different reported findings, since different studies used prominently different methodology and looked into different patterns as a reference.

a) CBF in shunt prognostication and its behaviour post-operatively

Assessment of outcome after CSF diversion is in itself a subject under development. Preliminary studies before 2001 had not consistently shown any relationship between CBF and outcome. 8 identified studies tend to agree that restored CBF and even rCBF in certain regions after CSF diversion surgery could be an objective marker of improvement, correlating with clinical improvement when assessed carefully. No response to shunting respectively lead to no change in CBF(168,186–188). On the other hand, 5 studies attempted to prove the prognostic role of CBF at baseline, 3/5 showing a positive correlation between reduced CBF and shunt response and one of those identifying specific patterns. From the other 2, one showed no prognostic role and one successfully combined rCBF with 2 CVR measurements in order to increase its prognostic value(168,171). 3 of the aforementioned studies on CBF restoration also showed no prognostic value of CBF pre-shunting(153,186,189)

b) CVR as predictive marker of shunt response and its post-operative behaviour.

Preliminary evidence from the previous review were initially pointing towards no predictive role of preoperative CVR. We have now reviewed 4 studies reporting that worse rather than good reactivity to ACZ predicts a favourable outcome(152,153,168,190). One of them (190) interestingly stratified the patients in different groups depending on cardiovascular burden, resulting in worse reactivity predicting shunt responsiveness for high cardiovascular risk, however better reactivity was related to shunt responsiveness in those with low cardiovascular risk. This is an interesting finding that again highlights the importance of consideration of the degree of cerebrovascular disease in iNPH. 5 out of 5 studies that measured CVR

post-operatively agree it is significantly increased compared to pre-operatively and that restoration of CVR is a hallmark of shunt responsiveness(153,154,171,190,191).

Notably, there haven't been enough patients in the studies to associate global/regional autoregulation alone with outcome yet. CA and outcome after shunting showing different patterns of autoregulation depending on the presence of white matter lesions, exhausted compensatory reserve and other known factors, that the field is still under exploration and will require more investigation and patient stratification in the future.

c) Cerebral autoregulation and CSF dynamics in relationship with outcome

There were previously no articles involving monitoring and interpretation of CA in NPH. Since 2001, using TCD in a preliminary study with a small sample of patients, intact CA was shown in patients with raised Rout, versus impaired autoregulation in those patients with a low Rout; CA was measured using Mx. This inverse correlation was replicated in a later study by Czosnyka et al, this time using PRx as an index of global CA, with again a small number of patients. Most recently (70), the same correlation between PRx and Rout was replicated in a large cohort of NPH patients and also correlating the combination of disturbed autoregulation and high MAP with worse outcome after surgery. MAP was measured non-invasively in all of the above, PRx derived from non-invasive MAP having previously been validated(87). These studies highlighted the importance of preserved autoregulation prior to shunting in hydrocephalus and are in agreement with the burden of vascular disease on the cerebral mantle. Furthermore, they could be in line with the studies that correlate the severity of clinical symptoms and the chronic persistence of the disease with worse CBF and worse outcome (153,157,187,192,193).

Early experiments have demonstrated the pattern of increasing ICP in relationship to compensatory reserve, when volume is added in the brain known as the pressure-volume curve.(75,100,112) It is therefore known that, when the compensatory reserve is exhausted, CSF dynamics change rapidly compared to a state of normal compensatory reserve. It was similarly demonstrated in two papers that vascular compliance could be compromised, bearing potential weight on the ongoing disease

progress. Therefore, there is accumulating evidence that CSF and the vascular bed do not react autonomously in the mechanisms of the disease's pathogenesis and pathophysiology(176,177,194,195) . The loss of compliance of the cerebral parenchyma could precede or occur around the same time as CVR dysfunction and could have significant diagnostic and other clinical implications. These reports are preliminary and require new studies to validate the compensatory reserve hypothesis.

Overview and grading of evidence

After carefully reporting and reviewing the past and present research on CA in NPH the following could be stated:

On CBF in NPH:

- 1) Based on the previous as well as the current systematic review of the literature, there is no clear evidence of decreased, normal or even increased global CBF in NPH at baseline(14,157–159,196). Evidence has most likely revealed regional CBF patterns in specific regions and some correlation of reduction and duration/severity of symptoms (85,196,197). Overall, there is a high level of evidence on the presence of periventricular white matter pattern reduction of CBF in NPH, with moderate to low evidence of globalised hypoperfusion which could depend on different progressions of the burden of the disease.
- 2) There is no strong evidence of using imaging of CBF before surgery as a prognostic factor for shunt response(157,162–164,186,196). Combined, there is a low level of evidence of a specific predictive CBF or rCBF pattern in shunt response in NPH.
- 3) Post operatively, CBF returns to nearly normal or normal values (as expected by age-matched, healthy individuals). This restoration of CBF has been associated with clinical improvement after shunting(185–188,197) . This leads to a moderate level of evidence pointing towards CBF or even more strongly CA increasing after shunting, biologically marking improvement in patients' symptoms.

- 4) Combination of CBF imaging and drainage tests seems promising but nowadays the tendency for ELD has not been successfully combined with other measurements and is strictly aimed at clinically simulating the shunt's drainage (179,181,182). There is a low level of evidence that measuring CBF before and after CSF removal could be assistive in predicting shunt response.

CVR & CA in NPH:

There have not been enough investigations of CA in order to apply any level of clinical useful evidence to its use. However, there are some interesting findings associated with CA that could be assistive in designing future investigations and trials:

- 1) Studies on CA have been few, yet the number of CA investigations in NPH has still not increased, but instead has significantly decreased, while CBF studies have continued to be carried out in the same pattern (140,161,174). There were no prospective or randomised trials on CA.
- 2) From the existing studies, CA appears to play a role in investigating the mechanisms underlying CSF and CA disturbance(160,161,174,175) .
- 3) Global, unlike regional CA could be preserved in shunt responders, in contrast to disturbed CA in non-responders, both pre and post shunt insertion(174,175) .
- 4) CSF dynamics combined with assessment of CBF and CA/CVR, provide a solid ground for the assessment of CA combined with many different techniques, as well as the investigation of the relationship and the interaction between CSF circulation and CBF (35,73,161,174,175,198).

Bias assessment: Moderate to high risk of selection and prognostic factor measurement bias was unfortunately frequent in the current evidence, mainly due to the absence of unified criteria on defining and selecting the study participants. Furthermore, there are no randomised trials specifically designed to assess outcome in the current literature, utilising CBF or CA/CVR as a prognostic factor. As observed in the previous systematic review, stricter definition and inclusion criteria require

agreement between authors and priority should be shifted towards producing higher level evidence, with reduced risk of bias, on this topic.

Future directions

Autoregulation in hydrocephalus shows a lot of promise, possibly both for diagnostic and outcome predictive purposes.

Continuous ICP recordings combined with CA assessment are needed from more neurosurgical patients.

Different methods of autoregulation combined with brain imaging need to be performed and compared.

Unified consensus on criteria, as well as methods and investigations at a research setting, independent of clinical guidelines and criteria, might be helpful in generating higher quality of evidence. More randomised controlled trials based on this could elucidate the big question of the cerebral circulation in NPH and when its disturbance is reversible.

Conclusions

Autoregulation, as assessed by imaging, infusion studies and the different existing methods, seems to be universally accepted by authors as a key in differentiating NPH from the spectrum of “shunt-resistant” dementias, which could involve NPH with comorbidities (NPH with cerebrovascular disease, atrophy, etc) or a different disease from NPH (atrophy, Alzheimer’s disease, Parkinsonism, etc, alone).

CHAPTER 5

GLOBAL CEREBRAL AUTOREGULATION, CSF OUTFLOW RESISTANCE AND OUTCOME FOLLOWING CSF DIVERSION IN NORMAL PRESSURE HYDROCEPHALUS.

The results presented in this section have been published in Journal of Neurosurgery:

Lalou A, Czosnyka M, Garnett M, et al. Cerebral Autoregulation, CSF outflow resistance and outcome following CSF diversion in Normal Pressure Hydrocephalus. 2018; 160:1097–103.

5.1 Introduction:

In the introduction and chapter 3 of this dissertation, I have described what we know about NPH and the importance of understanding how to reverse it with shunting. Abnormal CBF has been demonstrated on several occasions for secondary and idiopathic NPH. I have briefly discussed reduced cerebral blood volume as a pathophysiological mechanism in NPH in chapter 3 and performed a systematic review of the literature on CBF, autoregulation and NPH in chapter 4. Despite evidence of disturbed CBF, autoregulation in NPH has not been studied in detail. Furthermore, causative, diagnostic and outcome implications of those findings have not been addressed.

Previous work showed an inverse relationship between R_{out} and CA in non-shunted patients tested for NPH using both a transcranial-doppler derived CA index, as well as ICP-derived PRx(174). Using those preliminary results, we were once again able to implicate impaired CA in the clinical presentation of NPH, as well as reveal new information relevant to differential diagnosis or shunt response for further exploration. Since the first two studies were based on small samples, we aimed to confirm this inverse relationship between PRx and R_{out} , and to relate this to outcome after shunting.

5.2 Materials and Methods

Patients

We collected infusion tests from probable and possible NPH patients performed between 2003-2015. The inclusion criteria were: baseline ICP <18 mmHg, age >30 (both included in the current definition of probable and possible NPH)(3), continuous recording of MAP and no use of GA, because its influence on PRx and other CSF dynamics calculation has not been determined.

Data acquisition

Continuous, non-invasive MAP had been recorded using a photoplethysmograph (Finapres®) finger cuff (Ohmeda, Englewood, CO), inputting the signal digitally to ICM+. ICP and infusion test parameters were recorded and collected in the same methodology as explained extensively in the previous chapters of this dissertation. I used ICM+® version 8.3 for all figures and data analysis (University of Cambridge Enterprise Ltd).

Signal processing

I always remove all artefacts from the raw data manually before data processing, as is the necessity in all bedside digitised recordings. AMP, RAP, Heart rate and MAP were extracted from the recordings and averaged. Rout was calculated with the same method as in all previous studies. In order to avoid physiologically impossible and inaccurate measurement, only static R_{out} was used for further analysis. The slope of the AMP-P line was also calculated as per disclosed methodology in chapter 3.

The calculations and significance of these parameters has been explained in the previous chapters.

I calculated PRx from standardised methodology as the moving correlation coefficient between slow waves of ICP and MAP (30 consecutive 10-second averages, capturing the frequency of slow waves of ICP)(199,200). I detrended ICP using a simple moving average filter, in order to avoid differences in slow waves due to artificial volume

addition and to allow for a wider window of calculation both at baseline and during infusion. The filter used was the same as the one used to process slow waves in Chapter 9 and explained later more analytically (moving average filter – results of detrending shown in **Figure 5.1**).

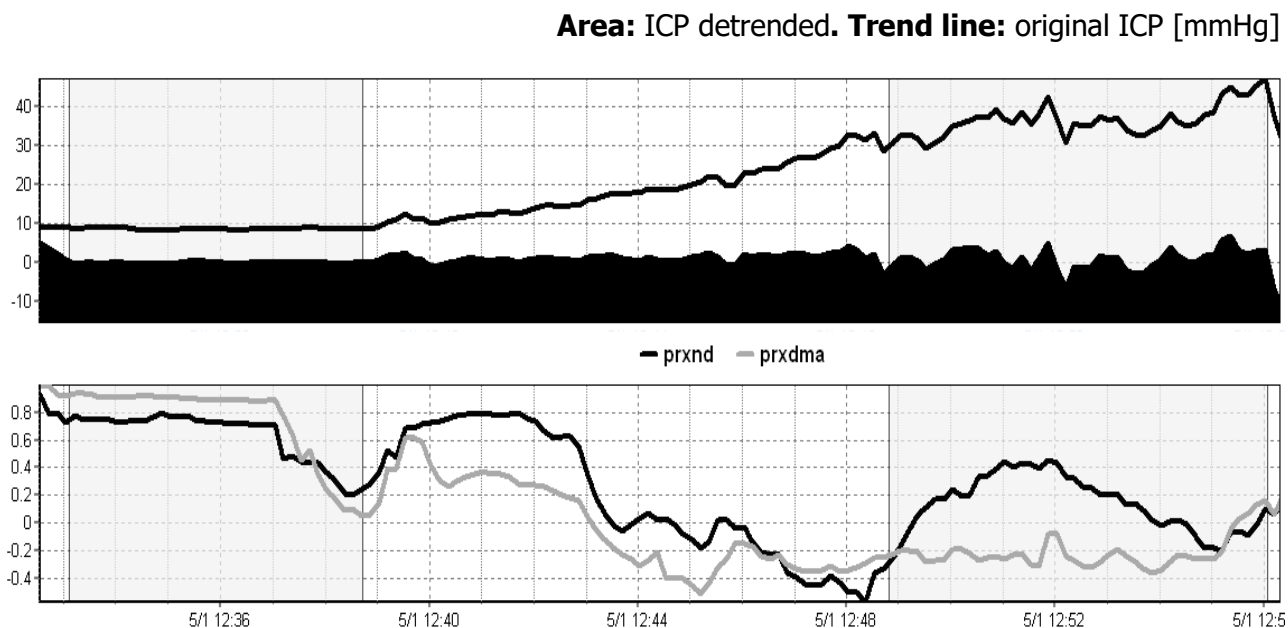


Figure 5.1 Difference in the trend between the original ICP and PRx (black area on the upper panel I& prxnd respectively) and the detrended signal (ICP& PRx respectively); selected calculation periods of PRx at baseline and during icpreal: Original ICP signal, ICP: detrended ICP, prxnd: PRx non-detrended, prxdma: PRx detrended with moving average filter.

We assessed PRx, HR and MAP during the baseline and plateau phases of the infusion test as well as during the entire test (duration 25-60 minutes). We assessed the potential differences in those variables at the baseline and infusion phase. Finally, we investigated whether a combination of parameters could be contributing to the relationship between PRx, Rout and outcome.

Patient follow-up

As per clinical routine and as explained in previous chapters, all patients were followed-up after their infusion tests to weigh the risks and benefits of shunting and propose treatment. Patients and their immediate family/caretakers were carefully informed and offered either a shunt surgery that included a programmable valve or an endoscopic IIIrd ventriculostomy (ETV). The criteria used from the consultant

neurosurgeon in charge of our NPH patients (JDP until 2013 and MRG after 2013) to diagnose NPH and select for shunting were as follows: A) before 2013: The patients had to have radiological evidence of hydrocephalus and classical gait disturbance for any further consideration. The diagnosis was definitive with proposed CSF diversion if the measure R_{out} from the infusion test was ≥ 13 mmHg*min/ml; If R_{out} was ≤ 13 mmHg*min/ml but there were minimal white matter changes on the MRI scan, probable NPH was diagnosed, and CSF diversion was offered to the patient with communication of the appropriate limitations. B) After 2013, an infusion test to measure R_{out} was still performed, however MRIs to quantify white matter lesion were discontinued in light of new evidence and because extended lumbar drainage was implemented in our practice for those with an $R_{out} \leq 13$. All those who demonstrated gait improvement with lumbar drainage were offered a shunt. Outcome was determined from the hospital records using a simple 3-level scale(62). Outcome of 1 indicated sustained improvement at a 6-month follow up, with objective and subjective (patient and those of their immediate surrounding-reported) improvement in gait as the main feature. Some patients had improved at 3 months, however at 6 months of follow-up they had started to deteriorate, and their outcome was marked as 2. Finally, an outcome of 3 signified no response to shunting.

Finally, we performed a preliminary subgroup analysis to compare ETV patients with shunted patients based on both the studied parameters and the outcome after shunting. Chi-square test was used to compare the outcome in ETV vs shunted patients.

Statistical Analysis

According to data normality or non-normality, I calculated Pearson's or Spearman's correlation coefficient as a simple estimator of the correlation between the different parameters described above. Paired-sample t-tests were used to compare means and between baseline and infusion values. Independent samples t-tests were used to compare the different group and subgroup means. Chi-square was used for qualitative data. Non-parametric tests (Mann Whitney U and Kruskal-Wallis) were used to

compare results among the three outcomes after shunting or between good (outcome 1+2) and poor outcome.

5.3 Results

131 patients met our inclusion criteria. Their mean age was 73 (± 7) years and the male to female ratio was $\sim 7:5$ (77 males, 54 females). Only 8 patients had secondary instead of idiopathic NPH, were below the age of 55 and their identified NPH causes were haemorrhage (subarachnoid/intracerebral), aqueduct stenosis, Chiari malformation or previously known, congenital hydrocephalus presenting with decompensation.

CSF compensatory parameters, as well as perfusion and autoregulation measures at baseline and during the infusion are presented in **Table 5.1**

There was a decrease in CPP at plateau compared to baseline ($\Delta = 14.45$ mmHg; $p < 0.0001$). PRx showed a tendency but did not appear to increase significantly during infusion compared to baseline. As a result, we have used the mean PRx over the entire test duration from further analysis now on.

Table 5.1 Patients' demographics and comparison of their compensatory and autoregulatory parameters during the baseline and during infusion.

Mean	Baseline	During infusion	p
AMP [mmHg]	1.09 \pm 0.05	3.55 \pm 0.15	< 2.2e-16
PRx	0.099 \pm 0.028	0.11 \pm 0.02	NS
CPP [mmHg]	72.03 \pm 2.38	57.63 \pm 2.5	3.647e-05
Slow [mmHg]	0.256 \pm 0.038	2.46 \pm 0.38	< 2.2e-16

Global cerebral autoregulation (PRx).

30/131 patients had disturbed autoregulation ($PRx > 0.25$), 51 good autoregulation ($PRx < 0$) and 50 patients were in the grey zone (from 0 to 0.25). Numerical values for autoregulating versus non-autoregulating patients (disturbed ($PRx > 0.25$) and $PRx < 0$) are shown in **Table 5.2**. Increase in AMP (dAMP) and RAP (dRAP) during infusion were significantly higher and lower respectively in the autoregulating than in the non-autoregulating group.

Table 5.2 Comparison of the difference -d- of the plateau and the baseline of autoregulatory and compensatory parameters between disturbed ($PRx > 0.25$) and preserved autoregulation ($PRx < 0$). *MAP: Mean Arterial Blood Pressure, HR: Heart Rate, Slow: Slow waves of Intracranial Pressure,*

	Mean for $PRx > 0.25$ (N=30)	Mean for $PRx < 0$ (N=51)	p
dMAP [mmHg]	2.39±1.76	5.36±1.95	NS
dHR [c/min]	0.68±0.44	0.04±0.3	NS
dSlow [mmHg]	2.2±0.55	2.77±0.4	NS
dAMP [mmHg]	2.13±0.21	2.94±0.18	0.014
dRAP	0.37±0.06	0.22±0.04	0.05

Interaction between PRx , R_{out} and with other CSF dynamics

R_{out} was ≥ 13 mm Hg*min/ml in 52 patients and within the ‘normal’ range (3.5 to 12.8 mm Hg*min/ml) in the other 79 patients.

R_{out} inversely correlated with PRx , rather weakly but significantly ($R = -0.18$; $p = 0.044$) [Figure 5.2].

R_{out} also correlated with AMP ($R = 0.30$; $p < 0.001$). The correlation was stronger between R_{out} and the increase in AMP during infusion (dAMP): $R = 0.46$; $p < 0.001$.

Correlation coefficients from the regression analyses between PRx and other compensatory and compliance parameters (elasticity, ICP, baseline ICP, baseline AMP, slope of AMP/P line) were weak and not significant. Mathematically, the power of slow waves and PRx showed a relative correlation ($R=-0.19$, $p=0.025$). PRx was not dependent on age ($R = -0.09$; $p= 0.3119$), while Rout was ($R = 0.33$; $p = 0.00015$).

Interaction between PRx, MAP and Rout and impact on outcome.

The clinical decision on diagnosis and treatment offer was based on the overall assessment by the consultant neurosurgeon, which included Rout. The clinician was not aware of any of the other parameters studied, like PRx. Following the infusion study, 83 patients were selected for shunt insertion ($N=51$), or ETV ($N=32$).

The inverse relationship between PRx and R_{out} was still significant when calculated for patients who were surgically-managed ($N=83$; $R=-0.28$; $p=0.03$) [Figure 5.2], however notably weak and insignificant in those who were not offered CSF diversion ($N=48$, $R= -0.05$; $p=0.7$).

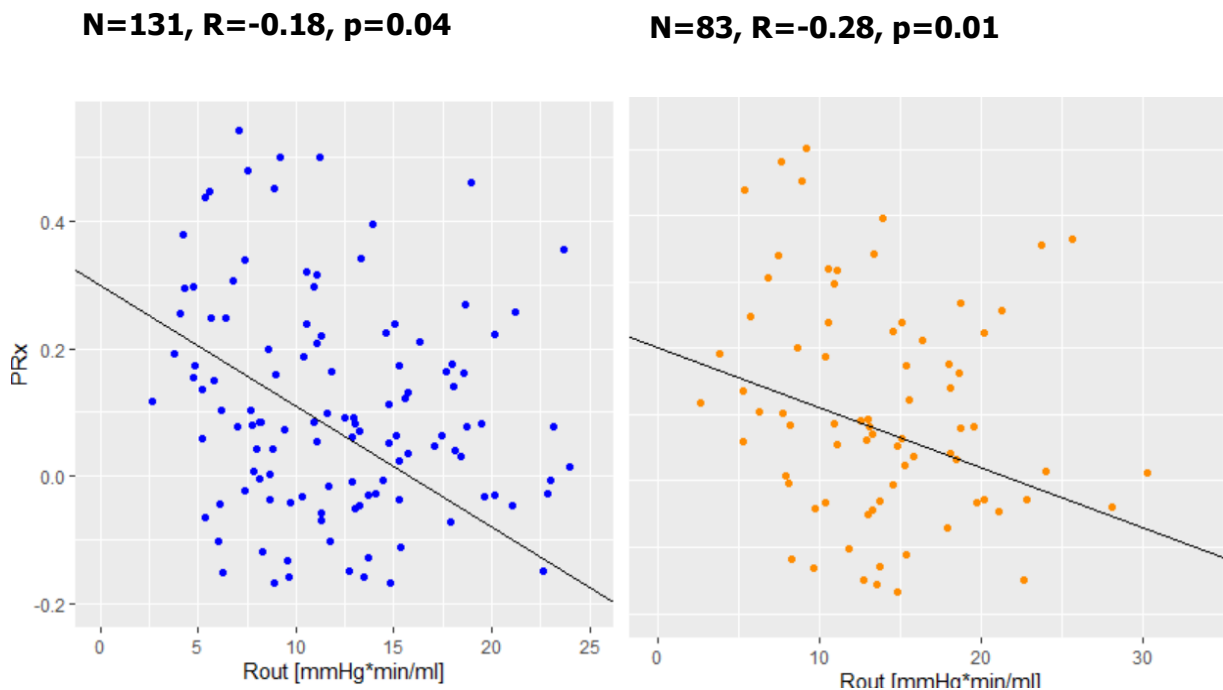


Figure 5.2 Relationship between Rout and PRx in possible NPH. Left: Relationship between PRx and resistance to CSF outflow in our cohort of 131 non-shunted NPH patients undergoing lumbar infusion studies **Right:** Relationship between PRx and resistance to CSF outflow in patients who were clinically managed with ETV or shunted after the infusion studies.

After CSF diversion, 64 patients improved at initial assessment (outcome = 1 or 2), whereas 19 did not show any improvement (outcome =3). The relationship between R_{out} and PRx for good versus poor outcome are shown in **Figure 5.3**. We detected the above negative correlation in outcomes 1 and 2, (N=64; R=-0.36; p=0.03), however not in outcome = 3 (N= 19; R=0.07; p=0.15).

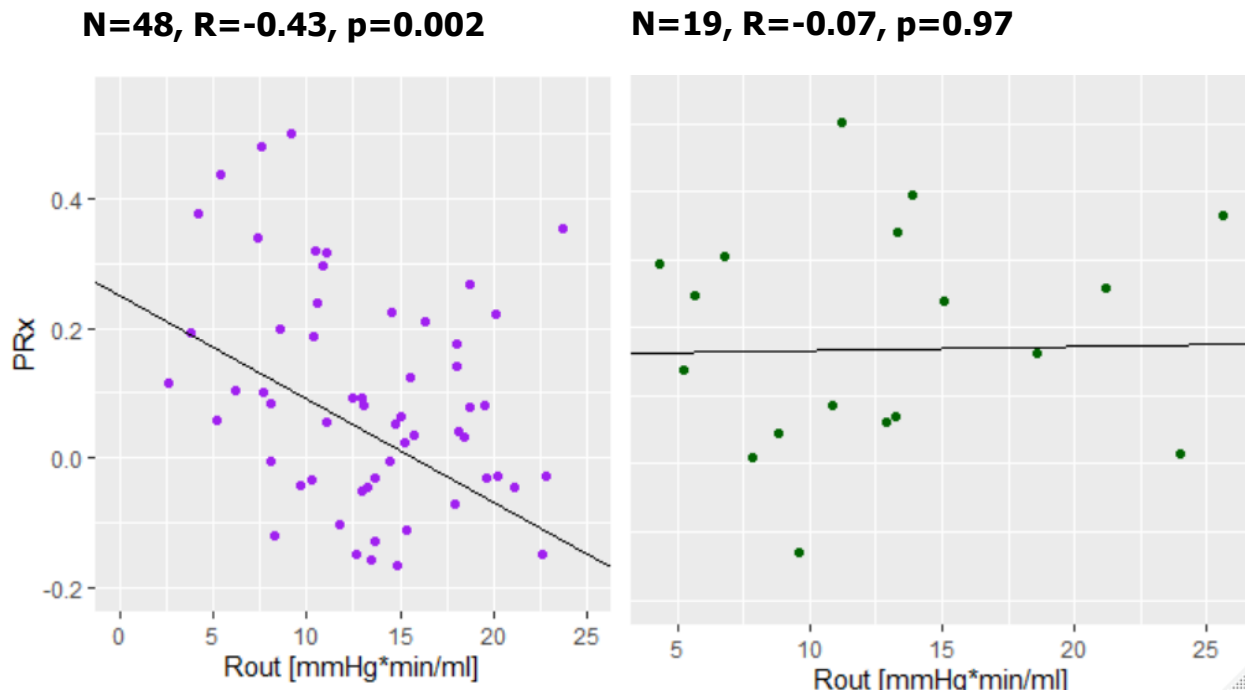


Figure 5.3 Relationship between PRx and Rout in CSF diversion responders versus non-responders. Left: Relationship between PRx and resistance to CSF outflow in patients who improved sustainably after surgery (N=48, R=-0.43, p=0.002). Right: Relationship between PRx and Rout in patients who did not improve after surgery (N=19, R=-0.007, p=0.97).

PRx tended to differ between poor and good outcome (PRx = 0.16 ± 0.04 vs 0.09 ± 0.02 ; p=0.061 respectively) and so did MAP (107.2 ± 8.2 in non-responders vs 89.5 ± 3.5 in responders; p=0.195). In exploring these relationships with outcome, combining PRx with MAP in the formula $MAP * (1 + PRx)$ seemed to significantly correlate with outcome. Multiplying MAP with $1 + PRx$ models the interaction between MAP and PRx in the negative and positive spectrum and is proposed as a simple measure to quantify these combined parameters.

MAP * (1+PRx) was significantly associated with outcome (p=0.013). Comparisons of autoregulation and MAP parameters in the different outcome groups are further presented in **Table 5.3**. R_{out} was not different between responders and non-responders.

Table 5.3 Comparison of autoregulation, R_{out} and vascular state in patients who improved versus the ones that did not improve. *MAP: Mean Arterial Blood Pressure, PRx: pressure Reactivity index, R_{out}: Resistance to CSF outflow*

	Improved	Not improved	P
MAP [mmHg]	83.12±3.08	91.51±6.29	0.195
PRx	0.09±0.02	0.16± 0.04	0.061
R_{out} [mmHg*min/ml]	12.61±0.65	11.73±1.17	0.519
MAP *(1+PRx) [mmHg]	89.56±3.54	107.21±8.25	0.013

ETV vs shunting subgroup analysis

From the 83 surgically treated patients, 27 underwent ETV and 56 were shunted. Mean age for the ETV group was 55.74 ±3.19 and 66.75 ± 1.53 for the shunted group; p-value = 0.001625.

Mean AMP differed significantly between the two groups (1.46 ± 0.14 for ETV vs 2.41 ± 0.16 for shunted; p=0.0005297), so did PRx (0.17 ±0.039 for ETV vs 0.07 ± 0.02 for shunted; p-value = 0.012). R_{out} as well appeared lower in ETV (12.0 ± 1.34 mm Hg *min/ml than in shunted patients (16.3 ± 1.21 mmHg*min/ml; p-value = 0.003). There was a negative but not significant correlation between R_{out} and PRx in both groups (ETV: R= -0.27 p-value = 0.176 vs shunted: R=-0.2555274; p-value = 0.05733).

As to the outcome of ETV versus shunted patients, 21/27 patients after ETV had a positive outcome [≤2,] vs 43/56 shunted patients. 6/19 had a negative outcome after ETV vs 13/57 shunted individuals. Shunted patients did not show a significantly more positive outcome than ETV patients (chi-square = 0.0102; p-value= 0.91).

5.4 Discussion

In this paper, we have increased the external validity of the inverse relationship between Rout and PRx. This relationship, although not very strong, appeared significant. In relationship to outcome however, our study is currently not adequately powered to address diagnostic and outcome implications of PRx and MAP. Nonetheless, the combination of cerebral autoregulation and mean MAP correlated significantly with outcome after CSF diversion and could be a quantitative reference in determining outcome based on those parameters.

The state of cerebral blood flow and autoregulation has long been investigated but yet to be determined in NPH, especially translated to clinically useful findings or in the context of tests applicable at the bedside. It is not often that ICP and cerebrovascular reactivity or autoregulation tests have been applied in NPH with scope to apply the methods on a large and practical scale and to adopt them into clinical practice(168,178,201). Most frequently, imaging of CBF has been used for research purposes in small series of patients(14,156–158,162,186,202). From a research point of view, a detailed review of CBF/CA methodology is required, as well as assessment of the feasibility of applying them clinically. On the other hand, clinical practice has long called for a systematic approach to create a consensus over the very definition, ambiguous diagnosis and shunt prognostication in NPH, that used to be strongly based on Rout but has recently moved away from it(3,26,178).

CSF dynamics and autoregulation assessment during infusion tests

Despite the long span of recruitment, our methodology, including infusion studies, ICM+ software and continuous MAP recording have been the same since 2003, with essential upgrades and maintenance. Especially between 2003-2013, diagnosis and shunt selection criteria were standardised and homogenous. Even after major changes in the lead consultant, the criteria remained fairly stable, except for the changes in imaging (discontinuation of MRI) and the introduction of extended lumbar drainage. Those changes have no effect on our current report. However, we cannot provide a detailed account of all notes and data derived from the clinical evaluation

process and decision making of neurosurgical consultants other than the lead hydrocephalus neurosurgeon, as well as the results of neuropsychology and gait testing. All of the above constitute their own entity and such reporting is outside the current aim of our study.

Increased R_{out} , despite extremely optimistic or extremely pessimistic reports in the literature, appears to contain useful information relating to shunt response (1,26,45,62,65,91,111,174,203–205). Above all, it seems to be a major component of NPH, since it objectively describes disturbed CSF circulation. There are multiple ways in which R_{out} could be used to understand NPH, however when it is used as a sole predictor of shunt response in large cohorts of patients, it fails to provide an accurate indication for surgery, as the negative predictive value of the traditional threshold of 13 remains too low (16,26,62,63). It is therefore becoming increasingly evident in the literature that R_{out} as a sole descriptor of intracranial dynamics is missing important information (4,26,62,111,183,206,207). Our current finding of decreasing R_{out} with disturbed autoregulation could be an indicator of part of this missing picture. A closer look at which of those cases are indeed reversible and why, related to CBF, CA, R_{out} and altogether vascular disease burden and magnitude as well as length of symptoms could elucidate this picture further.

Relationship between R_{out} and PRx

We detected a negative correlation between R_{out} and PRx that agrees with the previous reported findings suggesting that autoregulation is maintained in patients with abnormally high R_{out} and disturbed in low R_{out} . On a first glance, this appears paradoxical, since abnormal CBF, and therefore a failure of autoregulation, has been found in several reports in NPH (14,158,165,180,208). On closer examination, this relationship also re-opens the debate on who could have a diagnosis cerebrovascular disease, who could have “pure” NPH and whether some patients have both. It is possible that neither failure of autoregulation nor $R_{out} > 13$ are inherent descriptors of NPH, and those two parameters should be assessed together in an attempt to

achieve both a diagnosis and an outcome association. We did not possess further data to support this hypothesis at that time.

We have observed that when 83 of the patients studied were clinically diagnosed with hydrocephalus and underwent surgery, the correlation between disturbed autoregulation and lower R_{out} tended to be stronger. Even more interestingly, in the patients in whom the clinical decision was that they would most probably not benefit from surgery, no correlation between R_{out} and PRx was present. This finding could possibly suggest a distinction between patients who might benefit from a CSF diversion and whose clinical symptoms could be caused by disturbed CSF circulation, with or without cerebrovascular disease, and at least not by vascular disease alone. Autoregulation appears to have the potential to serve as a supplementary index for clinical decision-making. The presence of vascular disease, both as differential and as comorbidity in hydrocephalus, constitutes one of the biggest hurdles in clinical practice and management(6,59,209–212). There is still no alternative clinical test and consensus to aid the clinical decision whether there is concomitant disturbance of the CSF circulation and cerebrovascular disease, or whether the CSF circulation is normal, and the problem lies purely in the vasculature. Since testing of autoregulation at the bedside using PRx is cheap and feasible, it would be interesting to validate PRx as a method in comparison to CBF imaging, or even develop similar simple and safe tests that could bring autoregulation testing to the bedside routinely in NPH.

PRx did not show any correlation with age, which is surprising, as significant correlation may be seen in anesthetized and ventilated patients after traumatic brain injury. A similar correlation was shown between age and dysautoregulation in patients undergoing non-neurosurgical elective surgery(213). It appears that the age-autoregulation relationship (higher age associated with dysautoregulation) may be magnified by general anaesthesia, which is used in all studies reporting age relationship, and obviously not routinely used during infusion tests(124,213,214). On the other hand, R_{out} is known to positively weakly correlate with age. This relationship was successfully replicated in our cohort of NPH patients; a possible

investigation of different R_{out} thresholds for different ages remains to be performed separately, for better future directions. Sex does not appear to have any particular influence on R_{out} .

As a unique method of monitoring ICP and its dynamics, with opportunities to add adjunct modalities, the CSF infusion test seems to provide ideal conditions for measurement of cerebral autoregulation. We demonstrated a significant decrease in CPP during infusion. Another autoregulation-associated parameter, the magnitude of slow waves, correlated weakly but significantly with PRx. Slow waves, in context of measurement of PRx or transcranial-Doppler investigation, are carriers of the information about autoregulation mechanism. This correlation has not been reported before and it is worthwhile to consider its role in NPH patients, since both the frequency and the magnitude of slow waves are involved in possibly distinguishing NPH patients without vascular problems and predicting their benefit from a shunt insertion.

Significance of PRx, MAP and outcome after CSF diversion

The correlation between R_{out} and PRx appeared stronger in the patients that improved after CSF diversion, and tended to be absent in the patients with no improvement. However, there were not enough patients to demonstrate this stronger relationship statistically. Outcome after shunting in NPH is very much multifactorial, it requires reassurance that the valve indeed opens and drains(48,95,96,215,216). Therefore, associating it with one measured parameter is probably naïve. This can be demonstrated by the finding that neither PRx nor R_{out} differed between the outcome groups but the correlation between PRx and R_{out} was found to differ significantly.

Methodologically, PRx is a global autoregulation index, which means that it reflects the state of autoregulation in the entirety of the cerebral parenchyma(148,217). It is a continuous index with low values meaning better autoregulation and high values denoting impaired autoregulation(218–220). Autoregulation in hydrocephalus is still an uncertain territory and this is the first time PRx was used in a large cohort of patients. The numerical thresholds for good autoregulation (<0), grey zone (0-0.25) and impaired autoregulation (>0.25), were determined in TBI patients and their

applicability in hydrocephalus is unknown and needs to be studied. Over one third of the patients (62/131), had a PRx in the grey area: (PR =0-0.25) and we need more data in the future to determine the interpretation and the significance of this relationship with the R_{out} and with outcome. Our results create a new framework of consideration for patient outcome, moving further from the unsuccessful attempts to associate a single parameter, such as R_{out} or CBF alone, strongly with shunt response; The addition of systemic and cerebral vascular disease markers, joint with autoregulation indices would be worth further investigating for outcome consideration in NPH in appropriately designed RCTs.

It was not within the scope of this study to compare ETV versus shunting as a treatment option for hydrocephalus, nor did we possess enough patients to conclude this. The question of when ETV or shunt should be selected for different hydrocephalus patient remains to be answered(221–225). However, there were some differences in PRx and R_{out} between ETV and shunted patients, that we cannot interpret at the moment but should be investigated separately at a larger cohort. The influence of those differences in our overall results does not appear significant by our current number of patients, at least as far as the correlation of PRx and R_{out} and outcome are concerned. Finally, as the guidelines on ETV and shunting in NPH have been ambiguous and the reasons for performing an ETV on our patients can vary, it is not easy to investigate this matter further as we are not able to report more information on the patients' clinical course, from the first consultation to the final decision for surgery.

Finally, perhaps our most significant finding was the quantitative correlation between a lack of response to shunting and vascular burden (higher MAP), as well as autoregulatory dysfunction combined. There is an abundance of data suggesting an interaction between haemodynamics and CSF circulation(6,57,59,210–212). Cerebrovascular diseases has always been a major component of the differential diagnosis of NPH, and recently has been hypothesised as a pathogenetic mechanism for NPH. Strengthening the significant but not quite ideal predictive value of R_{out} could prove valuable in clinical practice and spare patients from undergoing difficult,

repetitive diagnostic procedures to determine their further management. Most importantly, it would assist us in better defining and diagnosing NPH, regardless of outcome after shunting, as well as to understand and map co-existence of NPH with other dementias, that would open a new multidisciplinary pathway for the ageing brain.

Limitations

MAP was not monitored via an invasive arterial line as is the gold standard, but non-invasively using a Finapres® finger cuff photoplethysmographer, and while this has been shown to be accurate compared to invasive methods its accuracy in this particular patient group (elderly with comorbidities) is unclear. This limits mainly the absolute value of MAP but not PRx, which was calculated from the MAP waveform. On this latter point, infusion studies have a limited duration and do not always allow optimal calculation of PRx, which ideally require longer calculation windows.

In this group of patients, we had not obtained any measurements of cerebral blood flow via PET scan or other imaging means during the infusion studies. Furthermore, we have assessed autoregulation through PRx, which is a global and indirect index of autoregulation that has not been validated yet in NPH. Predominantly, we have not explored the meaning of “inconclusive” PRx in hydrocephalus or whether the same threshold of 0.25 applies as in TBI. Further work is required on autoregulation in NPH, validating and comparing different methods. We did not possess an adequate number of patients with MRIs in order to quantify white matter lesions and compare them with Rout and PRx, however a study designed to address this question would be useful to address the question of the causality of our reported correlation.

Even though there is a lead consultant on hydrocephalus referring and assessing the bulk of cases, a number of other hydrocephalus patients are referred from all neurosurgical consultants. We have designed a retrospective study with a long recruitment timeframe, that makes it impossible and off our aim to report and analyse all the clinical information and further testing of patients, including the exact gait

and cognitive scores. Based on evaluation from a multitude of clinical specialists, all of these patients were possible or probable NPH cases.

Finally, our cohort was large in order to validate a significant linear relationship with PRx and Rout, however our numbers that could correlate parameters or combinations of parameters with outcomes were relatively small, especially for the patients with poor outcome. Unfortunately, we did not have enough patients to make stronger outcome inferences and appropriate methodology should be used to design and perform studies that would generate higher levels of evidence.

CONCLUSION

We have provided a quantitative reference to explore vascular disease, autoregulation and CSF circulation in hydrocephalic patients. The association between Rout and PRx, although present, appears rather weak and factors influencing this interaction should be explored. Prospective trials should be conducted, quantitatively assessing cerebrovascular disease, cerebral blood flow and autoregulation, as well as systemic hypertension on the symptomatology and CSF dynamics in NPH. Outcome implications of such findings could then be assessed further and more objectively.

CHAPTER 6

CSF DYNAMICS IN NORMAL PRESSURE HYDROCEPHALUS

6.1 Davson's equation in Normal Pressure Hydrocephalus

The results presented in this section have been published in Acta Neurochirurgica:

Lalou A, Levrini V, Garnett M, et al. Validation of Davson 's equation in patients suffering from idiopathic normal pressure hydrocephalus. 2018; 160:1097–103.

6.1.1 Introduction

NPH is a complex syndrome characterised by semi-quantitatively by the finding of ventriculomegaly, and the variable clinical triad of gait ataxia/gait disturbance, dementia and urinary incontinence(3,12,65). It is most likely a CSF circulatory disorder, since high Rout has been described as a diagnostic and shunt prognosticating factor(4,62,65,66). However, recent clinical studies have questioned this traditional concept of high Rout(26,226), creating further need to elucidate the pathophysiology of this disorder.

It is nowadays almost established that the CSF circulation is not the only contributor to the processes underlying the clinical manifestations of NPH. A variety of interacting endocranial factors, possibly including tissue distortion, cerebral ischaemia and other damage in the vasculature, could contribute and interact with the CSF circulation(1,80,174,227). Unlike some causes of secondary NPH, where the hydrodynamic disturbance is clearly attributed to a cause, in idiopathic NPH (iNPH) the aetiology leading to poor CSF circulation and ventricular dilatation is not yet clear. There is accumulating evidence highlighting the importance of systemic vascular disease, implicating cerebrovascular disease, in NPH causation, however high grade evidence demonstrating vascular disease as a causative rather than a co-existing parameter is yet to be generated(6,16,59,210,211).

In 1970, Hugh Davson, using an experimental set-up of both constant-flow and constant-pressure infusion in rabbits, described the now called “Davson's equation”,

used as a fundamental equation in the perception and study of CSF hydrodynamics in physiological individuals⁷. It expresses baseline intracranial pressure (ICP) as a linear function of Rout, formation of cerebrospinal fluid (I_f) and sagittal sinus pressure (SSP), as shown below(113):

$$ICP = R_{out} * I_f + SSP$$

The above relationship is true when ICP is greater than SSP and CSF circulates freely. Below SSP, ICP may have any value, the description of which is more difficult and related to the pressure-volume compensation 'exponential' curve(228) .

The detection of Rout from linear regression between ICP and formation rate was also validated by later measurements in human from Ekstedt(229) on 58 normal subjects. To the best of our knowledge, the relationship between Rout and ICP in NPH has not been validated, and if anything has been negated by Eide et al when investigated in 16 NPH patients, comparing Rout from lumbar infusion test with overnight ICP, as well as 28 children(102,226,230). This is another finding that possibly contradicts the theory that disturbance of Rout is the main marker of NPH and whether Davson's equation is applicable to patients with NPH. Nonetheless, shunt surgery is aimed at draining CSF controllably, but also reducing Rout to very low values(40,42,43,45,48,96,216). It is therefore not surprising that older studies had replicated the finding that this reduction in Rout, from around 12-18 to below 6, reverses NPH(40,44,63,65,192,216,231) and that a short 2018 cohort analysis on Rout thresholds for predicting shunt responsiveness concluded that a Rout of 12mmHg/ml/min is most appropriate for accurate prediction. On the opposite end, the latest multi-centre European iNPH study found that in 115 patients Rout had no correlation to clinical outcome and unacceptable NPV(26).

Finally, if Davson's equation is not detected and Rout is not the disturbed CSF dynamic component in NPH, this could raise a lot of questions and opportunities on an alternative explanation, such as pathology in the venous compartment or abnormally increased formation rate. No such findings exist that have described the

presence of such disturbances in NPH or iNPH. We have therefore aimed to investigate the relationship between ICP baseline and Rout in a large cohort of patients with infusion studies. We have also investigated other parameters related to ICP and Rout, such as age and the fundamental amplitude of ICP.

6.1.2 Materials and Methods

Patient selection

We retrospectively recruited from our database patients undergoing investigation for possible iNPH via a lumbar infusion test. All patients had documented and reported radiological evidence of ventriculomegaly on CT and/or on MRI scans, without any signs of global atrophy. All brain imaging is reviewed by expert neuroradiologists and neurosurgeons. Baseline CSF pressure had to be below 18 mmHg and at least two of or a complete symptom triad (gait disturbance, cognitive impairment, urinary incontinence). They attended Cambridge University Hospital Hydrocephalus Clinic between 2009-2013 and the lumbar infusion test formed part of their clinical investigations, according to hospital guidelines and in line with the National Institute for Health and Clinical Excellence (NICE) guidelines(232). Dementia had been diagnosed byneuropsychologists and gait was assessed by physiotherapists. Unfortunately, the data for cognition and gait were not available for analysis.

There is some data overlap between this study and previous publications from our group, with patients recruited from the same database in overlapping time periods(62,70).

Infusion test

We used the established technique of ‘computerised infusion test’(64,66) which has been introduced to clinical practice in 1988 in Poland(25). The procedure takes place as described in Chapter 3.

Patient follow-up & outcome assessment

After undergoing all desired clinical investigations, the patients are booked for a final follow up by the clinical team in order to evaluate all results, weigh the risks and

benefits of shunting and discuss with the patient and family. The clinical criteria established in our Cambridge centre until 2013 to make the final diagnosis and offer a shunt included the Rout (threshold of ~13 mmHg/min/ml) and the proportion of deep white matter lesions (low degree was best for shunt response). Outcome was assessed using a simple scale, as reported in Chapter 5(62).

Statistical Analysis

All computerised data are recorded and processed using ICM+ software. There are multiple independent studies in the literature in agreement for using Rout estimators derived from the computerised CSF infusion test, with values appearing to correlate very well(228,233,234). When analysing infusion-derived Rout numerical values, there are two modes of calculation, static and dynamic mode, the principles of each have been introduced in Chapter 3. ICM+ allows for calculation of Rout using both methods, depending on how clean of artefacts the acquired data are and whether the acquired pressure-volume curves deviate from the expected models. As such, the dynamic calculation is almost always preferred, unless those latter reasons yield it unreliable or incalculable.

We performed simple linear regression between variables to calculate Pearson or Spearman product correlation coefficients and p-values. Between-group differences (e.g. different outcome groups) were tested using the Wilcoxon signed rank test or the student t-test, after checking for normality and confirming parametric assumptions. Given the large sample, our data met all required criteria for normal distribution. For colinear parameters we performed multiple linear regression to correct the detected relationships and include the influence of other variables. ADL and VL performed statistical analysis independently and compared for accuracy and errors.

6.1.3 Results

During the selected time frame, 229 patients had undergone infusion tests for possible iNPH: 137 males and 92 females, male-to-female ratio of approximately 1.5:1. Their

age ranged from 36 to 96 years [median age 75years, mean age of the cohort was 70.4 (± 13.82)] at the time of the infusion test.

Numerical values for the infusion test parameters as mean \pm SD are represented in *Table 6.1*.

Table 6.1: Demographics and mean values of CSF test parameters for male versus female patients. Values are represented as mean \pm the standard deviation.

	iNPH (N=229)	Male (N=137)	Female (N=92)	p-value
Age [years]	70.4 \pm 13.82	71.6 \pm 11.9	68.69 \pm 16.07	0.5737
Rout [mmHg*min/ml]	13.18 \pm 5.53	13.48 \pm 5.5	12.7 \pm 5.57	0.33
CSFp baseline [mmHg]	9.0 \pm 3.64	9.28 \pm 3.57	8.59 \pm 3.74	0.1449
AMP [mmHg]	1.01 \pm 0.62	0.98 \pm 0.58	1.06 \pm 0.68	0.4469

The correlation between Rout and ICP/CSFp baseline is shown in *Figure 6.1 A*. When investigating male versus female subjects, the same correlation was absent in females but present in males ($r=0.26$, $p=0.002$). Rout was also positively correlated with AMP ($R=0.27$, $p=3.577e-05$), as shown in *Figure 6.1 B*.

Lastly, Rout appeared to increase with patients' age ($r=0.16$, $p=0.01306$) – *Figure 6.1 C*. The correlation between Rout and age was also absent in the male subgroup, but present and strong in the female subgroup ($R=0.33$, $p=0.001$). ICP decreased with age ($R=-0.22$; $p=0.0006238$)

When we integrated age in a multilinear regression model as an influencing parameter, the correlation improved in strength ($R=0.31$, $p= 5.935e-06$).

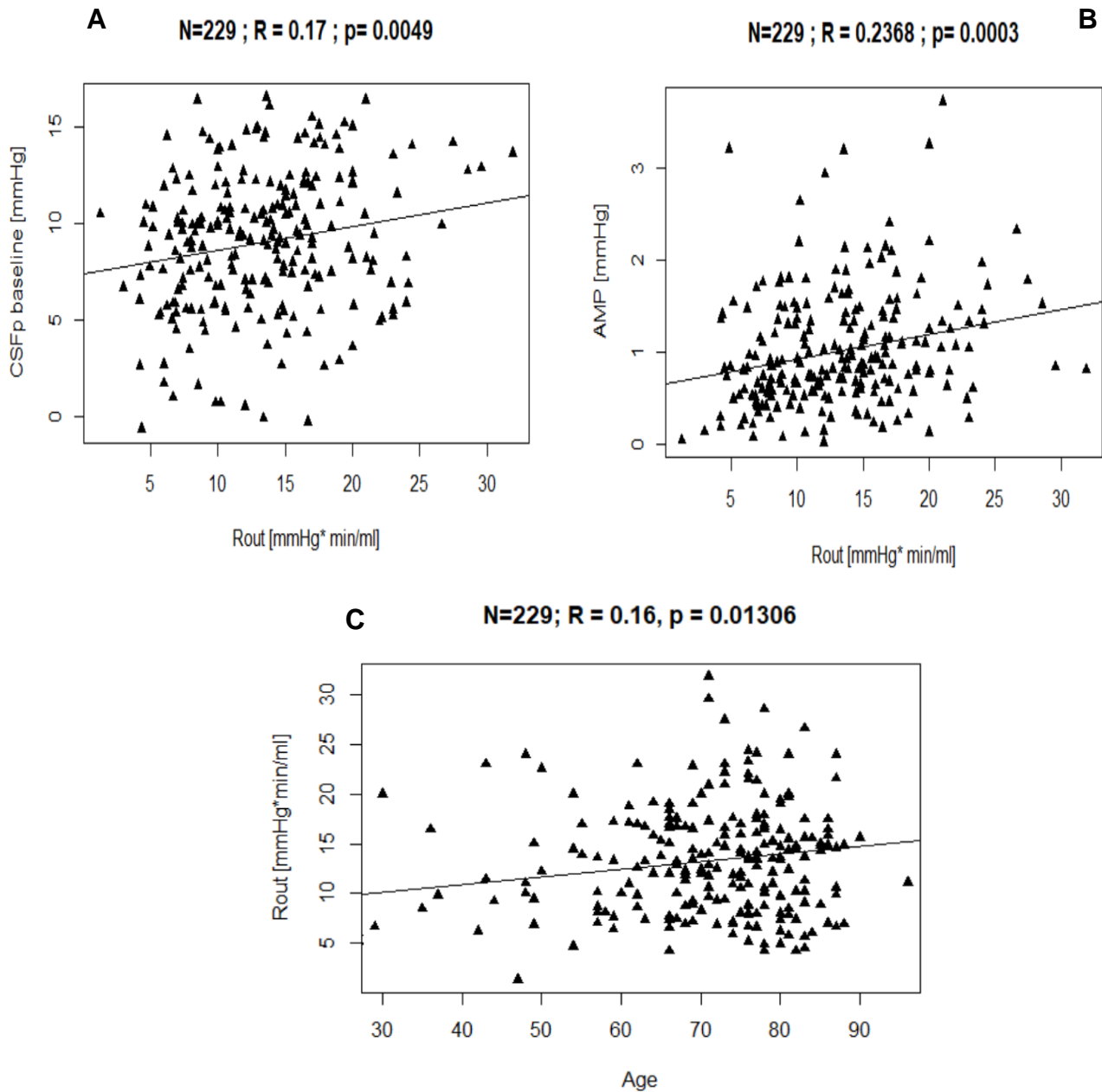


Figure 6.1: Relationship between Rout and different parameters: **A:** Scatter plot showing resistance to CSF outflow versus baseline CSF pressure. **B:** scatter plot showing resistance to CSF outflow (Rout) versus amp at baseline.

Relationship in different diagnosis & outcome groups.

ADL (author) collected the electronic records for surgery and outcome after surgery. From the patients investigated, 149 patients received a final diagnosis of NPH and 51 did not, whereas the rest of the patients (total of 29) were lost in follow up. 143 underwent surgery and we could trace and assess their follow up records from the

hydrocephalus clinic (6 declined surgery or had other health issues that prevented them from having the surgery or died before they could have it). 5 patients underwent ETV and the remaining 138 shunt insertion (various valves used). Each pre-operative decision and post-operative assessment was made on a case-by case basis, and from the consultant neurosurgeons attending to the patients. 119 of those responded well to the CSF diversion (outcome =1 or 2) versus 15 who did not demonstrate any improvement (outcome=3). 9 patients were lost in follow-up or their records were not available in the electronic database due to changes from paper to electronic records, with the paper records being stored in a not easily accessible location. The CSF infusion studies parameters calculated for different outcome groups are demonstrated in **Table 6.2**

TABLE 6.2 CSF dynamic parameters in patients who received a clinical diagnosis of INPH versus those who did not, and patients who responded favourably to shunting/ETV (outcome =1 represents sustained clinical improvement for >6 months and outcome =2 represents temporary improvement after 3 months but deterioration after 6 months in our reported scale) vs those who did not respond .

	Diagnosed N=149	Not Diagnosed N=51	p-value	Responders (outcome = 1,2) N=119	Non - responders (outcome = 3) N=15	p-value
Rout (mmHg*min/ml)	14.49 ± 5.45	10.03 ± 3.63	1.377e-07	14.63 ± 5.32	15.26 ± 5.5	0.8434
CSFp baseline (mmHg)	9.42 ± 3.74	8.92 ± 3.07	0.3363	9.87 ± 3.69	8.96 ± 3.57	0.4215
AMP (mmHg)	0.97 ± 0.62	1.018 ± 0.66	0.3413	0.99 ± 0.60	0.90 ± 0.58	0.6242
Age (years)	69.05 ± 12.72	74.75 ± 10.11	0.00018	68.57 ± 12.89	71.4 ± 10.83	0.1261

The correlation between Rout and CSFp baseline (CSFpb) was initially insignificant in the group of patients with a final clinical diagnosis of NPH without considering the effect of age (R=0.1; p=0.0533). When we used a multilinear regression to correct for age, their relationship became stronger and significant (R=0.3993; p=3.095-06). Furthermore, the relationship was absent in the patients who did not receive an NPH diagnosis. Finally, a positive relationship was only present when the interaction between Rout and Age was considered in patients with

favourable outcome, -outcome=1 or outcome=1 or 2- (R=0.43; p = 6.302e-06) while being absent in the non-responders (outcome =3). CSFpb decreased with age in those with outcome 1 or 2 (R= -0.36; p=6.129e-0.5) but not in those with poor outcome (R= 0.20; p=0.465).

6.1.4 Discussion

We have, to the best of our knowledge, reported for the first time a weak but significant correlation between Rout and CSFp in a large cohort of iNPH patients. This result validates the presence of a linear relationship between CSFp at baseline infusion tests and Rout, that overtakes the negative mathematical relationship between them [Rout = (CSFpplateau – CSFpbaseline)/Infusion rate]. However, this was not a holistic experimental set-up, and therefore the formation rate and SSp of those patients remains unknown. A possible positive association between Rout and CSFp baseline provides evidence supporting Rout as a valid measure and possibly key disturbance in NPH and causative factor in intermittently raised ICP, as seen in overnight monitoring. Comparison of Rout and ICP from overnight monitoring is also still pending and not performed in this study.

Relationship between CSFp, AMP, Age and Rout

We detected a significant, however weak linear relationship between Rout and CSFp at baseline in these patients. This constitutes a counter-intuitive finding, however there are many possible interpretations behind this. Firstly, as derived from the equation itself, variable pressure in the sagittal sinus and CSF formation rate could account for some of these cases. In particular, these subjects could have a baseline CSFp that was lower or equal to SSp, due to reasons that could not be elucidated in such cases, where Davson's equation is not valid at all(228). Unfortunately, it is currently rare and challenging to measure SSp directly in our patients, at least simultaneously to an infusion test. We are aware of a few cases from our material where CSFp behaved as such in relationship to SSp (see Chapter 7.1), however such relationships should be evaluated in vivo anew(32,194,203,228,235).. However, SSp and the entire cerebral venous system are known to vary significantly even amongst healthy individuals. Ekstedt et al initially reported important normative data for

SSp, where it ranged from 0.7 to 1.35kPa (5.25 – 10.13 mmHg)(228,229). I_f has recently been a subject of significant controversy and not fully established in NPH(236–238). Even though I_f is traditionally presumed as stable at 0.35 ml/min, we are not aware of any studies with reliable I_f measurements for NPH/hydrocephalus. Combined with the issue there are no standardised animal models and the variable use of MRI techniques to quantify CSF flow, there is a lot of unexplored ground in investigating CSF formation in the context of normal and disturbed pressure-volume characteristics(212,239,240). Phase-contrast MRI is a promising technique that could allow measurement of CSF and cerebral blood flow, and can easily be combined with infusion tests(159,161,208).

We also demonstrated an increase of R_{out} with age, confirming such a reporting in a variety of previous publications(226,241). Therefore, as a co-linear variable, we considered age in a multivariable model and indeed uncovered a stronger and more significant relationship between R_{out} and CSFp, despite what appeared initially as weak coefficients. If age is one of the factors that influences this relationship, all the factors mentioned above could similarly have influenced the regression in several ways. Furthermore, the influence of age itself on I_f and SSp renders us into an unexplored territory. Paradoxically though, ICP appeared to decrease with age, which explains the importance of age correction in detecting the relationship. Moreover, this decrease in ICP with age could be a cause or effect for the increased R_{out} . The causality of this phenomenon needs to be elucidated with appropriate methodology.

The significantly higher percentage of males (59.82%) versus females (40.18%; $p < 0.001$) prompted us to investigate the difference between those two groups. Although none of the originally calculated CSF infusion parameters differed significantly between the two groups, there were significant differences in the correlation coefficients between R_{out} and CSFp, AMP and age. The male and female subgroups each contain a different number of patients, and further power analysis to elucidate this lack of correlation could confirm or refute this difference.

Values of ICP baseline

It arises from our results that nearly half of our iNPH patients have a baseline pressure between 0 and 4 mmHg. As 4mmHg is currently considered the threshold below which intracranial hypotension is suspected(242), it raises some questions. The explanation for this arises from 3 main underlying possibilities: 1) There could be a mild zeroing error when the reference pressure level is introduced in the machine – however this is only hypothetical as the zeroing process and level are standardised. 2) Our elderly patients can be challenging technically when performing an LP, especially as junior, inexperienced members of staff are often involved in performing them. It is frequently that multiple attempts can be made and given the larger diameter of the needle we use combined with the multiple attempts that often involve puncturing the dura more than once, CSF leak could be accounting for the low pressure readings. 3) It has recently been shown from a retrospective cohort of patients treated at a spontaneous intracranial hypotension centre that Rout with a cut-off of 5mmHg*min/ml is a more reliable marker of CSF leak whereas the opening CSF pressure, even though significantly lower in patients with leak, was not <4mmHg and ranged from -1 to as high as 12.8 mmHg in 14 patients with proven leak (mean pressure 5.26 mmHg)(243). It is unfortunately not possible to currently understand which of the possibilities represents the truth.

Shunt responders vs non-responders

Rout and CSFpb appeared to not correlate in shunt responders, unless age was used again to model all interactions and correct the linear regression. When we applied this expanded linear model, the correlation appeared stronger than in the overall 229 patients with mixed features and diagnoses. The age-dependence of Rout is a subject of discussion in itself, however the main interest in this relationship would be whether it improves our understanding of NPH and whether it is important in attempting to predict outcome(241,244–246). A strong age-dependence of Rout in shunt responders could highlight the importance of such an evaluation in future attempts to utilise Rout in the clinical setting.

Limitations

It is difficult to define and include only definite NPH. As a result, our patients were probable NPH with clinical and radiological features strongly suggestive of NPH. Despite clinical manifestations, we currently do not possess or have used any tools to establish whether a patient has NPH, pure NPH or NPH plus other co-morbidities. Response to shunting is an indication, however, remains relatively subjective or semi-quantitative. What is more, the influence of alternative of comorbid diagnoses on Rout is naturally unknown and almost impossible to determine unless there is a future vastly more widespread use of infusion tests in all dementias. Finally, as expected, the majority of our shunted patients responded to the surgery, and there were very few patients with no response to shunting (N=15), so the results from this analysis are subject to the relevant limitations. In the end, the objective truth on the diagnosis of iNPH is unfortunately still open for debate.

As previously reported, the patients referred for infusion studies are referred from a multitude of neurosurgical consultants(70). Therefore, we are unable to report clinical information, pre-and post- operative assessment of the magnitude of the symptoms and the patients' improvement in great detail. This is due to a great loss of data that is part of the retrospective nature of the study. However, every patient undergoes thorough investigations by specialists before diagnosis and outcome classifications are made. Furthermore, our simple, 3-level scale does not report in detail the magnitude of improvement of the patients' symptoms, despite that the patients have been investigated, monitored and followed-up closely in order to determine their management and outcome reflected in our scale.

6.2 CSF dynamics in post-traumatic ventriculomegaly

This chapter includes work in press by Fluids and Barriers of the CNS.

Lalou AD, Levrini V, Czosnyka M et al: CSF dynamics in non-acute post-traumatic ventriculomegaly.

6.2.1 Introduction

In this chapter, I have started exploring potential influences on Rout as well as their subsequent diagnostic and clinical applications. To the best of our current knowledge, there are no detailed accounts of Rout dependent on different aetiologies of NPH or secondary NPH overall versus iNPH(69,119). Traumatic brain injury (TBI) is a well-known cause of hydrocephalus, acute or chronic. External hydrocephalus after TBI, presenting with an enlargement of the subarachnoid space instead of ventriculomegaly, has been frequently described in children but scarcely recognised in adults(247). Unlike iNPH, not many centres have utilised infusion tests and CSF dynamics as a tool to investigate the chronic form of post-traumatic hydrocephalus (PTH) that could develop after several months or years after the initial injury. There are conflicting studies on the incidence of both acute and chronic PTH(247–250). The evidence though does seem overall to suggest that chronic PTH is underdiagnosed and undertreated and could be one of the causes of poor outcome post TBI(247–249,251). Infusion studies could serve as a useful tool for investigating possible PTH, similarly to their routine use in iNPH, if the latter could be related to a CSF circulatory issue with increased Rout(4,105,215,252,253).

PTH has been described in previous reports, mainly diagnosed through clinical presentation and imaging(248). Lumbar manometries could not be useful, as the ICP is within the normal range, however risk factors such as decompressive craniectomy, age and subarachnoid haemorrhage have maintained clinical suspicion raised and shunting is often performed without additional testing(248,249,254,255). Marmarou et al (252) designed and carried out a prospective study on CSF dynamics in patients post TBI with repeated CSF infusions, demonstrating how they could aid in the detection of PTH over CT scans alone. They concluded with a recommendation for

shunting in patients with opening pressures greater than 15 mmHg or Rout greater than 6 mmHg/ml/min and called for a multi-centre randomised trial to confirm such findings. However, studies comparing the various infusion study methods (bolus vs. constant rate vs. constant pressure infusion) have found that Rout is calculated as significantly lower in the bolus-injection method compared to the other methods(233) .

In the context of a CSF dynamics disorder, a longer recording of baseline ICP is required in order to properly estimate CSF parameters. ICP monitoring would be a useful tool for reliable estimation of ICP and CSF dynamics analysis, though invasive(52,56,256–258). We have aimed to re-examine the use of CSF infusion tests for the diagnosis of non-acute PTH using further parameters besides Rout, including AMP and compensatory reserve. Furthermore, by comparing TBI patient to a group of iNPH shunt-responders, we aimed to investigate if the “traditional” threshold of Rout 13mmHg*min/ml, as well as other reported CSF dynamics thresholds in iNPH apply to PTH, since a lower threshold of 6 mmHg*min/ml has been proposed by Marmarou(252).

6.2.2 Methods

Patient selection

We retrospectively recruited from our infusion study database at Cambridge University Hospital. All subjects had undergone infusion studies between January 2011 and February 2019, on clinical request, with possible features of PTH and ventriculomegaly reported by expert neuroradiologists on CT/MRI. We excluded all patients that had undergone decompressive craniectomy (DC) and or had a cranioplasty in situ inserted very recently (less than around 1 month)(105,253,259).

Patients with low Rout (<6 mmHg*min/ml) and clear signs of global atrophy were also excluded from the group. We used a group of iNPH shunt responders to compare possible differences between iNPH and PTH. iNPH patients were selected based on the following criteria: 1) presence of at least two of the three cardinal symptoms from the NPH triad, ventriculomegaly on CT or MRI scanning 2) positive response to

shunting (clinical documentation of improvement of symptoms at 6-month follow-up) and 3) youngest patients of the available cohort, in order to achieve a slightly better age match for young TBI patients. They had undergone infusion studies between 2003 and 2018. A few of the patients in this cohort have been previously reported (70,259).

Infusion study

Infusion studies were carried out as per standard clinical procedure, as described analytically in Chapter 3.

Data Collection & Analysis

CSF dynamics parameters were collected from our stored ICM+ files and included ICP baseline (ICP_b), ICP at plateau (ICP_p), Rout, AMP, RAP and Elasticity. Elasticity, as calculated from the pressure-volume curve, is inversely related to brain compliance from the formula $\text{compliance} = 1/(\text{elasticity} * \text{ICP})$ (109). Infusion test parameters, such as Rout, AMP and RAP have been extensively reported before in normal subjects, TBI (from neurocritical care long-term monitoring) and hydrocephalus(50,75,100,103,105,260). The slope of the amplitude-pressure linear regression line correlates with Elasticity and is expressed as a combination of $\text{elasticity} * \text{cerebral blood volume}$ (107).

ADL and VL (authors) used our local EPIC software or its older version eMR and collected patient demographics (age, gender) and all the available clinical information as following: date of TBI, date of infusion study, decompressive craniectomy/cranioplasty date, severity of TBI and brain imaging. Follow-up and shunting information, as well as outcome after shunting were also extracted.

Comparisons between groups were tested using non-parametric tests, mainly the Wilcoxon test for independent samples.

6.2.3 Results

Patient Population and classification

We identified a total of 46 infusion test recordings from 44 unique patients during the selected time period. 10 cases were excluded due to suspected global atrophy. The

remaining 36 patients were included (Group A), of which 12 females and 24 males. The average age was 53.17 ± 17.05 years. 26 tests were done via LP and 10 via ommaya. The time interval between the TBI and infusion study varied widely amongst subjects, with the minimum interval of 10 days and maximum interval of 33.5 years. For 11 subjects, the TBI date could not be retrieved. Of the remaining 24 subjects, the average time interval between TBI and infusion study was 56 months. From the available data, 19 patients had been classified as having ‘severe’ and 6 ‘mild’ TBI according to GCS on initial presentation. 5 tests had been performed under GA.

An example of the CSF dynamics of a possible PTH (Group A) patient is shown in **Figure 6.2**. Numerical results for the CSF dynamics in Group A are shown in **Table 6.3**

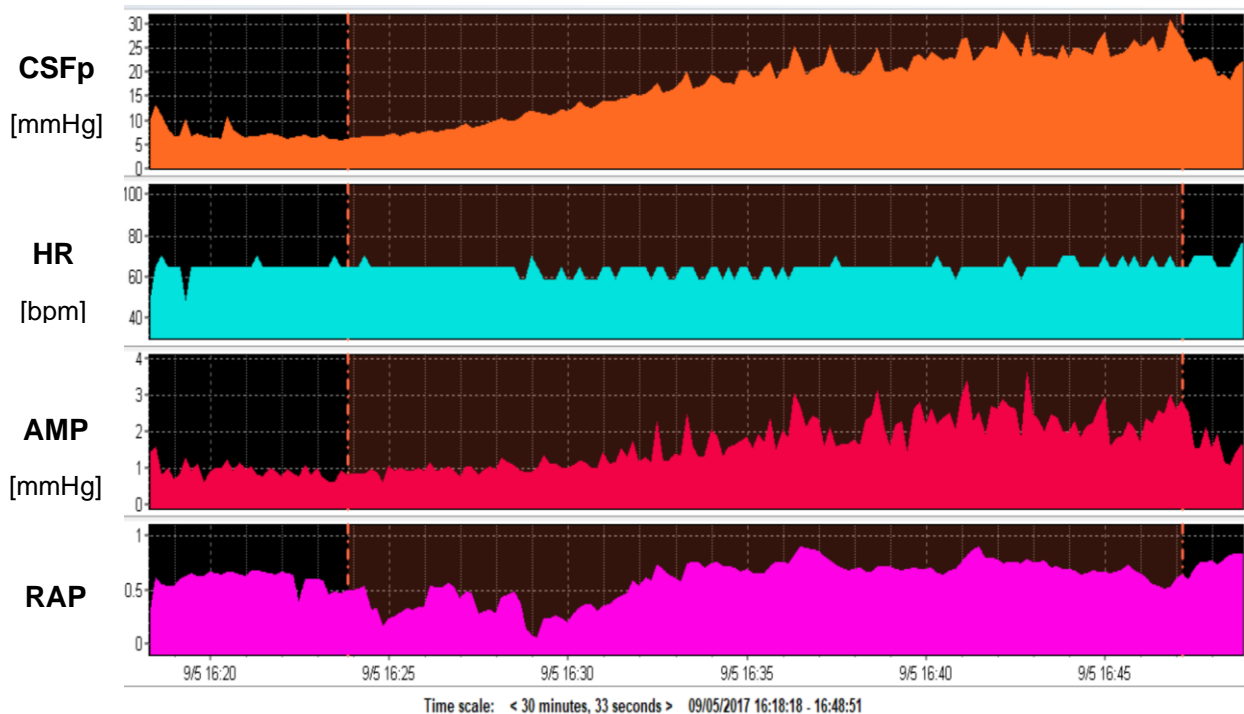


Figure 6.2 Representative example of CSF dynamics in a patient tested for Post Traumatic Hydrocephalus CSFp increasing briskly after start of infusion, with an Rout around 11-13 mmHg*min/ml. AMP at baseline ~1mmHg, also reacting briskly to infusion until a plateau of 5.6 mmHg. RAP at baseline ~0.6, clearly increasing to almost 1 after infusion of only a few mLs, indicating exhaustion of compensatory reserve.

The comparison group B had 45 iNPH shunt responders. We selected 45 of the youngest available patients in order to approximate a similar number to Group A,

Their average age was 66.16 ± 12.80 years and there were 19 females and 26 males. Numerical results of CSF dynamics comparison between group A and B are shown in **Table 6.3**.

Table 6.3 Comparison of CSF dynamics in Groups A (Post traumatic hydrocephalous) and B (idiopathic NPH).

Mean	Group A (N = 36)	Group B (N = 45)	p-value
ICPb [mmHg]	9.31± 4.12	9.48 ±4.57	0.6933
Rout [mmHg*min/ml]	13.53 ±5.21	19 ±8.91	2.91e-11
AMPb [mmHg]	0.55±0.39	1.02±0.72	0.001944
dAMP [mmHg]	1.58 ±1.21	2.76 +/- 1.50	0.0002139
Slow [mmHg]	0.66 ± 0.68	1.26 ± 1.5	0.2505
AMP-P slope	0.09 ± 0.05	0.14 ± 0.08	0.01267
Elasticity [1/ml]	0.19 ± 0.13	0.19 ± 0.1	0.5487
RAPb	0.57±0.18	0.38 ±0.21	0.5338
RAPinf	0.95±0.07	0.92 ± 0.075	0.5058

Shunt surgery and follow-up

After completing all assessments for PTH, 16/36 patients were shunted with a ventriculoperitoneal shunt. There were 5 clearly documented cases of improvement after shunting on follow-up, two documented cases of complications post shunting (one case of haemorrhage and one of infection) and one documentation of shunt malfunctioning. In 7/36 cases, we could not find further follow-up documentation. In the remaining 13/36 cases, a decision against shunting was made after clinical consideration.

Results from comparing shunted versus non-shunted PTH patients, shunted PTH with 45 iNPH shunt responders are shown in **Table 6.4**.

Table 6.4 Comparison of CSF dynamics in the shunted versus not shunted patients of Group A (Post traumatic hydrocephalous) with the shunt responders of group B (idiopathic NPH).

Mean	PTH shunted N=16	PTH no shunt N=13	p-value (col. 1&2)	iNPH (Group B)	p-value (1&B)	p-value (2&B)
ICPb [mmHg]	8.79 ±4.47	9.91 ± 3.6	0.7551	9.48 ±4.57	0.579	0.9154
Rout [mmHg*min/ml]	16.69 ±5.87	10.56± 3.06	0.003094	19 ±8.91	6.104e-05	0.0004883
AMPb [mmHg]	0.53 ±0.41	0.59± 0.43	0.7143	1.02±0.72	0.0204	0.04915
dAMP [mmHg]	1.78 ±1.56	1.35±0.66	0.8291	2.76 +/- 1.50	0.02764	0.02188
RAPb	0.6 ± 0.16	0.54±0.2	0.4015	0.38±0.21	0.418	0.6698

Relationship with imaging

We reviewed the reports from CT/MRIs closest to the infusion date (maximum time difference 2 months). Encephalomalacia or ex vacuo ventriculomegaly had been reported in 12/36 cases in Group A. Ventriculomegaly, with no clear description of hydrocephalus or the degree of hydrocephalus, was the main finding in all patients, with only three cases reported as having a mild to moderate degree of hydrocephalus and one case of major lateral ventriculomegaly.

6.2.4 Discussion

We have given a preliminary account of Rout, pulse amplitude, compensatory reserve and compliance in possible PTH.

Rout and AMP were significantly lower in PTH compared to iNPH and did not always reflect the degree of hydrocephalus or atrophy reported on CT/MRI.

In patients with symptoms and radiological signs of PTH, there was a variable Rout, as well as other dynamic parameters such as AMP and RAP. We have not studied

atrophy in this cohort, and excluded all patients that could fall into this category, based on results of Rout <6 as per Marmarou et al(252) and imaging.

Regarding comparing patients tested for PTH with those tested for iNPH, we found significant differences in AMP and dAMP. Rout also differed significantly in these groups. It is possible that a generally lower AMP in the TBI group could reflect a different reactivity of the vascular bed and vascular damage sustained as a result of the injury(107,261). Such a hypothesis could also be investigated by testing cerebral autoregulation in PTH patients. Since both possible iNPH and possible PTH constitute very heterogeneous and complex pathologies, future randomised trials could assist in defining the significance of those findings. Infusion tests appear useful as an additional test for PTH with normal baseline ICP and could also further be explored to validate a high ICP baseline versus LP manometry or overnight monitoring. A lower Rout, similarly to lower AMP in PTH, could direct towards findings of impaired cerebral compliance and possibly cerebral blood flow and autoregulation(45,73,150,161).

Regarding pressure-volume compensation, this appeared depleted in both iNPH and PTH, as demonstrated by $RAP \geq 0.6$ in both groups. Elasticity was also increased in both groups, also indicating decreased cerebral compliance. On the other hand, the AMP-P slope, which is related to elasticity, appeared decreased in PTH compared to iNPH. Such a relationship could be attributed to the second descriptor of the slope, which is the cerebral blood volume. A decreased AMP-P finding, with increased or even normal elasticity, could therefore underpin decreased cerebral blood volume in PTH.

Interestingly, the main difference we could find between those selected for shunting and those where the clinical decision was not to proceed to shunting, due to resolution of symptoms or other reasons, only a significant difference in Rout. This difference could however also be due to a performance bias linked to the fact that the consultants also make the decision to shunt based on Rout, at least partially. Furthermore, this

finding appears preliminary since we did not have enough patients in these groups to conclude on the presence or absence of these differences adequately.

The strong difference in AMP and dAMP seemed to be maintained when shunted PTH patients were compared to iNPH shunt responders. In addition, Rout did appear to differ significantly between these two groups, however we did not have enough shunted PTH patients to determine whether this finding could also be random. The pathophysiological processes between increased Rout in iNPH and PTH however, would potentially differ and could merit as an explanation for a possible difference in Rout. Obstruction of the lumen of the cortical subarachnoid space was a hypothesis from Czosnyka et al (259) for the increased Rout in PTH patients after cranioplasty, as a result of an irreversible ventricular enlargement caused by the missing bone flap. We have not checked in our dataset whether there was indeed any difference in Rout between those who never required craniectomy and those who had, as well as the length of time with craniectomy. It could be worth, at a future study, to select more patients with post traumatic ventriculomegaly and attempt to validate a potential influence of craniectomy on Rout, however this was not possible or within the aims of our current study.

We could not find enough patients with MRI that could characterise atrophy in better resolution than a standard CT, as those are not routinely performed for PTH patients in our hospitals. Nonetheless, when encephalomalacia or ex vacuo ventriculomegaly were reported from expert neuroradiologists for our patients, we could not always detect atrophy based on the CSF dynamics results and if anything, some of those patients did have PTH. Atrophy versus PTH, and even atrophy versus iNPH, constitute ongoing subjects of investigation and debate in the radiological and neurosurgical fields(252,262). A localised instead of a generalised degree of encephalomalacia in PTH patients, e.g. from previous sources of bleeding, could be an area of slightly increased compensatory space and could be contributing to lower Rout in PTH patients vs iNPH. It would be desirable to validate such a hypothesis utilising both appropriate imaging and infusion tests, with or without assessment of regional cerebral blood flow. We are unable to propose a threshold of Rout for shunting in PTH

patients with normal baseline ICP, however it appears that Rout could be lower than patients without previous TBI, and therefore Rout <13 should not be used to exclude patients from shunting. Finally, repeated infusions through time were not performed, in contrast to Marmarou et al(252), and we could not explore whether GOS related with Rout and how this relationship changed with time.

Limitations

We have selected a heterogenous group of TBI patients, with different types of injuries (SDH, SAH, contusion) and different severity of injuries (mild-severe). Furthermore, the timeframe post TBI varied from weeks post trauma to years. In some cases, the exact date of the TBI date was not available.

Unfortunately, due to lack of an organised medical database before 2014, it was difficult to retrieve some patients' notes, and this resulted to patients being lost to follow up. Subsequently, documentation and association to improvement post-shunting was not possible for many patients.

There is currently no definitive data demonstrating the effects of GA on compensatory reserve and CSF dynamics, other than it suppresses slow waves, which were not used here as a descriptive parameter.

CHAPTER 7

CSF DYNAMICS IN PSEUDOTUMOUR CEREBRI

7.1 COUPLING OF CSF AND SAGITTAL SINUS PRESSURE IN ADULT PATIENTS WITH PSEUDOTUMOUR CEREBRI.

The results presented in this section are published in Acta Neurochirurgica: Lalou A, Czosnyka M, Czosnyka Z, et al. Coupling of CSF and sagittal sinus pressure in pseudotumour cerebri.

7.1.1 Introduction

In section 1 of this chapter, I have introduced PTCS. The name Pseudotumour Cerebri Syndrome perhaps best describes the disorder, including most of its complex pathogenetic, pathophysiological mechanisms and clinical presentation(29,34,39). Despite uncertainty on its probable cause, its underlying mechanism has been shown to be abnormalities of the venous system leading to impaired CSF drainage, therefore classifying the condition as a syndrome, the Pseudotumour Cerebri Syndrome(34,35,39). Early MR and CT venographies suggested fixed stenosis of the sinuses not amenable to CSF withdrawal with a CSFp - sagittal sinus pressure (SSp) gradient, which lead to the use of stenting as a management option in PTCS(33,35). When investigating CSF and venous circulation in PTCS, little is known about the relationship between CSF and sagittal sinus pressures (SSp). In this study, we aimed at demonstrating this relationship and the coupling between CSFp and SSp waveforms in adults suffering from PTCS by using lumbar infusion studies to measure CSFp with simultaneous direct measurements of their SSp.

CSF dynamics investigations, in parallel with cerebral haemodynamics (arterial and venous circulation), demonstrate great interest in understanding CSF disorders(1,66,80,263). Davson's equation(113), as analysed in section 5.1 describes the relationship between SSp and CSFp.

This equation has been described and validated in normal individuals, detected in patients with symptoms of normal pressure hydrocephalus(264), however requires investigation in other CSF disorders.

Our aim was to show the interactions between CSFp and SSp at steady-state (baseline), during infusion, and during/after CSF drainage in PTCS. There appears to be a constant, positive feedback loop between increased CSFp and SSp in patients with PTCS and MRV findings of venous narrowing, that we think could assist in understanding the disease pathophysiology and in improving management and treatment(32,265). With such a combination of CSFp and SSp monitoring, we aimed to firstly understand why and perhaps which patients improve with CSF drainage, whereas some do not. Secondly, to assess the significance of the venous sinus stenosis, the gradient between CSFp and SSp and therefore to better determine the management of these patients. Finally, we are proposing a re-arrangement of Davson's equation for PTCS patients based on our findings.

A preliminary report of this study has been previously published (32)

7.1.2 Patients and methods

We tested the intracranial circulation of 10 selected patients (9F:1M) presenting or referred to Cambridge University Hospital in the time period between 2004-2006. They all had clinical features of PTCS who fulfilled the modified Dandy criteria [signs and symptoms of raised ICP (including papilloedema and headaches in all patients), no focal neurological signs, normal neuroimaging apart from MR venography, raised CSFp >20 mmHg and normal CSF composition](29,34,36,38,39,266).

Such patients with identified cerebral venous stenosis and no other abnormality undergo two standardised clinical investigations in our centres, that we combined in one: constant-rate lumbar CSF infusion studies, to assess the CSFp and CSF dynamics, and direct retrograde cerebral venography (DRCV) whereby a catheter was placed within the sagittal sinus under fluoroscopic guidance, in order to assess the significance of the stenosis.

As mentioned above, we had selected those particular 10 patients because they would benefit the most from more thorough investigations with both procedures, in order to establish a diagnosis and plan treatment(33,35,267) NJH (senior author, neuroradiologist) and JDP (co-author, neurosurgeon) collaborated clinically to perform these tests simultaneously, as part of a multidisciplinary care approach.

Lumbar infusion studies

The procedure for lumbar infusion tests was identical to what has previously been described in Chapter 3, with the difference that two 21 gauge Quincke needles were used, as a preferred means to separate the monitoring from the infusion line(45,48). The protocol includes a safety measure that require the infusion to stop if ICP increased to 40mmHg or above. After the end of the infusion test, pressure-controlled withdrawal of CSF was carried out whilst continuing to record the pressure.

Lumbar infusion studies, methodology and result interpretation have also been reported in the literature extensively(75,92,268). Our pressure monitoring equipment Edwards Lifesciences™ consists of fluid-filled manometry lines 180 cms long and 1.2 mm wide (internal diameter).

Direct retrograde cerebral venography

The venography technique and measurement of venous pressures in our hospital has been previously described in detail(35,36,269). Using the monitoring and sampling equipment of the infusion test, we recorded and extracted the mean pressure level, slow vasogenic waves and fundamental amplitude of the SSp waveform, (AMSSP_p), all identically to those processed from CSF_p. The venography catheter used however was longer and narrower (specific diameters unavailable retrospectively).

Data points of all parameters were distributed normally, and therefore we used paired student t-test for statistical difference in mean pressures. We explored that relationships between parameters with simple linear correlation.

7.2.3 Results

Mean age of the patients was 41 years (range 22-55). CSFp and SSp showed a strong coupling both statically as mean pressure averages (**Figure 7.1a**), as well as dynamically in their content of slow waves (**Figure 7.1b**) and pulse waveforms. Pulse waveforms increased as expected during an increase in both pressures provoked by infusion. We could not detect AMPSSp in 3/10 cases. In the 7 cases where AMSSp was visible, both waveforms were closely linked in their diastolic phases and divergent during systole (**Figure 7.1c**).

Statistically, mean SSp values correlated very strongly with mean CSFp at baseline: $R=0.94$; $p < 0.00005$; $N=10$ (**Figure 7.2a**). The pulse amplitudes of CSFp and SSp at baseline ($N=7$) were also strongly and significantly correlated (**Figure 7.2b**).

The coupling was also present during infusion, with SSp rising in parallel to CSFp ($R= 0.92$; $p<0.003$; $n=7$, and the changes of both pressure correlated strongly ($R=0.97$; $p=0.0007$; $N=7$) (**Figure 7.3a**). The slopes of the amplitude – pressure lines, as mentioned in Chapter 3 (slopes of the linear regression between AMP of CSFp and CSFp versus SSp and AMP of SSp), also correlated strongly during infusion ($R = 0.97$; $p<0.005$; $N=7$)(**Figure7.3b**).

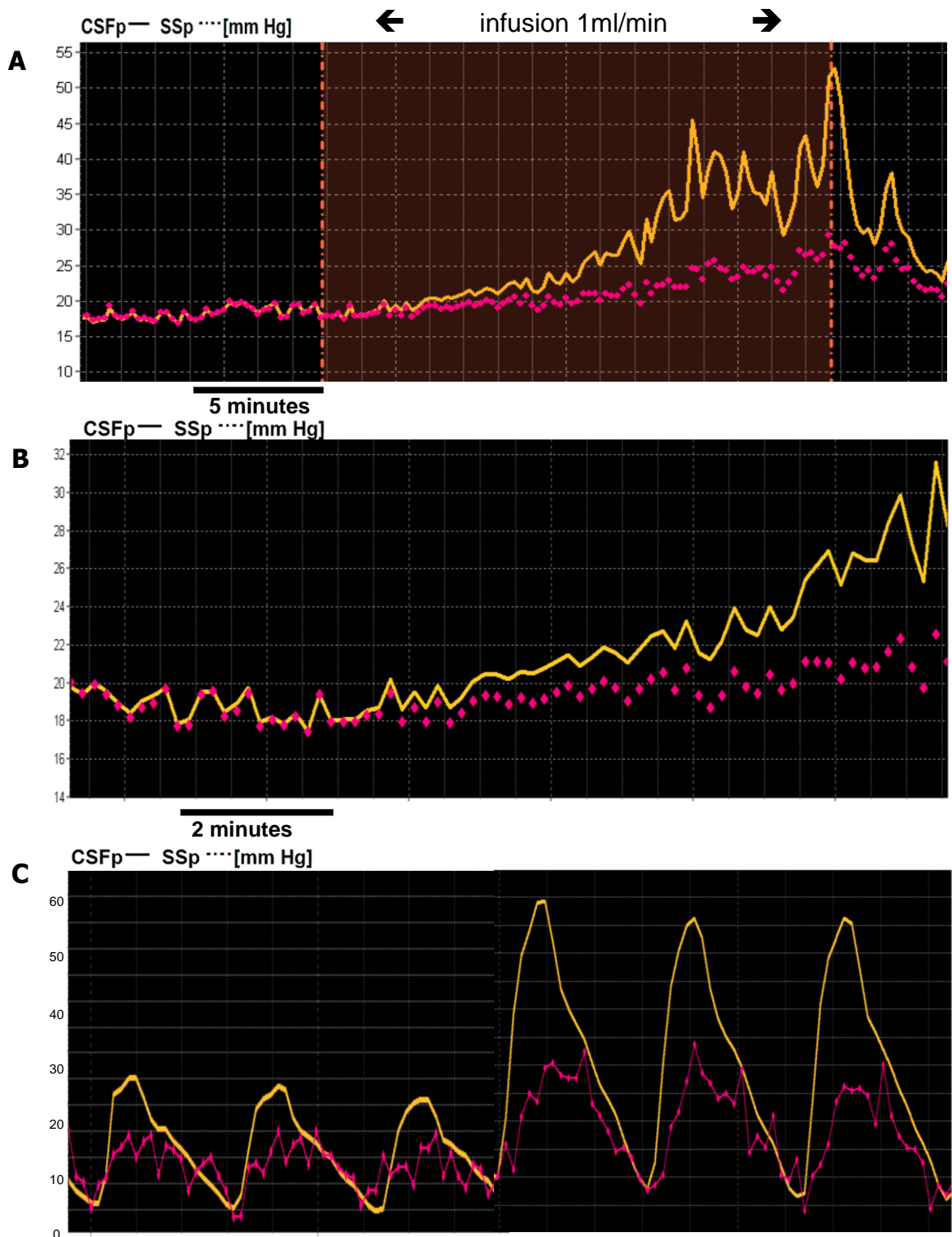


Figure 7.1: Observational demonstration of the static and dynamic coupling between CSFp and SSp. **A:** Static coupling between the mean CSFp (upper, darker trend) and mean SSp (lower, dotted trend) values at baseline, during and after the end of infusion (the infusion period is marked as an event represented by the white area in the graph). **B:** Dynamic coupling between the slow vasogenic waves of CSFp (upper, darker trend) and SSp (lower, dotted trend). **C:** Coupling between the pulse amplitudes of CSFp and SSp at baseline and during infusion.

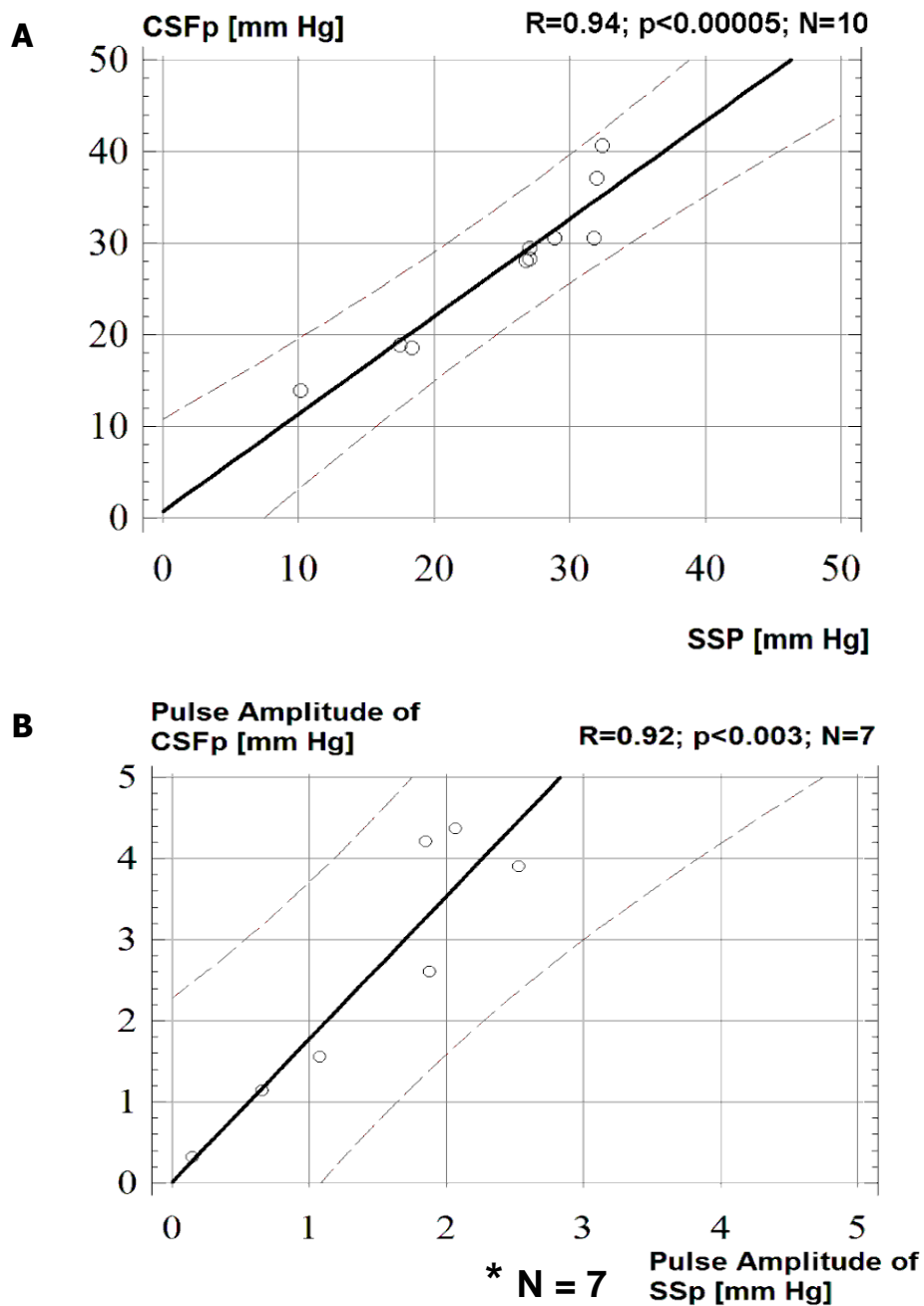


Figure 7.2: Coupling of CSFp and SSp at baseline. A: Linear regression demonstrating the coupling between CSFp and SSp at baseline B: Coupling between the pulse amplitude of CSFp and SSp at baseline. Recording of the amplitude was only possible in 7 out of the 10 cases.

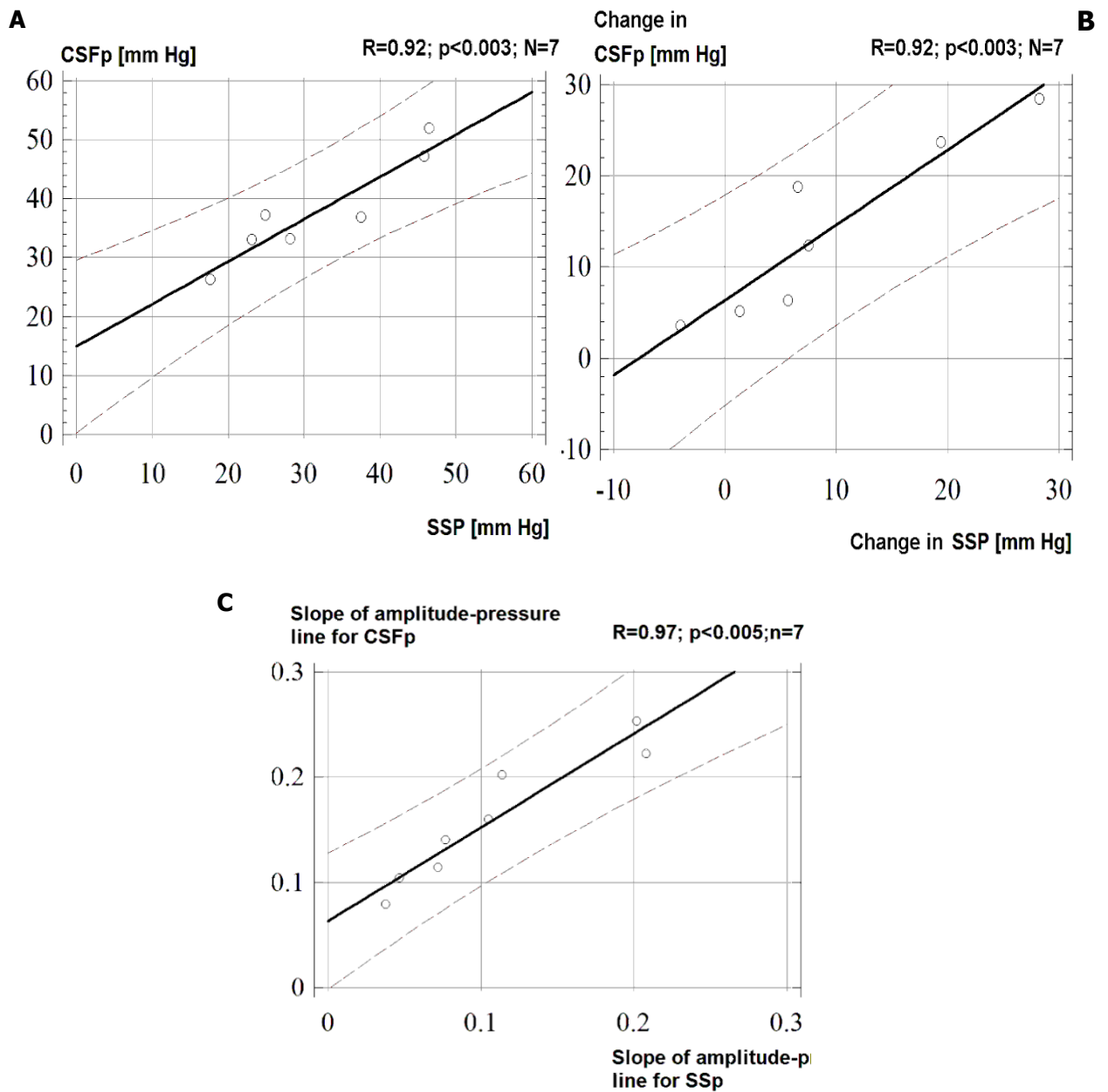


Figure 7.3: Coupling between CSFp and SSP during infusion. A: Linear regression demonstrating the maintenance of the coupling between CSFp and SSP during infusion B: Strong correlation of the changes between CSFp and SSP during infusion, when CSFp is increased artificially using Hartmann's solution.

Table 7.1. Mean values of pressures during baseline, infusion and drainage.
CSFp: Cerebrospinal Fluid Pressure. SSp: Pressure of the Sagittal Sinus

	CSFp [mmHg]	SSp [mmHg]	p-value	CSFp – SSp [mmHg]	p-value
Baseline	27.0±2.3	25.2±7.5	0.026; N=10	2.34±2.72	0.01953
Infusion	38.0±8.0	33.1±12.0	0.01; N=7*	4.9±4.0	0.026; N=7*
Drainage	12.7±5.6	16.0±2.7	0.02; N=8	-3.2±3.9	0.0097; N=8

* In 3 patients only drainage was performed, as baseline CSFp was >40 mm Hg

We obtained a Jugular Venous Pressure (JVP) measurement in 5 patients, measuring on average 10.43 ± 3.8 mmHg. JVP during one of the infusion tests is shown in **Figure 7.4a**. Central Venous Pressure (CVP) was measured on one patient and was relatively stable during infusion and on average 11.6 ± 2.2 mmHg.

During drainage the overall correlation between the 2 pressures was $R=0.78$; $p=0.065$, $N=6$ (**Figure 7.4b**). While draining down to a certain CSFp and SSp, SSp appeared to stabilize at a level close to JVP, while CSFp naturally continued to decrease.

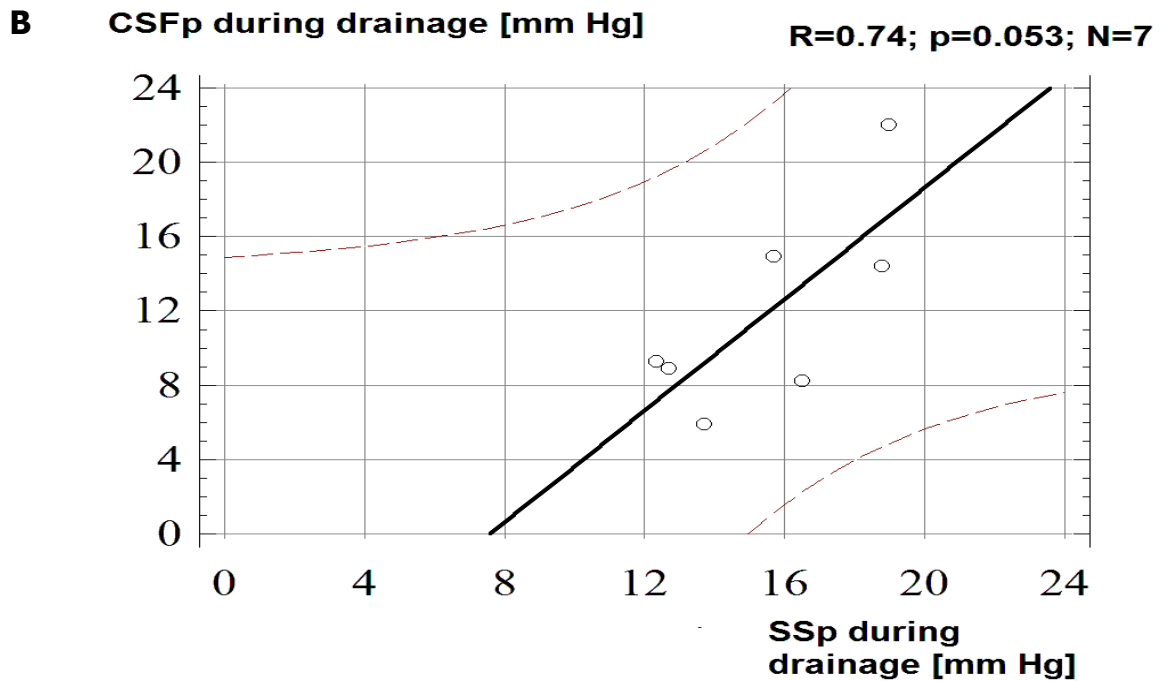
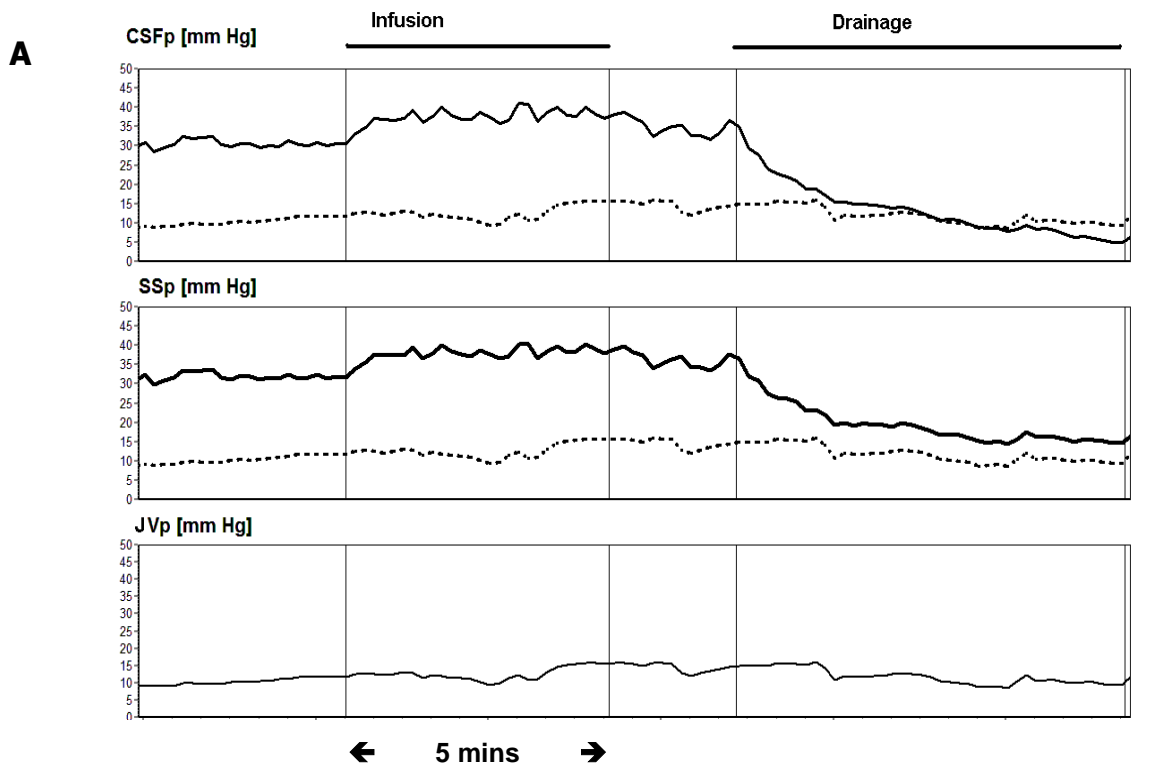


Figure 7.4: Correlation between CSFp and SSp during CSF drainage. A: Overview of CSFp and SSp and JVP during infusion and during drainage of CSF. JVP is projected as a dotted line on the CSFp and SSp (SSp) panels, demonstrating that CSFp continues to drop after reaching JVP; in contrast, SSp reaches values close to JVP (CVP) and remains stable at this value as CSFp continues to decrease. **B:** Correlation between CSFp and SSp during drainage of CSF. JVP: Jugular Venous Pressure

Table 7.2 summarises the differences between CSFp, SSp and JVP at the end of drainage

Table 7.2. Differences between CSFp, SSp and JVP at the end of drainage in N= 5 patients

	Difference [mmHg]	Significance of difference
CSFp -JVP[mm Hg]	-2.2±3.4	P=0.026;
SSp –JVP [mmHg]	4.27±3.0	P=0.004;

Davson’s equation re-visited for PTCS

After investigating the results of SSp and CSFp coupling in PTCS, we sought to simplify Davson’s equation in these patients

As a result of their linear relationship, SSp could be replaced with a function of CSFp in the format $SSp = a * CSFp + b$. An example of the performed linear regression is given in **Figure 7.5**. In the one patient where CVP was measured and was found around 11 mmHg, the intercept of the correlation was 9.21, which is within limits for measurement error (zeroing of external transducers).

The average slope of all linear regressions, a, was calculated as 0.70 ± 0.14 for N=9 patients and the intercept b were calculated as 6.3 ± 3.53 mmHg and appeared to physiologically correspond to the measured CVP.

R = 0.9962; Slope = 0.7763; Intercept = 8.969

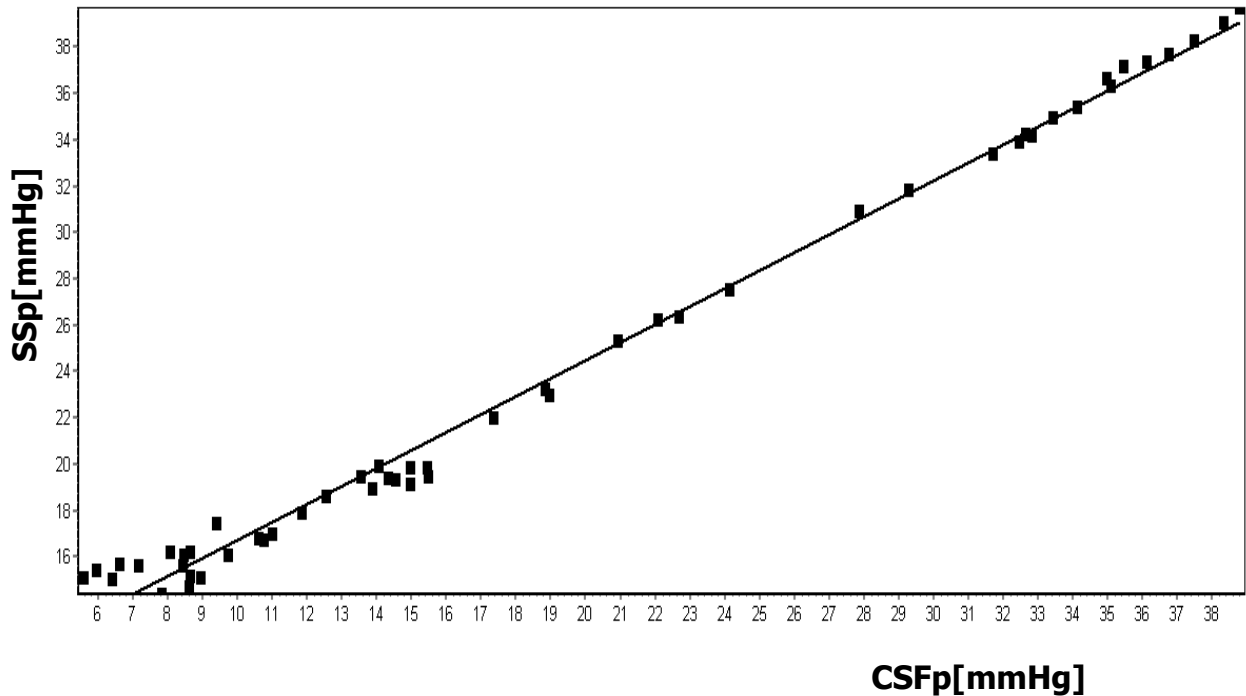


Figure 7.5: Example of the linear regression analysis between CSFp (ICP in the figure) and SSp (Venous in the figure) for 1 out of the 9 studied patients. The slope and the intercept of the regression for each patient were averaged and were used to express SSp as $SSp = a \cdot CSFp + b$, $a =$ slope and $b =$ intercept. SSp, expressed this way, can be used in Davson's equation to simplify the calculations of its parameters in PTCS patients. Notice that below CSFp 10 mmHg, SSp stopped to decrease further, while CSFp was easily drawn down by further drainage (JVP was 8 mm Hg in this patient, CVP was ~ 11 mmHg).

Therefore, Davson's equation could be rewritten for PTCS as:

$$CSFp = Rout \cdot If + a \cdot CSFp + b$$

and subsequently:

$$CSFp = (Rout \cdot If + b) / (1 - a),$$

The average product of $Rout \cdot If$ is 3 mmHg(229) 1.5 in PTCS with the corrected Rout (see below), therefore the average $CSFp = (1.5 + 6.3) / 0.3 = 26$ mmHg.

Corrections needed to estimate Rout in PTCS

In hydrocephalus, when SSp is not coupled to CSFp, constant rate infusion study enables calculation of Rout as:

$$R_{out} = (CSFp_{plateau} - CSFp_{baseline}) / \text{Infusion rate}$$

This is a simple use of Davson's equation under the assumption that SSp remains constant.

In PTCS SSp increases with CSFp. R_{out} calculated as above is therefore overestimated. It should be decreased by a correcting factor equal to:

$$(SSp_{plateau} - SSp_{baseline}) / \text{Infusion rate.}$$

In our material, R_{out} calculated without correction was 16.1 ± 2.1 mmHg/ (ml/min), while after correction 5.2 ± 1.4 mmHg/ (ml/min) ($p < 0.001$), therefore approximately 67% lower.

Discussion

We have presented physiological data that show pathophysiological and therapeutic understanding of CSF dynamics and CSF drainage in PTCS. In addition, we showed that:

- Davson's equation can be simplified in PTCS, by expressing SSp as a function of CSFp with our proposed formula
- R_{out} calculated during infusion test without measurement of SSp is overestimated, and does not have the same meaning like in hydrocephalus

Our results demonstrate a direct coupling between the CSFp and SSp not only in static, mean values but also in their dynamic contents of the two pressures, mainly the pulse amplitude and the slow waves. Thus, we can confirm the role of venous sinus collapsing in generating significantly raised CSFp, or at least contributing to the pathophysiology of PTCS via a circular coupling between CSFp and SSp.

Traditionally, SSp in normal individuals is perceived as constant, with many variations(114,194,235). However, in PTCS, SSp and CSFp exhibit remarkable parallel variability and are more than a single number.

There are known conditions where SSp does not remain constant during infusion or other causes of CSFp rise, among which are an open fontanelle, the presence of a myelomeningocele, Chiari malformation and individual variations(35–38,156,194). On the other hand, secondary thrombosis and narrowing of the cerebral venous sinuses that in turn are recognised causes of PTCS have been shown to increase SSp without any changes during infusion(35,235)(& brain physics laboratory unpublished material).

The direct and significant coupling between changes in CSFp and SSp was maintained during infusion, however the two pressures appeared to diverge compared to baseline (as shown in Figure 7.6). This increase in distance between waveform peak of the two pressures is most likely caused by the fact that initially all the infused fluid is stored in the intracranial compliant space, and within the time closer to plateau, absorbed to the sagittal sinus through R_{out} (48,75). Baseline pulse amplitude was well correlated in CSFp and SSp (as shown in Figures 7.6 and 7.8). During infusion, both amplitudes increase proportionally and linearly. Similarly, there was a proportional rise in respiratory amplitude in CSFp and SSp. From the correlation of the two pressures, it is not possible to conclude on causation, i.e. mainly whether raised SSp is the result of raised CSFp as a primary cause, or vice versa, as is the case e.g. in venous sinus thrombosis.

Stenting versus shunting in PTCS

High CSFp is clinically observed in PTCS and can range from 20 to 40 mm Hg. Our study indicates also that ‘low CSFp’ steady - state may be achieved by draining CSF until CSFp falls below central venous pressure. Theoretically, ventriculo-atrial shunt should be sufficient to control CSFp below CVP. However, in PTCS, where ventricles are usually small, placement of a ventricular drain may be disputable. If a shunt is used, it should have hydrodynamic resistance greater than classic differential shunts (3-4 mm Hg/(ml/min) – e.g. the Orbis-Sigma valve can be considered (41). In our case, we have demonstrated how CSF drainage, represented in neurosurgical treatment by shunting, can help reduce and stabilise SSp in PTCS by interrupting a “positive

feedback loop” of increases in CSFp causing increases in SSp and vice versa. During drainage, both pressures decreased until a certain point (most probably JVP) when CSFp can decrease further while SSp remained constant. This CSFp level could possibly be targeted therapeutically when attempting medical or surgical treatment. Unless this decoupling is achieved with treatment, it is possible that symptoms and syndrome activity will persist.

Another concept was proposed in the early 2000s and incorporated in clinical practice: to stent the transverse sinus, when MRI venography demonstrates its collapse(33). But if the whole sinus system is collapsible, narrowing may ‘travel’ along the section of stented sinus and it may collapse in most distal non-stented part of the vessel. Furthermore, it is not certain if the decrease in venous pressure can equivocally promote a decrease in CSFp. We do not have such corresponding data to support what happens to CSFp and venous pressure after stenting. The response of our patients to CSF drainage could mean that our selected patients may be successfully treated with shunting. Further investigations related to persistent venous stenosis and CSFp-SSp gradient after CSF drainage could elucidate the pressure correlation in relationship to management outcome.

Elucidating the pathophysiology of PTCS

Finally, from the simplification of Davson’s equation in PTCS, CSFp is mathematically increased and is estimated to be around 26 mmHg. This number is almost identical to the mean baseline CSFp in our patients, which was 27 mm Hg. Subsequently, both theoretically and from in vivo data, this formula may explain why in PTCS with CSFp- SSp coupling the baseline intracranial pressure is elevated. Additionally, since Rout reported until recently could only be estimated through the classical Davson’s equation, we are able to report a new estimation of Rout in PTCS: in our patients, this was on average <7 mmHg*min/ml and perhaps this is the case for many similar patients. Based on observation from our experience with most of our other PTCS patients, that unlike hydrocephalus patients CSFp plateaus relatively close to the baseline value, signifying normal CSF circulation,. Empirically though, we have also observed a few exceptional cases, where a higher rise in CSFp is observed

and therefore especially for these, knowledge of the SSp could provide valuable information on disease activity and differential diagnosis.

If part of the transverse sinus is compressible, any rise in CSFp can decrease its lumen, increase the hydrodynamic resistance for sinus blood flow, increasing in the same way the SSp (if cerebral blood flow stays constant), which in turns increases CSFp, according to Davson's equation. This mechanism works as a 'vicious circle' until CSFp and SSp reach an elevated state of equilibrium. This has been previously numerically simulated using an elegant mathematical model. The model forecasted that the system with collapsible transversal sinus (represented as a 'Starling Resistor')(270) has two steady states: at low and at high CSFp.

Generalisability of these findings in PTCS & other cerebral venous pathologies

Furthermore, an important question that arises from our study is, whether the direct coupling of CSFp to SSp is limited to PTCS with particular underlying pathology, all PTCS patients or may also play a role in acute intracranial hypertension seen during cerebral oedema (head injury, stroke, meningitis, etc.). Studies in TBI from early work suggested that >60% of ICP should be directly related to vascular mechanisms, rather than CSF circulatory component.(57,211,271–273) We have previously investigated SSp and CSFp during infusion on a single case of a post-TBI patient (case not published). SSp appeared to stay constant despite rises in CSFp. This interesting finding potentially indicates that the coupling does not exist in every condition involving raised ICP.

Finally, even though our results involve only 10 patients, we obtained quite strong and significant findings that could potentially be translated to some or the majority of PTCS patients, both in the adult and paediatric populations. Prospective studies leading to randomised controlled trials should be designed, aiming at investigating the mechanisms of SSp and CSFp, effect of stenting versus shunting and at generalising these current findings and at stopping the reported pathophysiological coupling of the two pressures.

Limitations

We did not record or collect any information about arterial pressure waveforms and therefore its potential influence on the interaction between the CSF and SSp. Detailed analysis of the frequencies of the CSFp and SSp/JVP was not possible using these retrospective data, as the predominantly clinical design of the tests did not permit us to ensure we obtained all required information of frequency properties of the two pressure measurement setups: in CSFp, as mentioned in methods, a shorter (180cms only) and wider monitoring line connected to its own transducer was used, however in SSp a longer, thinner catheter was used connected to an external transducer. This makes accurate spectral analysis on CSFp-SSp questionable.

Conclusion

CSFp and SSp are coupled in at least some cases of PTCS, both at baseline and during infusion. CSF drainage can lead to uncoupling of the two pressures, terminating this pathological positive feedback loop. Rearranging Davson's equation according to an increasing SSp may explain why in PTCS baseline ICP is elevated and usually >20mmHg.

7.2 CSF dynamics in paediatric pseudotumour cerebri syndrome

The results presented in this section have been published in Child's Nervous System:

Lalou AD, McTaggart JS, Czosnyka ZH, Garnett MR, Krishnakumar D, Czosnyka M. Cerebrospinal fluid dynamics in pediatric pseudotumor cerebri syndrome. Child's Nerv Syst. 2020;36(1):73–86.

7.2.1 Introduction

In chapter 6, I have reported the results from examining CSF dynamics in NPH. Pseudotumour cerebri syndrome (PTCS) differs in many ways from NPH, and has been traditionally known as a disease of post-pubertal biological females, most commonly with raised BMI(29,34,39). After many reports for over 120 years, different names and nomenclature including benign and idiopathic intracranial hypertension, the syndrome has also been established as a cause of headaches and papilloedema in pre-pubertal children. PTCS is diagnosed clinically using the modified Dandy criteria (see above section 7.1, patients and methods paragraph for the criteria) (31,274) or by using the recent Friedman classification [papilloedema, normal neurologic examination except for cranial nerve abnormalities, CSFp>20 mmHg (28 cmH₂O), normal brain imaging and CSF composition] (29)Lumbar puncture (LP) has been utilised clinically in order to obtain CSF pressure (CSFp) measurements and establish normative thresholds both for adults and for children. The most recent evidence and guidelines report a threshold of 28cm CSF for obese and/or sedated children and 25cm CSF for normal weight and non-sedated children, in order to meet one of the criteria for a diagnosis of definite PTCS (29,30,266). Those thresholds have been derived from years of “snapshot” measurements of CSFp, utilising data from paediatric populations distributed at the higher percentiles (30). Neither has ICP monitoring methodology been used to validate the accuracy of such values, nor have there been randomized studies to reliably confirm that the thresholds are clinically relevant (29,30,55,56).

Years of continuous monitoring and analysis of intracranial pressure (ICP) has shown that ICP should be monitored using appropriate materials and methods, that do not include “snapshot” manometry. LPs are prevalent and useful in everyday clinical practice, however it is well-known that the measurements can be affected by posture, movement, pain/stress, sedative/anaesthetic agents etc, which can lead to unreliable

estimation of CSFp . It is also important to consider in everyday clinical practice that ICP levels are dynamic (50,52,56,115), which creates a lot of pitfalls for accepting “normal” and “raised” values based on a random and single datapoint measurement. This is one of the principal reasons why overnight ICP monitoring remains the gold standard for understanding and interpreting ICP (52,56,114,131,220,275). A shorter and more practical recording with an infusion test, with baseline ICP for around 20 minutes, together with infusion of artificial CSF to unravel any disturbances that would need long-term monitoring to be otherwise detected, is reported to be more reliable than a single opening pressure measurement (25,45,118,139) (Figure 7.6).

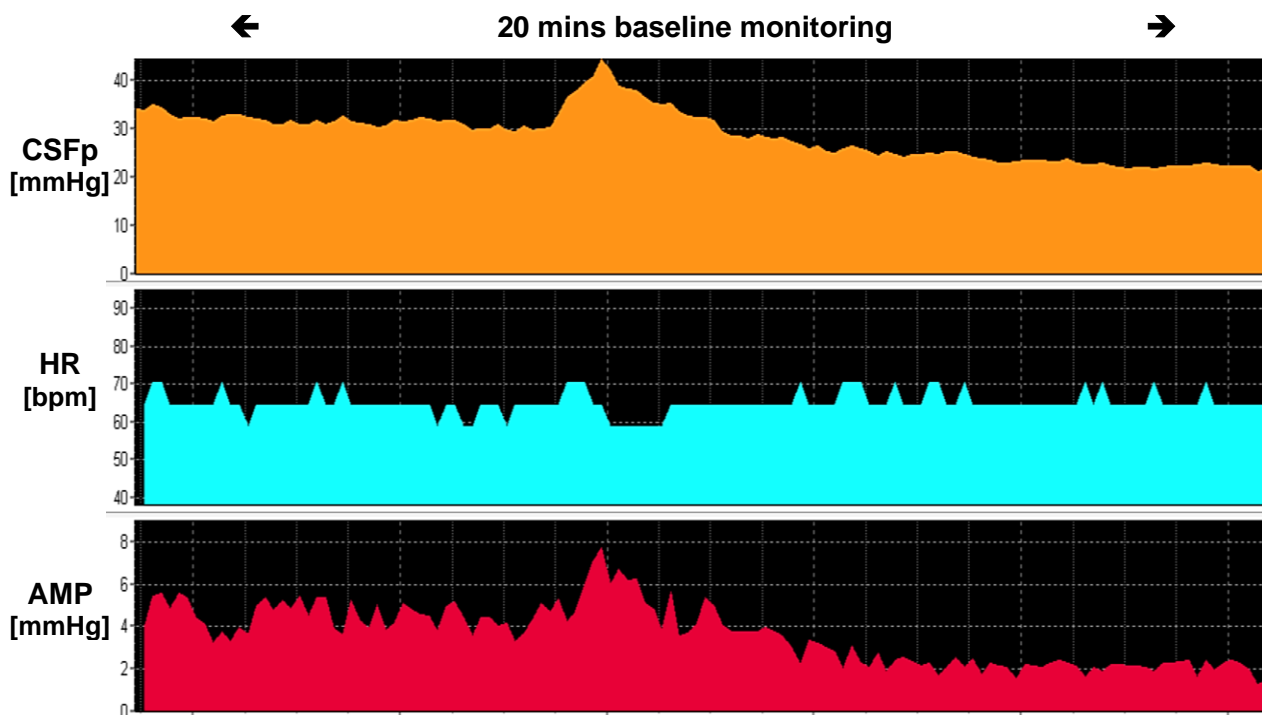


Figure 7.6 Variability of CSF pressure. Upper panel: Paediatric patient after a LP and connection to the computer for monitoring, showing initially raised CSFp of 32 mmHg, spontaneously receding to 20 mmHg after 20 minutes of monitoring.

For the sake of clarity and accuracy, we refer to CSFp when connection for pressure manometry is obtained through the spinal canal via LP, and ICP when the connection is directly intraventricular or intraparenchymal.

At Cambridge Paediatric Neurology in collaboration with Academic Neurosurgery, we accept referrals of children with suspected PTCS, that under our service routinely

undergo a lumbar infusion study(276,277), with recording, storage and analysis of CSFp and its dynamics, including AMP, vasogenic waves (b-waves), elasticity and RAP (24,100,278–280). As such, they can be accurately diagnosed with a raised CSFp (definite PTCS) and “normal” CSFp (probable PTCS more reliably than with standard LP, but also investigate the CSF dynamics of each child.

Since clinical testing of CSF dynamics has been so far mainly applied to paediatric and adult hydrocephalus, there is little reported information on CSF dynamics PTCS, especially in paediatric patients. In adults with PTCS and venous stenosis, a coupling between CSFp and sagittal sinus pressure (SSp), at baseline and during infusion has been shown (32) and is described analytically in section 1 of this chapter. Our previous paper (276), constitutes to the best of our knowledge, the only preliminary account of CSF dynamics in paediatric PTCS. We have aimed to investigate the CSF dynamics of paediatric PTCS patients and what information they offer compared to established guidelines and investigations. For this purpose, we performed a retrospective review for all patients referred to our tertiary paediatric services (≤ 16 years old) for consideration of a diagnosis of PTCS from 2006-2016.

7.2.2 Methods

Patient selection

We selected 31 children that underwent infusion test due to clinical necessity in our centre for primary PTCS. 40/72 of the total children referred to our specialist service from 2006-2016 had undergone an infusion test, however 9 of these had an identifiable, possible cause for PTCS that could further confound our findings. We therefore analysed the results of the remaining 31, all of whom underwent CSFp monitoring via LP connection, with or without infusion. The results of 7 of these patients have been published previously (276).

Patient classification

We have not analysed clinical, papilloedema and neuroimaging correlates. Papilloedema had been confirmed or excluded by a neuroophthalmologist and

neuroimaging reported by a neuroradiologist. Further investigations and clinical evaluation by DK (one of the authors) led to the final Friedman classification: 5/5 criteria required for definite PTCS: 1) Papilloedema. 2) Normal neurological examination except for cranial nerve abnormalities 3) Neuroimaging: Normal brain parenchyma on MRI for typical patients (female and obese), and MRI ± magnetic resonance venography for others. 4) Normal CSF composition 5) CSFp >25 cm H₂O (20 mmHg) of 28 cmH₂O if obese/anaesthetised.

13/31 children fulfilled criteria 1-5 were classified as Definite PTCS [**Group A**], 13/31 only had criteria 1-4 and were therefore classified as Probable PTCS [**Group B**], and 5/31 classified as Not PTCS since none of them had papilloedema and did not meet the criteria for PTCS without papilloedema either [**Group C**] (29).

Infusion Test

The infusion test procedure, exactly as performed in Cambridge, has been thoroughly described in multiple publications(25,48,66,71,97,112,268), as well as in Chapter 3.

We always aim, as per local protocol, to perform the procedure on awake children with local anaesthetic (lidocaine and prilocaine cream). We also use Entonox (50% nitrous oxide 50% oxygen mixture) until intrathecal access is assured. For children with high BMI and/or non-compliance, GA and/or x-ray guidance, with MAP, ETCO₂ and temperature maintained stable and within the recommended normal ranges. GA is induced by standard procedure of our paediatric anaesthesiologists (propofol, remifentanil, rocuronium). We also compared GA versus non-GA children. MC and ADL re-analysed all raw infusion test data using ICM+ as shown in chapter 3.

Some children had undergone a standard LP at their local centre of referral before our infusion test, and we used linear correlation to investigate how similar these values were.

We used the thresholds for CSF test parameters from previously suggested thresholds in hydrocephalus patients, keeping in mind that those could be altered in PTCS. The calculated SSp is a derivative of a theoretical model and does not necessarily reflect

the individual's real SSp. Thresholds for SSp, and AMP have been reported as 7mmHg and 2mmHg respectively(107,229). For PTCS, infusion test cannot reliably estimate resistance to CSF outflow, as SSp usually rises with CSF pressure, making the value of this parameter overestimated (see section 7.1). The lower breakpoint (LBP) of the amplitude-AMP-P linear regression line has mainly been described in NPH, defined in Chapter 3 and the slope of AMP-P has a threshold of >0.16 (233,261). The upper breakpoint (UBP) of the same line has been reported in TBI patients and experimental animal models of intracranial hypertension as the breakpoint above which the AMP-P relationship becomes negative. It probably represents a critical point of CSFp, above which cerebral perfusion pressure has reached the lower limit of autoregulation and approaches the level of critical closing pressure of cerebral arterioles(281), therefore ischaemia develops with passive arteriolar collapse, resulting in decreased pulsatility in the cerebrovascular bed(94,100,282,283).

Statistical analysis

ADL performed all statistics. After testing for a normal distribution, parametric or non-parametric tests were used accordingly to compare differences in CSF dynamics parameters between the paediatric PTCS groups. Single-sample Wilcoxon test and t-test were used to compare parameter means to their reported normative values from the literature. We used the Kruskal-Wallis test followed by pairwise Wilcoxon test to analyse differences among 3 groups. The correlations between different CSF dynamics parameters were sought using Pearson's or Spearman's correlation coefficient. Multiclass ROC was performed to test the diagnostic value of CSF dynamics versus the 3 clinical groups using the package pROC(284).

7.2.3 Results

Demographics

Ethnicity, BMI and other characteristics not of significance for our current analysis were not included. Female: male ratio was approximately 5:1 and mean age around 12 ± 3 years in all 3 groups. BMI did not differ significantly between the analysed groups.

Infusion test CSFp and LPs

10 children had a CSFp measured using traditional LP manometry columns on a timeframe of 2 weeks – 3 months prior to the infusion. The correlation between the LP CSFp and infusion-derived averaged, baseline CSFp was weak and non-significant ($R=0.30$; $p=0.3977$, **Figure 7.7**).

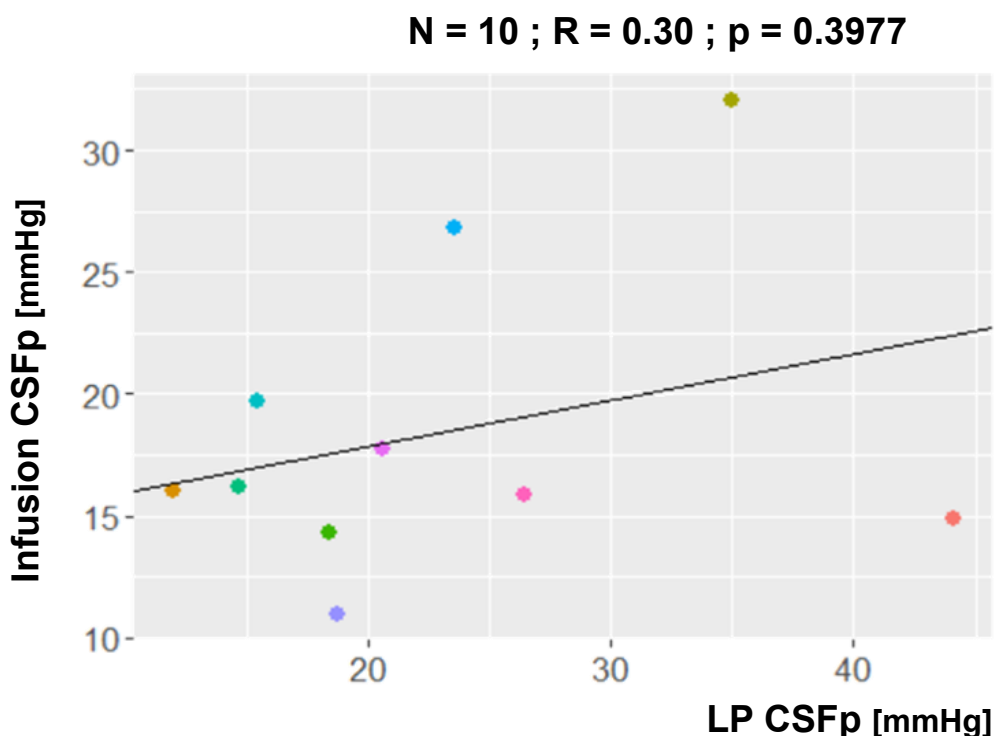


Fig. 7.7 Discordance between CSFp derived from LP performed either right before the CSF infusion study or within 3 months before the infusion study

CSF dynamics in definite, probable and excluded PTCS diagnosis

3/13 Definite PTCS children only had baseline CSFp monitoring followed by CSF drainage, due to significantly raised CSFp (≥ 40 mmHg).

None of the parameters, except for SSp, were distributed normally. CSFp was de facto increased in definite PTCS (29.18 ± 7.72 mmHg), and significantly higher than the probable (15.31 ± 3.47 mmHg; $p=1.644e-05$) and not PTCS (17.51 ± 5.87 ; $p=0.014$) groups. AMP was also higher in the Group A (2.18 ± 2.06 mmHg) than in Group B (0.68 ± 0.37 ; $p=0.014$). However, there was no difference in either CSFp or AMP at baseline between Groups B & C ($p=0.70$ and $p=0.77$ respectively). **Figure 6.8** depicts

a representative example of a CSF infusion test results in Definite PTCS vs probable and not PTCS.

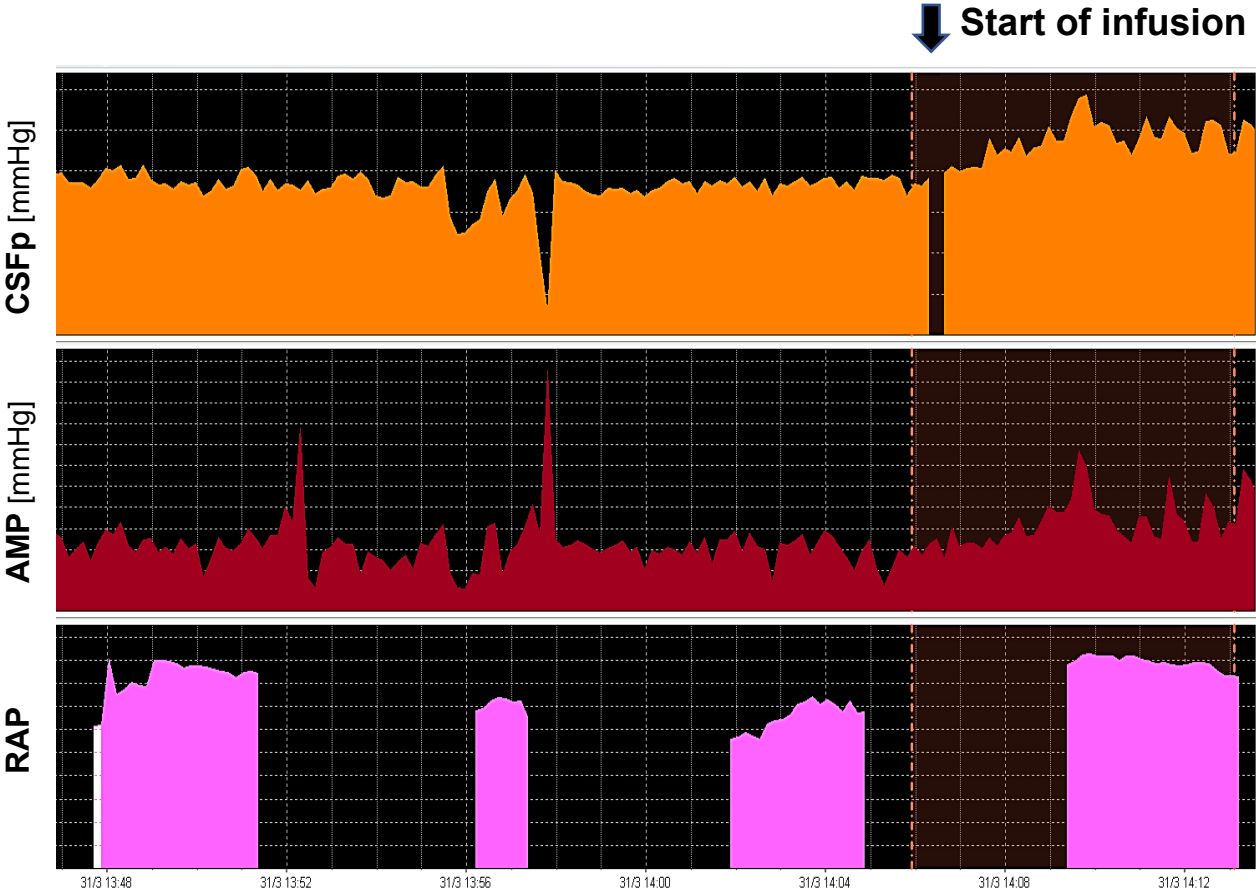


Fig.7.8 Representative example of a CSF infusion study on a paediatric patient with definite PTCS. A 10-15 minutes baseline is monitored to ensure stable baseline pressure. The start of infusion is indicated with an arrow and the infusion period is highlighted after the start on the right end. CSFp is elevated, usually >20 mmHg, with low resistance to CSF outflow demonstrated from the generally low plateau of CSFp during infusion.

Numerical values of CSF dynamics in the 3 groups are shown analytically in **Table 7.3**.

Table 7.3: Baseline and infusion-based CSF dynamics CSF dynamics parameters of the 3 clinically classified paediatric PTCS groups. Values are represented as mean \pm SD. A different Number of patients (N) is shown in each row for **Group A**, since only baseline parameters were monitored in 3/14 patients. RAP: index of compensatory reserve, from the correlation of AMP and ICP.

Variable	A: Definite PTCS	B: Probable PTCS (N=13)	p-value A- B	C: Not PTCS (N=5)	p-value A - C	p-value B - C
Baseline CSFp [mmHg]	29.18 \pm 7.72 (N=13)	15.31 \pm 3.47	1.644e-05	17.51 \pm 5.87	0.01368	0.7028
AMPb [mmHg]	2.18 \pm 2.06 (N=13)	0.68 \pm 0.37	0.01382	0.89 \pm 1.03	0.1433	0.7673
Baseline RAP	0.58 \pm 0.3 (N=13)	0.46 \pm 0.18	0.2813	0.37 \pm 0.12	0.2075	0.4016
Elasticity [1/ml]	0.36 \pm 0.19 (N=10)	0.39 \pm 0.26	0.9505	0.15 \pm 0.06	0.002671	0.1031
SSp [mmHg]	18.99 \pm 4.08 (N=10)	9.55 \pm 11.9	0.0014	8.65 \pm 1.17	0.007992	0.6928
CSFpp [mmHg]	32.89 \pm 2.92 (N=10)	25.42 \pm 4.47	0.0002243	25.25 \pm 6.1	0.03996	0.775
AMPp [mmHg]	2.1 \pm 1.11 (N=10)	1.55 \pm 0.86	0.2264	2.13 \pm 1.86	0.953	0.8436
CSFpp – CSFpb [mmHg]	7.44 \pm 2.73	10.11 \pm 4.06	0.1661	7.74 \pm 2.9	0.953	0.3873
AMPp – AMPb [mmHg]	0.93 \pm 0.7	0.88 \pm 0.7	0.99	1.24 \pm 1.15	0.6787	0.775
Amp-p slope	0.15 \pm 0.09 (N=10)	0.09 \pm 0.05	0.1621	0.13 \pm 0.08	0.8539	0.3233
LBP [mmHg]	NA (N=0)	10.5 \pm 2.12 (N=2)	NA	15.5 \pm 3.53 (N=2)	NA	0.3333
UBP [mmHg]	36.36 \pm 5.01 (N=8)	34.5 \pm 11.39 (N=4)	0.99	29.5 \pm 7.78 (N=2)	0.5714	0.8
Slow waves at baseline [mmHg]	1.16 \pm 1.43 (N=13)	0.83 \pm 0.85	0.8798	0.79 \pm 0.56	0.99	0.99
Slow waves at plateau [mmHg]	3.21 \pm 2.51 (N=10)	4.9 \pm 7.07	0.7501	1.5 \pm 1.33	0.2828	0.5427

The LBP of the AMP-P line could not be detected in any of the patients in Group A, and it was present in 2/13 and 2/5 patients in Groups B and C respectively. An UBP was present in all groups, however not in all patients. In 2 of the children with definite PTCS, the UBP was observed at baseline (UBP at 36.36 \pm 5.01 mmHg), a phenomenon not occurring in the other 2 groups. The observed pattern of CSF dynamics in these 2 cases, is demonstrated for one of the patients in **Figure 7.9**.

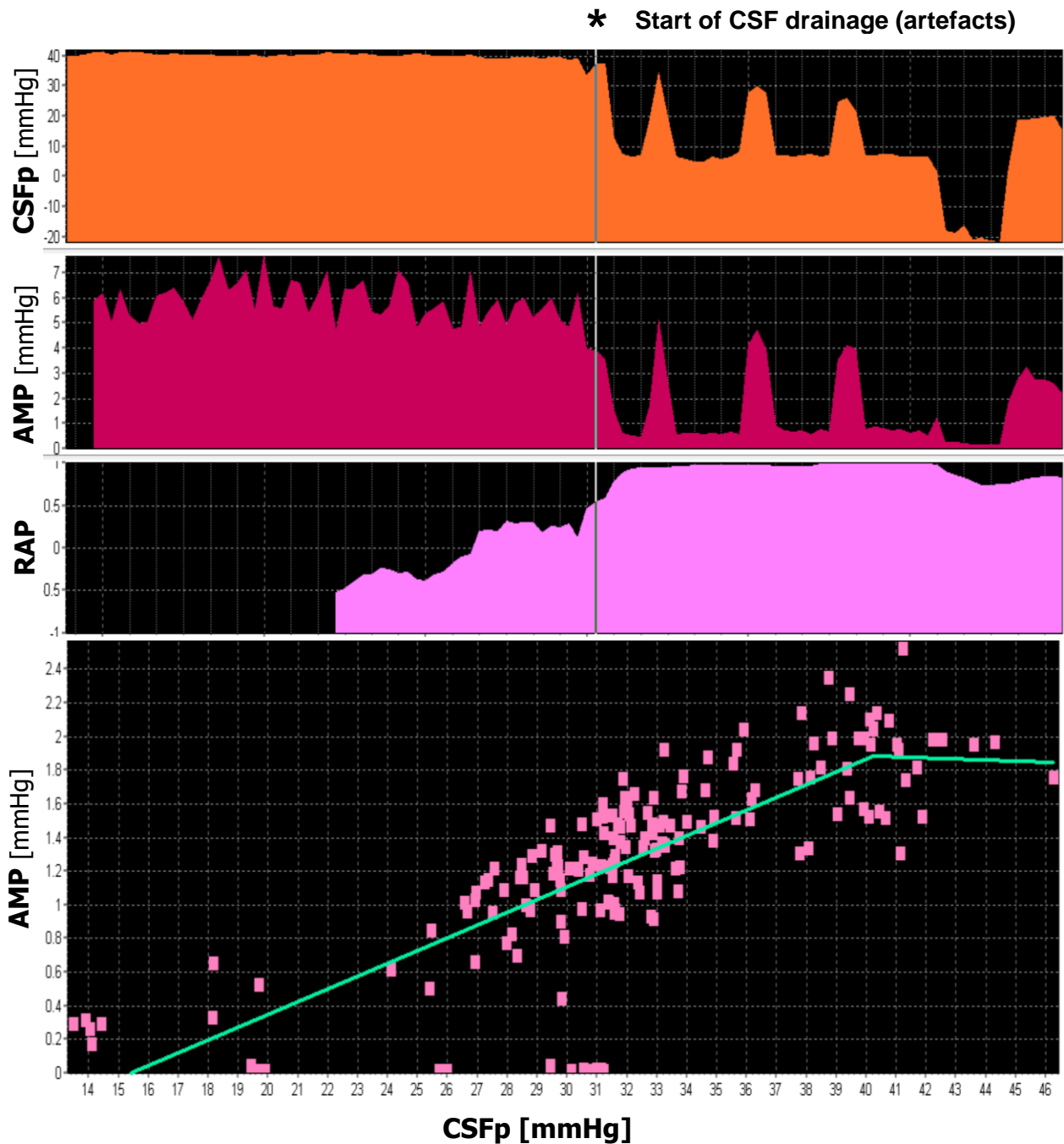


Figure 7.9: Upper panel: Critically high CSFp (42 mmHg), monitored in operating theatres under general anaesthesia. Initially, ischaemia is possible, caused by low cerebral perfusion pressure (CPP): mean arterial blood pressure was 65 mmHg, therefore CPP was 23 mmHg. During drainage, the positive correlation between AMP and CSFp was restored (RAP positive). It can be observed that CSFp, AMP and HR after the start of drainage contain a lot of artefacts. **Lower panel:** The transition point between low CPP and restoration of normal CPP represents the upper breakpoint of the Amplitude-pressure regression line, above which the linear correlation between AMP and CSFp tends to turn negative.

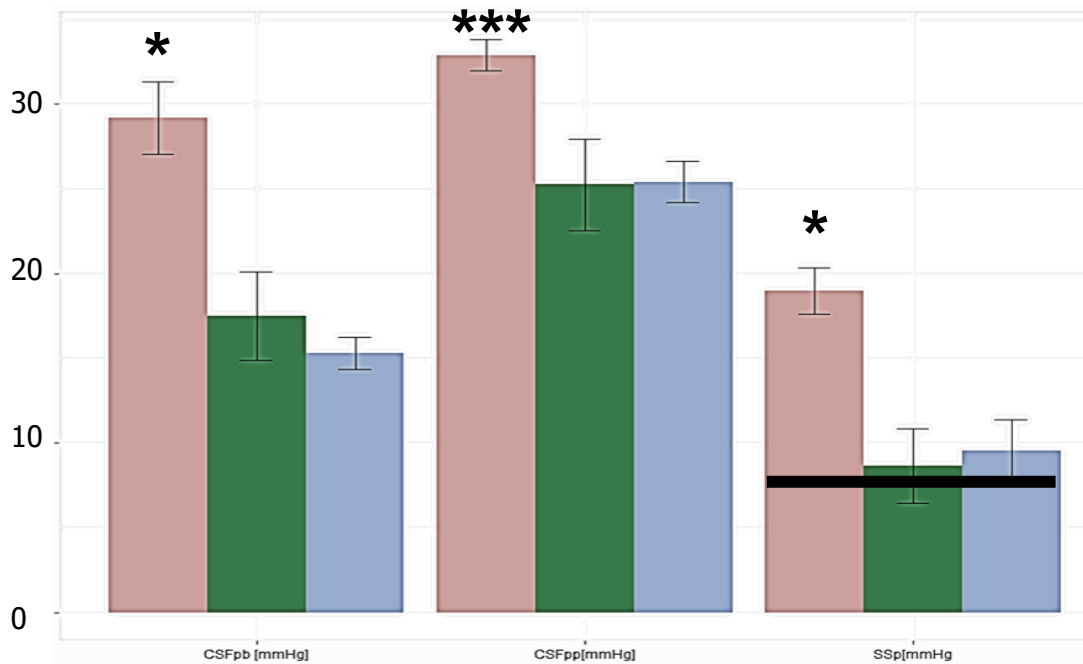
In Group A, SSp and elasticity were the only ones above their reported threshold (thresholds 7 mmHg; $p = 4.2e-06$ and 0.18 1/ml; $p = 0.001953$ respectively)(48,110,215,285–287). AMPb was not higher than 2 mmHg ($p=0.6848$).

In Group B, only the Elasticity was significantly higher than the threshold ($p=0.04257$). For Group C all values were not significantly different from the published normal range. These main CSF dynamic parameters of the 3 groups are illustrated in **Figure 7.10**.

Relationship between the CSF dynamics parameters in Groups A-C

SSp correlated with baseline CSFp in Group B ($R = 0.59$; $p\text{-value} = 0.03403$) and tended towards the same correlation in Group A ($R = 0.60$; $p\text{-value} = 0.05034$), with no correlation in Group C ($R = -0.016$; $p\text{-value} = 0.9833$). Similarly, elasticity showed a significant correlation with SSp in Groups A ($R = 0.67$; $p\text{-value} = 0.02807$) and Group B ($R = 0.59$; $p\text{-value} = 0.03193$), and not in Group C (negative correlation, not significant). There was no correlation between CSFp and RAP or AMP with SSp and Elasticity.

a Mean CSFp & SSp



b Mean AMP & compensatory reserve parameters

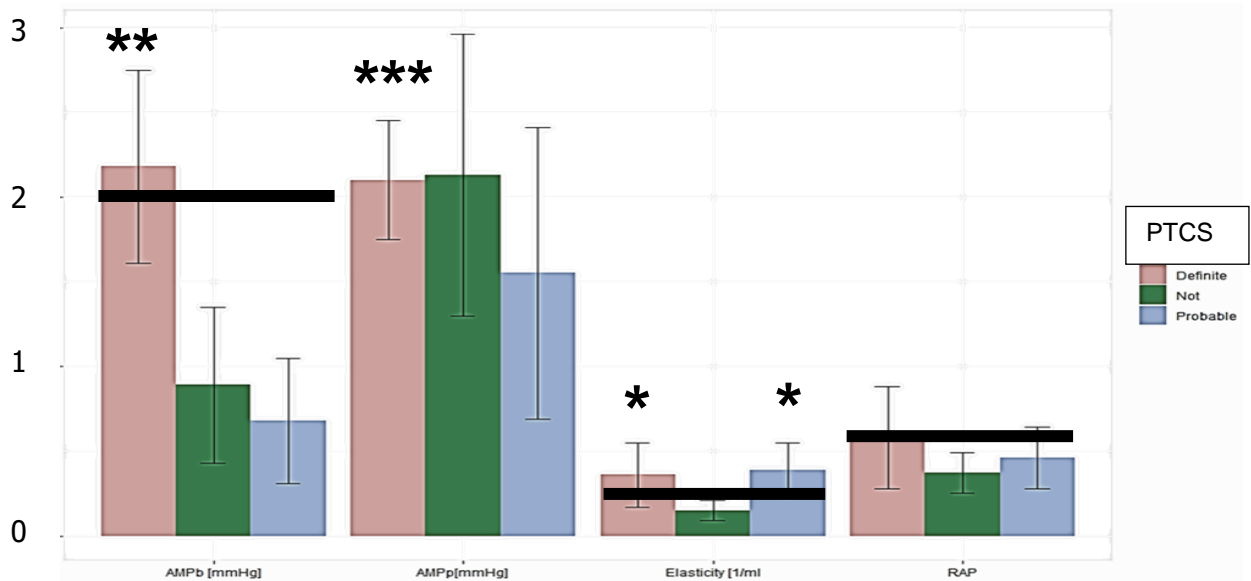


Figure 7.10: CSF Infusion Study parameters versus thresholds. Summary data of CSF Infusion Study per clinical diagnosis. Normal thresholds for each parameter are indicated with the horizontal black lines. **A:** Pressures: CSFp at baseline and plateau and SSp, as calculated during infusion. **B:** AMP at baseline and plateau, as well as compensatory reserve coefficients RAP and Elasticity. The threshold for AMPp, 4mmHg, is not shown as it is much higher than the average in the figure.

* indicates significantly higher mean than the other groups and from the normal threshold, ** indicate significantly higher than the other groups but not from the threshold, *** denote the difference in the number of patients in Group A (N=14 vs N=11), because 3 patients only had baseline values; hence AMPb is higher than AMPp in that group.

ROC Analysis between clinical classification and CSF dynamics

No single baseline or infusion-derived parameter could yield a satisfactory AUC from multiroc analysis of the 3 groups (AUCs <70%). However, given the significant differences among the 3 groups in mean CSFpb, SSp and Elasticity the best AUC was when the correlation between CSFpb, SSp and Elasticity were integrated into a linear model, with a resulting AUC 93.8%, with 84.8 – 100% CI (95% CI) in multiclass ROC analysis among the 3 different groups (**Figure 7.11**).

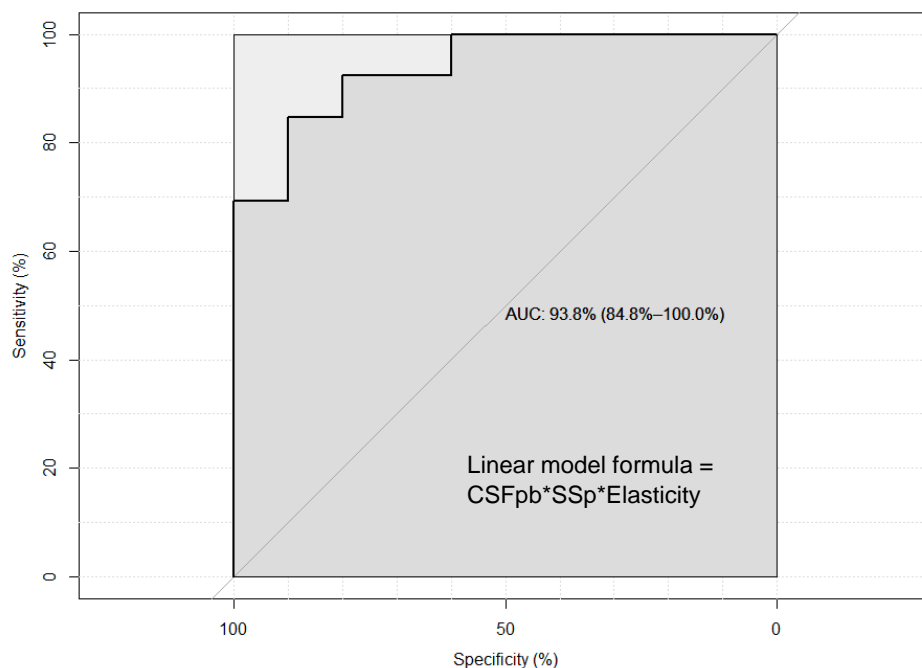


Figure 7.11: Area under the curve (AUC) and 95% CI among Friedman classification of Groups A-C and CSF dynamics, in particular the linear model of interaction of CSFp at baseline, Elasticity and Sagittal Sinus Pressure.

Influence of GA

11/31 (35%) children in total had received GA: 6/13 patients in group A had required GA, 4/13 in group B: and 1/5 in group C.

CSFpb was higher in the definite PTCS group that received GA (34.8 ± 7.44 vs 23.06 ± 5.43 ; $p = 0.0452$). When the 3 children with critical CSFpb and no infusion were removed from this subanalysis, the difference appeared to no longer exist. No other parameter differed within group A in GA versus no GA. In the probable PTCS group, only SSp and Elasticity appeared to possibly be lowered by GA (0.12 ± 3.48 vs $13.16 \pm$

6,59; $p = 0.006851$ and 0.11 ± 0.08 vs 0.53 ± 0.16 ; $p = 0.006774$. The amplitude of slow waves was consistently suppressed by GA at baseline and plateau within all groups.

7.2.4 Discussion

In this section of chapter 6, we have reported in depth the CSF dynamics of paediatric PTCS. This has been, to the best of my knowledge, the first study to describe such parameters in the paediatric population. We have emphasised the importance of using precise methodology for measuring CSFp, which is crucial in this condition, as well as the importance of monitoring CSFp and not just measuring a momentary value. Secondly, we have underpinned possible diagnostic implications of monitoring the pressure and its dynamics in paediatric PTCS, in order to provoke further investigation and implementation to clinical practice.

Monitoring CSFp with infusion test vs Measuring CSFp via LP

It is known that CSF disorders hide a complicated circuit of dynamic disturbances, including an interaction between the CSF circulation and the cerebral blood circulation . It is also known that a single value of raised CSFp does not give a diagnosis or understanding of the patient's disorder, however knowledge of the CSF circulation is a criterion and assists in diagnosing the disease. Therefore, obtaining a reliable CSFp measurement remains essential to clinical practice. Unfortunately, a lot of CSFp readings from single manometry can often prove unhelpful or even misleading, since methodologically a proper average CSFp and/or view into the CSF circulation cannot be obtained without a longer-term monitoring . Furthermore, even if we treat a baseline value of CSFp derived from manometry as adequate, there are a lot of factors influencing the number shown on a manometer, such as stress, position, sedation etc. Even these parameters and how they influence the CSFp cannot be studied and comprehended without cerebral multi-modality monitoring . Studies in adults and children have already indicated that lumbar manometry is not always reliable for CSFp . Therefore, a lack of correlation between manometry and baseline CSFp from infusion tests in our cohort would be adding to this pool of evidence. Unfortunately, these readings were not taken at a very close time, but on 1-3 months apart on average. Nonetheless, they represent a clinical routine and the

execution of current guidelines of attempting diagnosis, classification and treatment from separated LPs and/or drainages.

"Critical" CSFp in PTCS

Raised CSFp (>20 mmHg) at baseline was used as one of the criteria for definite paediatric PTCS. Interestingly, in this group, there were 3 children with a CSFp even >30 mmHg, 2 of them already reaching critical levels of CSFp with compromised cerebral perfusion, therefore "dangerous" levels of intracranial hypertension, compatible clinically and radiologically with the syndrome. These are unique opportunities to learn about what could CSF dynamics monitoring could reveal for their CSF circulation, even if infusion is not possible. Indeed, a pattern of negative AMP-CSFp relationship was observed, overlapping with the idea of low cerebral perfusion pressure. We know from the literature in TBI and experimental intracranial hypertension that, when ICP reaches upper thresholds for ischaemia (usually >20-25mmHg in TBI), the AMP-ICP relationship becomes negative (100,283), which appears to also be the case with these two patients. However, more patients are needed in order to confirm this pattern and association. In only one of the patients, MAP was measured and it was 65mmHg, therefore this patient had a CPP of 23 mmHg, which is below the physiological values for the lower limit of autoregulation(124,288,289), likely exposing this patient to ischaemic insults. These cases, although seemingly rare, highlight the importance of multi-parametric monitoring of the cerebral circulation, including systemic arterial pressure and possibly cerebral autoregulation, blood flow and oxygenation.

CSF dynamics in definite, probable and not PTCS

It was interesting to show that in Group B, where the CSFp wasn't raised (average 15mmHg), the mean value of CSFp did not appear to differ to Group C. In such cases, it could be of significance to investigate the dynamics of the CSFp. AMP baseline did not seem to be the parameter that separated the 2 groups, however both elasticity and SSp were significantly lower in Group C and could potentially provide this separation. Elasticity and SSp were also elevated in both definite and probable PTCS,

showing further potential markers of the disease besides CSFp. On the other hand, they could be erroneously calculated with lack of understanding of the analysis, and SSp is calculated from a theoretical model and does not represent the patient's actual SSp. With our current data, it is not possible to clearly pinpoint what CSF dynamics each of the three groups is comprised of, without further patients, as well as follow-up related to treatment response. Lower SSp as well as elasticity could possibly represent a "lighter" pathology or an earlier manifestation and presentation of the syndrome, that hasn't evolved to the severity of the definite group. Duration and severity of symptoms are not routinely documented and have not been reported, therefore leaving ground for the natural progression of the disease to be explored, perhaps in relation to the above.

Unlike elasticity, RAP was not >0.6 in any of the three groups, however for a lowered threshold of 0.4, Group A showed a tendency for increased RAP and therefore depleted compensatory reserve. No other parameters were above the previously reported thresholds (0.16 for the amp-p line, 4 mmHg for AMPp), except for slow waves at plateau the magnitude of which exceeded 1.5 mmHg in groups A&B, but not in group C. There are no established thresholds for slow wave magnitude (24,27,278). It is possible that the highest magnitude of slow waves could be found in Group A decreasing in Groups B and even further in group C, however this could not be demonstrated statistically. It would possibly be of interest to explore slow wave magnitude alongside the concept of depleted compensatory reserve in PTCS. The absolute rise in CSFp during infusion was the same in all groups. As denoted in section 1 of this chapter, there is a likely overestimation of R_{out} , however the average calculated R_{out} was <10 mmHg*min/ml. Finally, the presence or absence of a LBP in the AMP-P line could also contain reliable information on the state of pressure-volume compensation(149). None of the children in the definite group presented with such a breakpoint, again likely signifying exhausted compensatory reserve, whereas it was observed in 2 children for each of the other groups.

CSFpb was positively correlated with SSp. Although, as discussed above, this SSp value is not derived from in vivo monitoring, it could also approximate a similar

coupling between the two pressures, as in adults with PTCS (32). Careful weighing of risks and benefits of exposing paediatric patients to SSp measurements would be required to attempt SSp monitoring in the future. A positive correlation between SSp and Elasticity was more prominent in the definite group as opposed to the others and could also be part of the pathophysiology of PTCS, whereby an abnormal and compressible venous system allows passive transmission of the CSF pressure and initiation of a CSFp-SSp positive feedback loop. It might as such be that in children with CSFp anywhere in the “normal range” of 10-19mmHg but abnormal haemodynamics or compliance (290) could lead to disease and symptoms.

Finally, we have shown that no singular CSF pressure or dynamics parameter at baseline or during infusion could accurately differentiate among the 3 groups with an AUC >0.80. It is the combination of a few parameters, CSFpb, SSp and elasticity, that describe the clinical syndrome and agree with the classification. This once again highlights the importance of monitoring the CSF circulation and the use multiple parameters, whilst infusion is essential to calculate these. We did find a discordance in CSF dynamics and the Friedman classification in Group C, in one patient without papilloedema and not adequate radiological criteria for a diagnosis of PTCS without papilloedema. This patient demonstrated disturbed CSF dynamics, identical to those in Group A. It is not easy to speculate on this case without further information. It is likely that confirmed intracranial hypertension could not automatically translate to PTCS, and hence the venous compartment in addition to CSFp contents could mandate more testing. Moreover, PTCS without papilloedema and its differentiation from migraines remain controversial subjects(29,291–293). In Group B, where there is a lot of heterogeneity among the patients, we could not conclude on similarities and differences.

Utility of CSF infusion tests in paediatric PTCS

Overall, we could not show the added value of using infusion tests in addition to clinical classification. More patients for groups B and C are required, as well as randomised and blind methodology in order to eliminate circularity and bias from our sample selection. We were able to detect a slight discrepancy between clinical

radiological classification and CSF dynamics in Groups B and C that would merit further exploration. Furthermore, the use of infusion tests in those patients could assist in understanding the limitations of certain criteria (such as opening CSFp as an isolated measurement) and how these could be improved by using alternative/additional parameters.

With reference to what is known for adult PTCS and what I have mentioned in section 6.1, paediatric PTCS remains a challenge. Adult PTCS is an uncommon condition on its own, with paediatric patients representing an even smaller demographic and one that would be very challenging to investigate with tests such as venography and long-term ICP monitoring. Diagnostic criteria for adult and paediatric PTCS are currently the same, however whether the condition is exactly the same in both age groups will require further investigation and long-term follow-up of those paediatric patients in adulthood.

Lastly, we have performed a preliminary exploration on the effect of GA on CSFp and CSF dynamics. Our percentage of children with GA (35%), was lower compared to a reported national average of 45% (294), and we also recorded a longer-term average CSFp monitored continuously. It has been reported in NPH and TBI patients that GA possibly has no effect on baseline CSFp or elasticity, but significantly dampens the magnitude of slow waves (214). This study was derived from the same centre (our centre in Cambridge) and therefore included a similar GA protocol as the NPH group (propofol +remifentanyl/fentanyl infusions and a muscle relaxant, usually rocuronium, naturally with different doses in adults versus paediatric patients). Since this study was not designed and powered to address this question, the fact that CSFpb was increased in definite PTCS under GA versus non-GA could be insignificant. It could be possible that anaesthetic agents somehow contribute to a raised CSFp in paediatric PTCS, however this is not justified from the evidence on the influence of GA on cerebral blood flow and metabolism. Another study and the guidelines commenting on CSF threshold in GA, could have similarly found that children requiring GA tend to have a higher BMI, rendering them less likely to tolerate a LP. It could also perhaps validate the correlation with increased BMI and worse PTCS symptoms, as well as

potentially increased abdominal pressure in those patients. Lower SSp and elasticity in anaesthetised probable PTCS patients from our current data would require a power calculation for future studies to verify or refute this finding.

Limitations

Although our recruitment timeframe spans 10 years already, due to the rarity of the disease in the paediatric population and the careful selection of children to undergo infusion tests, we were not able to collect a large cohort with enough patients in each group and subgroup. Analysis of a larger cohort is needed to generalise these results to all children with PTCS. Despite the fact that we tried to keep the selected cohort relatively homogenous, e.g. by not including the children with secondary PTCS, there seems to be significant heterogeneity within our cohort as well as the groups.

Furthermore, we are currently unable to utilise normal controls as comparisons, since no such data exist, and no “normal”, asymptomatic children would undergo these tests. If we were to consider group C as the “normal” group, firstly we do not have enough such patients, and secondly, they do not always appear to be completely free of CSF dynamics disturbances. Current parameter thresholds have been validated only in hydrocephalus and TBI. From our analysis, thresholds appear similar but will require validation with appropriate design and methodology.

One of the limitations when performing infusion tests instead of overnight ICP monitoring, is the small duration of monitoring. RAP standard calculation window is 4 minutes, and in the short time of the infusion test the smallest artefacts could make the calculation unreliable; however, we obtained a good value without noise in 31/31 patients. Compensatory reserve can also be estimated in various ways, as reported above, and the most reliable for infusion test can be selected. Slow waves also have a similar window and could be calculated both through overnight and during infusion tests (see Chapter 9), however there has been no direct comparison between the two methods, however many studies have utilised infusion tests to assess slow waves(21,23,101). Additionally, the effect of GA on slow waves(214) paediatric PTCS patients is awaiting exploration.

Conclusion

We have shown a CSF picture in PTCS that could be characteristic: an elevated baseline CSF pressure (although precise threshold remains to be determined), with depleted pressure-volume compensation and increased estimated sagittal sinus pressure. CSF circulation, as estimated by the difference between plateau and baseline pressure, appears normal. “Critically” High CSF pressure (>30 mmHg) may contribute to low cerebral perfusion pressure, exposing patients to chronic sub-acute ischaemia.

CHAPTER 8

SHUNT TESTING IN VIVO

8.1 Outcome and financial implications of shunt testing in vivo: a single-centre study

The results presented in this section are published in Acta Neurochirurgica

Lalou A, Czosnyka M, Garnett MR, Nabbanja E, Petrella G, Hutchinson PJ, et al. Shunt infusion studies: impact on patient outcome, including health economics. Acta Neurochir (Wien). 2020;

8.1.1 Introduction

In my introduction, Chapter 2 of this dissertation, I have begun to lay out the main principles behind shunt properties and shunt testing in vitro and in vivo. There is an increasing need for developing better and less invasive methods of monitoring intracranial pressure (ICP) to quantitatively assess shunt function in shunted patients(40,75,295,296), especially in cases where the ventricular size and the clinical presentation do not suffice. Infusion tests have been reported as a minimally invasive, low risk and potentially useful diagnostic tool for testing shunts' function *in vivo*. They have been described and implemented in clinical practice since over 45 years ago(64,66,91,95,112). Despite many publications on their methodology and utility(66,71,91,95,97,112,297), there have not been enough studies of the health and financial benefits derived from that implementation. In this study we aim to show that the logic and logistics behind the shunt infusion test constitute it to be highly accurate as well as cost-effective.

With reservoir or shunt pre-chamber infusion studies in shunted patients, infusion tests assist in differentiating between a correctly functioning shunt from a shunt with possible problems like under-, over-drainage or blockage(41,74,298). It is hence possible to facilitate the decision to perform an emergency or elective revision on a malfunctioning shunt, or to manage the patient conservatively when the shunt appears to be patent and/or functioning as it should(44,299,300). It has been suggested(40,44,299,300) and experienced routinely in our hospital that it is possible

to provide patients with effective management for their symptoms without revising a well-functioning or requiring a change of shunt setting, when there is no clear test-derived evidence of any shunt malfunction. We aimed to investigate how many revision surgeries are avoided in our hospital and the outcomes and progress of patients after infusion studies. Primarily we sought to provide evidence of preserving good quality of life and relief of symptoms in patients without neurosurgical intervention. Our secondary aim was to determine the financial benefit derived from sparing shunt revision surgery when there is no actual need for them.

8.1.2 Materials and Methods

Patient Data

From January 2013 to December 2015, ADL (the first author) identified the results of infusion tests from shunted individuals. We chose a 3-year period in order to be able to analyse a significant amount (>300) of tests as well as be able to follow them up for at least 12 months (the work was carried out between January and May 2017). During this timeframe, we had performed 280 infusion tests to 210 different shunted patients. Patients who presented acutely with clinically obvious raised ICP and an unequivocal CT scan do not form part of this study as they would have had an urgent shunt revision. All of them had received a previous diagnosis of hydrocephalus of various aetiologies. In addition, we evaluated 85 tests on previously shunted pseudotumour cerebri (PTCS) patients [including idiopathic intracranial hypertension (IIH)] and considered their care separately because it is often more complex than in hydrocephalus patients. We collected the results of the computerised CSF infusion test and assessed whether the conclusion was normal function of the shunt or possible problem detected. All patients have consented on using their data recordings for research purposes.

The infusion studies results had been reported independently by a clinical scientist at the time of the clinical request and were not altered for this analysis. The criteria used for reporting infusion studies involve analysing the shunt properties, primarily the shunt critical pressure and its resistance(44,96,301); when these are exceeded, a

distal obstruction is expected. When there is no ICP pulse waveform detected when connecting the needles to the reservoir or prechamber, a proximal obstruction is suspected. Analysis may also suggest other problems associated with a shunt functioning, such as underdrainage, overdrainage, slit ventricles etc(43,44,48,97).

Follow-up and Outcome assessment

Using the electronic hospital records (e-MR and Epic), ADL (author) followed-up the course of the patients at 6 months and 12 months from the time of the test. Based on the clinical evaluation and relief of symptoms at follow-up, patients were classified as improving or non-improving.

Financial analysis

All financial data were provided by the hospital finance department and were all in pound sterling (GBP). Fixed tariffs have been set and updated in our hospital for many years for infusion tests, and the tariffs for shunt revisions and ICP monitoring were derived from the national tariffs for 2017/18.

As this was a single-centre study and infusion test have been a routine practice in Cambridge for over 25 years, it was not possible currently to compare the cost-effectiveness of infusion tests with other protocols and methods, such as overnight ICP monitoring or MRI.

We have approached the financial analysis in two separate ways: 1) we assumed that all our patients had presented with signs and symptoms that would have merited admission, observation and/or ICP monitoring/ shunt revision surgery, if access to infusion tests had not been possible and 2) based on our outcome cohort and on data the UK shunt registry , we used the percentage of patients requiring revision and/or further investigations, to design decision trees showing the comparison of patient flow and resulting costs in a general neurosurgical protocol without infusion studies integrated, versus when infusion studies are used.

We have selected to include both hydrocephalus and PTCS patients (including IIH), as shunts are one of the main treatments of choice in both diseases. However, since

there are important differences in their clinical course and management, we have investigated the outcomes of the two cohorts separately. We did not perform a separate financial analysis for the hydrocephalus and PTCS groups, because the costs related to their shunt management (infusion test/overnight ICP monitoring/shunt revision) are the same.

8.1.3 Results

Patient demographics and general characteristics

The mean age was 45 years and the male to female ratio was ~ 0.84 (127males /152 females). The ages of the patients ranged from 4 months old to 90 years old. 47 were paediatric cases (under 16 years of age). Overall, more than half of the tests (~55%, 155 out of 280) found no indication for shunt malfunction versus 125 detected a possible malfunction (over/underdrainage, blockage, etc). There were 24 patients both in the malfunctioning and functioning group, because they had repeated test over 12 months after their first infusion test. Results are discussed as unique cases, not unique individuals.

Outcome for hydrocephalus patients with normal-functioning shunt

Overall, the outcomes for Hydrocephalic patients are summarised in **Figure 8.1**.

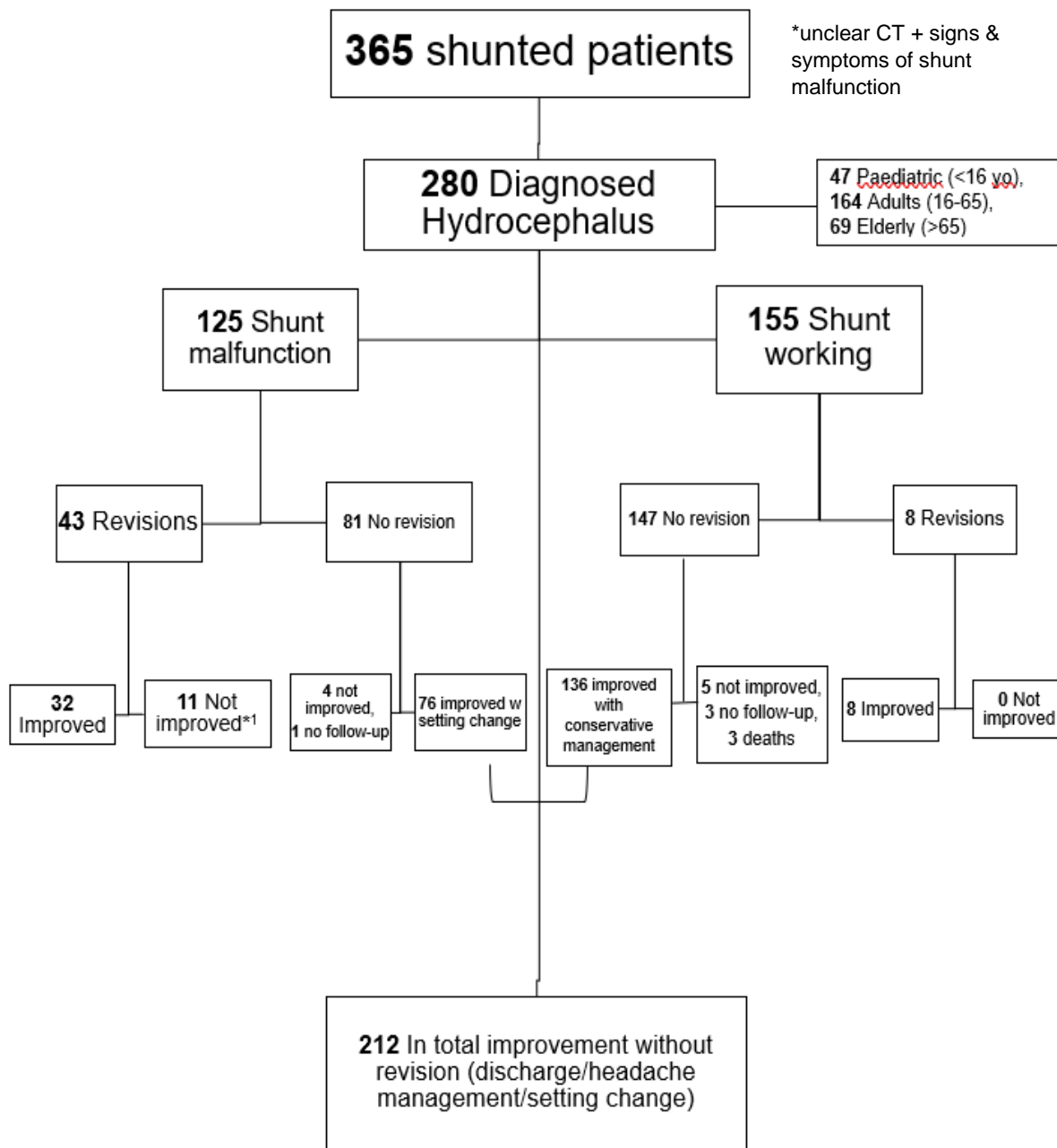


Figure 8.1: 1-year outcome of patients with diagnosed Hydrocephalus of multiple aetiologies undergoing CSF infusion studies for shunt function assessment in vivo.

**1: Not improved after revision: One patient came back with new blockage confirmed with infusion study, but improved after the second revision. One had a wound breakdown with CSF leak and improved after system and wound revision. Another patient developed significant scarring with cheloids that required revision. 3 more patients remained quite unwell, with long-term ongoing investigations between neurology and neurosurgery. 2 more were discussed in MDT meeting due to some osseous and venous lesions in further imaging. One deteriorated neurologically but the deterioration was most likely due to a spinal cord syrinx, but further follow up is not available yet. A NPH patient with complicated post shunting history never recovered and was placed in a nursing home. Finally, there was a very complex patient with very prolonged hospital stay that required multiple revisions and eventually died after years of intermittent, very long hospitalisations and very heavy problems related to her hydrocephalus.*

6-month outcome

140 of the patients in total with no malfunction detected with infusion improved with conservative management at 6 months of follow-up.

Out of the initial 155 patients with no signs of malfunction, only 4 ended up needing a revision before a 6-month follow-up period, due to random events shown in **Figure 8.2A**. Three patients were lost in follow up and three died of causes unrelated to intracranial hypertension or shunt complications (hip fracture, recurrence of aneurysmal bleeding and a complex epilepsy syndrome). There were 3 patients who, even though their shunt was patent, their ongoing symptoms required a different approach and had to be discussed in the Multidisciplinary Team meeting.

The remainder of 142 patients were either discharged from neurosurgical care with instructions. 140 improved with conservative management, including shunt adjustment or headache management. Two of 142 patients remained unwell; one had never been well before or after shunting for NPH and had previously have serious issues with overdrainage and evacuation of subdural haematomas bilaterally. The other had refractory headaches but no major incident that required hospitalisation or surgery; a change of setting did not help them.

12-month outcome

136 cases out of the 140 that had done well at 6 months continued to not require neurosurgical care for at least 12 months, with the exception of 4 patients who required revision within 12-14 months after their initial infusion test. 3 of the patients required a new infusion test that showed slight underdrainage that improved with shunt adjustment.

The reasons for revision in all these patients are illustrated in **Table 8.1**

Outcome of hydrocephalus patients with evidence of shunt malfunction

In 125 patients, underdrainage, overdrainage, or distal/proximal blockage was described.

Specifically we detected: 27 with underdrainage, 33 with overdrainage and 48 obstructed shunts, 14 with some inconclusive disturbance of CSF dynamics (e.g. increased resistance, possible overdrainage or blockage, slit ventricles or blockage and 2 with burr hole valves in situ which makes the interpretation of the results difficult due to the construction of the device), 1 elevated abdominal pressure 2 slit ventricles and.

Outcome after revision - 6 months and 12 months

43 revision surgeries were performed in patients who had evidence of blockage or other malfunction on infusion studies; 2 revisions as well as 2 infusions back to back were performed in 2 patients who required revision and their new shunts blocked shortly after surgery; for 33 of them the infusion study had indicated blockage (proximal, distal or both catheters), 6 underdrainage, 2 overdrainage and 2 had mild disturbances of their CSF dynamics but had to undergo a revision due to different reasons (one had an incision breakage a few days after the study for unrecorded reasons and one and the other one had no record of the reason for the revision due to a gap in transferring from our old to a new clinical database).

32/43 improved sustainably at 6 months and 12 months, 5 requiring shunt adjustment post-operatively; for some of the rest it could be possible that their setting was changed but it was not noted in our records and some of them were discharged or referred to neurology.

11/43 patients remained symptomatic, with persisting headaches dominating in all of them. 6 had to be discussed in our MDT meeting. Unfortunately, 5 showed no improvement even after their shunt setting was adjusted post surgically (for a long time of follow-up, 6-12 months, even after neurology referral).

The reasons for revision in this group of patients are illustrated in **Table 8.1**.

Table 8.1: Reasons for revision: Reasons for revision in the 8 patients with infusion test not indicating shunt failure, who required revision within a year of the test. 1 patient had an accident that exposed the shunt tubing, in 2 patients the distal catheter migrated, and one patient was clinically diagnosed with overdrainage and had an antisyphon device only inserted. 4 people were not improving with conservative management (turning down their setting) and further investigations showed underdrainage, with the neurosurgeon selecting to proceed with a revision. **B:** Reasons for revision in the group with evidence of shunt malfunction. Most revisions (34) were performed due to evidence of proximal or distal blockage after clinical review and decision. 6 patients had evident overdrainage that required an antisyphon device (2 cases) or even removal of the entire system (4 cases, due to desire to change the fixed valves with programmable ones).

Reason for revision	Functioning shunts	Malfunctioning shunts
Accident	1	0
Distal catheter migration	2	0
Overdrainage	1	6
Underdrainage	4	3
Obstruction	0	34

Outcome of patients with shunt malfunction but without revision

From the rest of the patients (81), 1 was lost in follow-up. 4 patients were classified as non-improving; Two presented with new episodes of epileptic seizure and had to be managed for those and the other 2 were discussed in a MDT meeting and selected for venous stenting or styloidectomy with appropriate indications(33,267).

76 patients with no revision and some alternative management of setting manipulation or discharge/neurology referral had no change or worsening of their symptoms and did not require additional care for at least one year after their initial encounter for infusion studies. Two of these cases had evidence of proximal shunt obstruction but clinical indications of improvement soon after the infusion study, sustained for at least a year, indicating resolution of the blockage, most likely from flushing the proximal catheter during infusion. One also had radiological evidence of significantly smaller ventricles.

The PTCS patients' CSF test results were as follows: 85 studied, 47 with possible problems and 38 without any indication for shunt malfunction. Some patients required more than 1 study within the selected period, therefore from the 85 studies there were 56 different individuals aged 10 to 77 years old.

Outcome of PTCS patients

In 47 patients, malfunction had been detected, versus 38 with normal function. 46/85 PTCS patients were successfully managed with no neurosurgical intervention, with either normal shunt function or malfunction that did not include obstruction. These patients likewise remained well with no further care needs for at least one year of follow-up.

12 patients in total had revision, after which 11 of them improved.

The 27 other patients investigated were found either as non-improving, requiring multiple revisions or different surgeries (usually venous stenting) and closer medical attention and discussions.

The overall outcome of PTCS patients is illustrated in **Figure 8.2**.

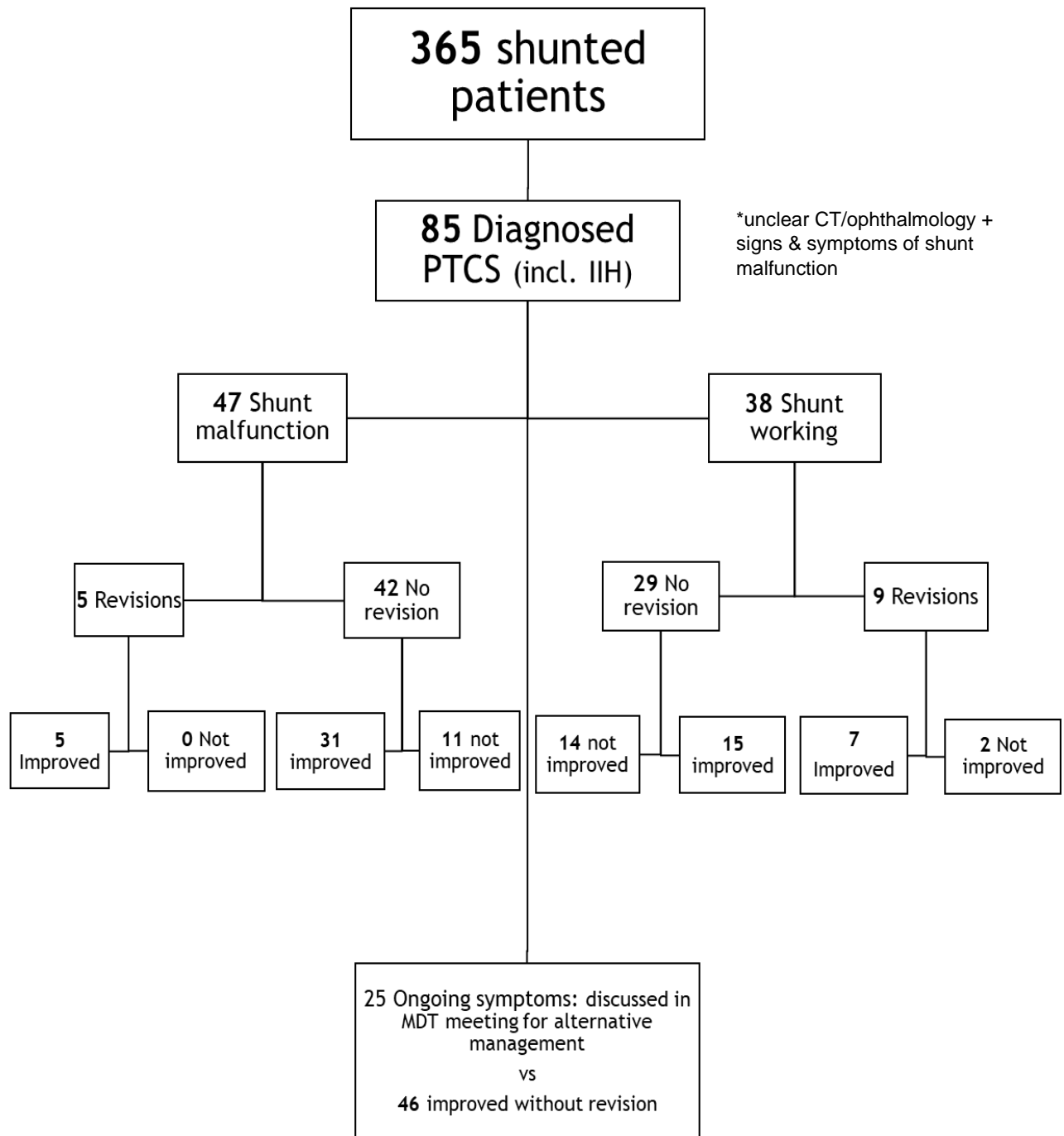


Figure 8.2: 1-year outcome of patients with diagnosed Pseudotumour Cerebri Syndrome undergoing CSF infusion studies for shunt function assessment in vivo.

Further investigations and complications

4 hydrocephalus patients underwent overnight ICP monitoring, two due to suspected but not definitive evidence of overdrainage and two because a proximally obstructed shunt catheter did not allow reading and recording of the ICP during the infusion test.

5 PTCS patients required overnight monitoring due to ongoing symptoms that suggested disturbed CSF circulation.

There were no infections associated with any of the 365 infusion tests, based on the patients' medical records and revision requirement.

Health economics analysis

Cost of and Income received for shunt reservoir infusion studies

An elective day admission for a shunt infusion test in total included:

- transport expenses,
- staff: nursing, medical physics and medical staff involved,
- cost of the shunt infusion studies equipment (including medical equipment for shunt tapping and for the computerised infusion study).

The total cost of each reservoir infusion study for our local Trust was 844 GBP and had been tailored to match the income received.

Tariff for a shunt revision

Shunt revision surgery tariffs have been formed nationally to include:

- anaesthetic and theatre time
- medical and nursing staff involved,
- theatre equipment and consumables including the cost of the valve and shunt catheters,
- total length of hospital stay, and
- the management of any related complications.

The total cost of a shunt revision procedure ranged from 9,437 GBP to 12,436 GBP (average of 10,937 GBP). The wide range in costing was due to different comorbidity

scores that affected the cost of the surgery, as well as perioperative complications, care needs and length of stay.

Overall financial benefit of CSF infusion studies

From the total patients in our cohort, we could calculate that:

(A) The total cost of 365 CSF infusion studies was £308,060 (365×844).

(B) The actual number and cost of shunt revision operations was $64 \times £10,937 = £699,968$.

(C) The total cost to the Trust of 365 studies plus actual number of Shunt revisions = £1,008,028 (A+B).

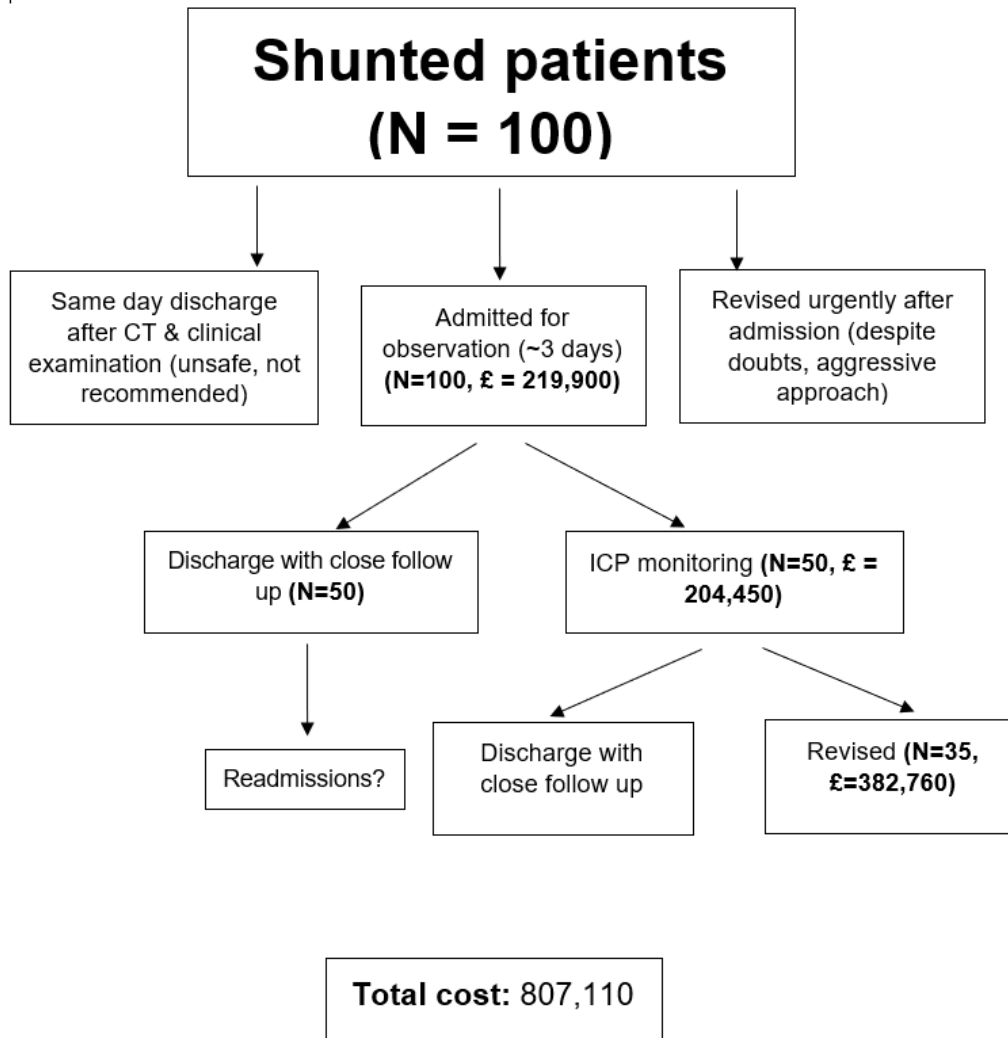
(D) The cost of shunt revision operations avoided was $281 \times £10,937 = £3,073,297$.

(E) The total cost to the trust if no infusion test available = $\sim £3,992,005$ ($365 \times 10,937$).

From **A-E**, it is derived that a CSF infusion service potentially saved our local trust \sim £2,766,081 over 3 years, or \sim £922,027 per annum.

On a different approach, comparing infusion studies to a common national and international protocol, using only ICP monitoring and exploratory surgery, the overall financial benefit could be approximately £442,710 per 100 patients admitted with possible shunt malfunction. An analytical decision tree showing a comparative cost analysis between using infusion studies versus no infusion studies is presented in **Figure 8.3**.

A)



(Figure 8.3 continued in next page)

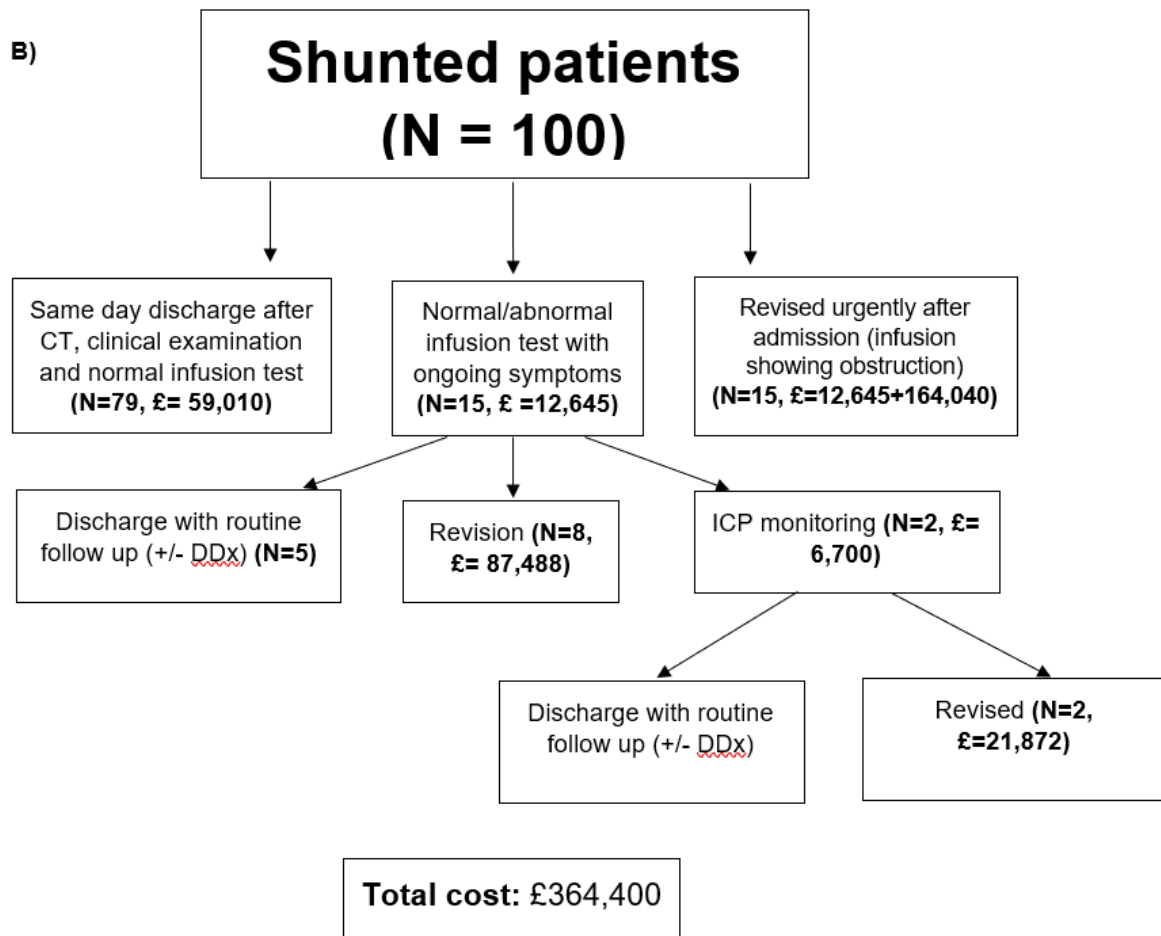


Figure 8.3: Elementary decision tree analysis of **A)** costs of shunt malfunction management without infusion studies **B)** costs of shunt malfunction management as derived from our infusion study patients. Data derived from national reference costs 2017/18 and hospital income/outcome records. On average, as derived from our dataset illustrated in Figure 6.2, around 35% of possible shunt malfunctions are due to shunt obstruction or are not amendable with shunt reprogramming. Around half of the patients do not require revision, with good resolution of symptoms. This rationale was used to calculate costs of managing patients without shunt infusions. The benefit of diagnostic information derived by infusions, allows routine instead of close monitoring and facilitation of differential diagnosis of symptoms. The cost of saving follow-ups could not be approximated with the current design and dataset from our hospital. Furthermore, Figure 6.4A cannot approximate the cost of extra hospital days in those receiving overnight monitoring with or without revision, as it is not common or standard practice in our centre.

8.1.4 Discussion

We have provided the first large cohort of patients managed with the help of infusion tests to include long-term outcomes and health economics. Our data shows the potential of infusion tests in providing safe evidence to avoid on average over 130 unneeded operations per year. Approximately 86% of these patients sustained improvement in follow-up for over 12 months. The financial benefit of about £922,027

per year is an important reference estimator for cost-saving in neurosurgical centres worldwide.

It appears that the management of non-obvious blockage can be complex and requires attention and careful selection between simple shunt manipulation and more invasive management. Shunt infusions are a reliable and safe diagnostic tool to achieve this.

The use of infusion studies in diagnosing shunt malfunction

Throughout our experience with infusion studies, it has been evident that we are most probably able to provide patients with effective management for their symptoms without revising a well-functioning shunt when not required(216,255,302). Despite the fact that infusion studies offer a minimally invasive, highly sensitive diagnostic technique for shunt malfunction, they are not performed in many centres worldwide; furthermore, we are not aware of an optimal, alternative tool to assist in resolving the ongoing clinical dilemma of whether or not to proceed to a revision surgery (44,228,302–305).

Infusion tests can potentially support everyday neurosurgical practice due to the two important pieces information they yield: A) Reliable evidence of low ICP at baseline, therefore it reassures against acute intracranial hypertension(44,95,216) B) Reliable evidence that the shunt is not obstructed and does not allow ICP to exceed a desired range (44,95,215,293). Patients can therefore safely be discharged home and be booked for a routine follow-up, that will allow more time and better planning to be invested into their review and care.

Furthermore, a shunt in situ does not mean that it will be the only source of a patient's symptoms and a reassurance against shunt malfunction provides value, evidence and time to the patients' differential diagnosis. As such, unnecessary and prolonged admissions, as well as more invasive tests such as overnight ICP monitoring, are also avoided if not necessary. In underdraining patients who later required revision, it is disputed that an early revision without evidence of obstruction or acute/subacute intracranial hypertension would be of benefit, especially with the use of a programmable valve and margin to increase drainage.

Hydrocephalus patients

Infusion tests appeared quite accurate and efficient in directing away from shunt malfunction in hydrocephalus, as demonstrated by the 212 cases that were managed conservatively without further hospitalisations. Shunt testing in vivo appears to be most valuable to our selected cases, that did not have a radiological signs substantiative of shunt malfunction and were not acutely unwell. This can often be the case with NPH patients, as well as younger patients with chronic or neglected hydrocephalus(44,306–311).

PTCS patients

Despite PTCS and hydrocephalus being different entities, with many differences in their presentation, diagnosis, and management, shunts are their common denominator. Venous stenting also constitutes one of the mainstay treatments for PTCS, however shunts, not only lumboperitoneal but also ventriculoperitoneal, are being used more and more frequently (32,35,48,198). In both cases, objective confirmation that a previously implanted shunt is patent can direct uni or multidisciplinary care. Therefore, despite the fact that there were 15 patients with presumably working shunts whose symptoms could not be relieved with conservative management, they were also able to move forward to a MDT pathway in order to undergo further investigations and seek alternative treatments, without being subjected to a revision that would most likely not have benefitted them and would have delayed their referral to a more appropriate service.

Value and accuracy of shunt infusion studies

Based on our clinical experience and our current data, shunt infusion tests are safe. Not a single patient presented with acute/severe problems after being discharged and no one was infected as a result of the test. It is our hospital's policy to remove shunt systems completely if there is a CNS infection. If any of the above patients had an infection attributed to their shunt infusion, either a severe one or a silent infection, they would have been sent to the hospital and the relevant team for review and management.

Additional clinical evidence and other paraclinical investigations can lead the clinical team to decide differently from an infusion result. The above is demonstrated in Figures 1 and 3, where we show cases of patients where the results of the infusion tests pointed away from shunt malfunction, yet the clinical decision was to proceed to a revision. Such was the case mostly in PTCS patients and not frequently in hydrocephalus.

Impact of avoiding shunt revisions on patient outcomes.

Shunt revision surgery can be lifesaving, however when inappropriately performed, could lead to devastating financial and health costs, including serious complications and multiple revisions (44,45,302,305,312). It has been highlighted by large cohorts of patients derived from the UK shunt registry, as well as from multiple reports of paediatric hydrocephalus patients, that an increased number of revision operations is a negative predictive factor for cognitive outcome and overall disability and quality of life for paediatric patients (44,302–304,312–315). For adults, this increased number also is a predictor of further shunt revision surgery requirements in the future and therefore constant care needs, many hospitalisations and low quality of life (216,302,314,316). We were therefore more than pleased to see >89% of our patients leading a symptom-free and neurosurgically uneventful life for at least 1 year of follow-up. A recent report from the UK shunt registry has indicated the revision rates in all UK centres, where our centre holds a lower revision rate compared to the average, especially after first implantation(300). We are not aware of an alternative, more accurate diagnostic method to achieve this. Furthermore, patients avoid longer hospital stays and additional complications of a shunt revision surgery, whose rates and sequelae have been reported extensively in the literature (305,314,316).

Financial impact of avoiding shunt revisions on the NHS

As expected, avoiding surgical revisions in shunted patients seems to be of considerable financial benefit to the NHS. However, as stated in the methods, it is not possible to know exactly how many of these patients would have been selected for shunt revision, if infusion studies weren't available. There are other methods that are

used worldwide in order to diagnose shunt malfunction. Overnight ICP monitoring remains the gold standard, but it is also quite invasive, involves cranial surgery and has its own cost implications. Other methods, less invasive, involve radiation (such as radio-contrast shuntograms, radioactive flow studies) or no radiation (MRI/ high resolution MRI, optic sheath diameter measurements etc). However, they all implicate the cost of a radiologist or other highly specialised clinical staff, expose the patient to radiation and even endanger the functionality and/or patency of the shunt (44,306,309,317,318). In addition, measurements of steady-state ICP cannot exclude shunt malfunction, nor does the detection of flow or lack thereof. No flow through a shunt does not automatically mean obstruction, but many other things, including inadequate pressure to open the valve or even collapsed ventricles (slit ventricles) around the proximal catheter, among others (44,309,311,313,317–320). Last but not least, our current protocol for performing shunt infusion studies, that includes strict aseptic technique and proper cleaning and disinfection, appears to be 100% effective in avoiding additional costs related to infections from the procedure.

Additionally, in our centre, the neurosurgeon performing the revision is made aware of the site of the shunt obstruction, since shunt infusion tests can detect proximal catheter obstruction versus distal obstruction (valve or distal catheter). A proximal catheter obstruction is detected when there are not pulsations detected from the ICP and confirmed with an attempt of retrograde flushing towards the ventricles(320). A distal catheter or valve obstruction can be differentiated from a proximal catheter obstruction, due to excessive rise of the ICP with increased R_{out} (44,48,309,318–323). The interpretation of shunt infusion tests has been thoroughly described before by other authors and is not the subject of this dissertation. This most probably decreases the cost of the revision surgery, since either the skull of the abdomen can be left intact, decreasing surgical time, use of equipment, complications and post-operative hospital stay. However, investigating this point in detail was not within the scope of our current paper and could be the subject of a different study, including more patient costing data than we were able to collect.

Limitations

Our main limitation is that this is a single-centre study; In order to compare the overall clinical and patient benefits, together with the cost-effectiveness of shunt infusion studies versus other methods, as well as the overall practice in our centre versus other centres, a different analysis involving at least another major hydrocephalus centre is required. We also could not report financial benefits from improving patient flow, follow-up appointments and additional monitoring. These would all be highlighted better when other centres are involved in the analysis.

A shunt infusion study ideally requires the shunt valve to be positioned after the proximal catheter. This shunt anatomy is present in most valves in the market, with the exception of the fixed-pressure burr hole valve(44). However, the distal catheter can still be tested and, if the valve is open, even the proximal part.

In the presence of a proximal shunt obstruction, the ICP cannot be determined via a shunt infusion. In such cases, that appear rare, a lumbar infusion study or overnight ICP monitoring to determine ICP and its dynamics are indicated. Similarly, and also rarely, other technical difficulties during the infusion test (needle positioning or patient tolerance) could lead to incomplete results or challenging cases, where longer-term monitoring with an ICP wire is required.

8.2 Value of infusion studies in the assessment of paediatric hydrocephalus shunt function: a two-centre observational study

The results presented in this section have been published in Child's Nervous System:

*Dias S*F, Lalou AD*, Spang R, Haas-Lude K, Garnett M, Fernandez H, et al. Value of computerized shunt infusion study in assessment of pediatric hydrocephalus shunt function—a two center cross-sectional study. Child's Nerv Syst. 2020;36(1):59–71.*

8.2.1 Introduction

In section 1 of this chapter, I have discussed the utility of CSF infusion tests in detecting shunt malfunction versus normal function in a mixed cohort of paediatric and adult hydrocephalus when ventricle size and symptoms are insufficient. As mentioned in this chapter, avoiding revisions of well-functioning shunts could be of most significance in developing children. Since we previously only studied 47 paediatric patients from a single centre, we aimed to further explore the usefulness of shunt testing in vivo for the paediatric hydrocephalus population in two different centres, Cambridge University Hospital and University Hospital of Tübingen. For this purpose, we performed a retrospective analysis of shunt infusion data from children (<16 years of age) from these two centres with long-term experience in infusion studies. We quantified the infusion test methodology for children in a comprehensive study of differentiating between patent and an obstructed distal catheter or valve. As in section 1, we have descriptively reported the clinical progress and outcome of the children after infusion tests.

8.2.2 Patients and methods

Patient selection

We retrospectively included all paediatric patients aged under 16-years, that underwent a shunt infusion study between January 2003 and August 2017 in both centres – department of neurosurgery from the university hospital of Tübingen (Germany) and department of neurosciences Addenbrooke's hospital in Cambridge (United Kingdom). The study was approved by the institutional ethics review board of Tübingen and was in accordance with the ethical standards laid down in the 2013 Declaration of Helsinki for research involving human subjects. For Cambridge, the

ethics statement for infusion tests as in Chapter 3 applies. Informed consent was obtained by the children and parents in all cases.

In Cambridge, as described in chapter 3, the criteria for selection involve any clinical doubt on shunt function with normal imaging (CT). In Tübingen, selection for infusion test is more rigorous, and an infusion is performed after the shunt pre-chamber fails to empty and fill as expected, whereby a distal obstruction is suspected.

Sedation and Anaesthesia

In Tübingen, usually children under the age of 8 years or who are unable to tolerate the test awake receive mild sedation with propofol (initial bolus of 2-4 mg/kg) at a rate of 1-4 mg/kg/h. All others are studied fully alert. Leisure activities, such as listening music or audiobooks were sometimes provided.

In Cambridge, as described also in methods (Chapter 3) shunt infusions can be done with the child fully conscious, mild sedation with chloral hydrate/entonox or under GA.

Shunt infusion study technique & shunt testing in vivo

Shunt testing in vivo has been introduced in Chapter 3(43,324) including clinical utility and translatability described in the previous section of this chapter. The main procedural difference with the lumbar infusion technique is that the shunt pre-chamber/ separate reservoir is tapped, after cleaning and disinfection, using two 25-gauge hypodermic butterfly needles.

Result interpretation follow – up and classification of shunt function

As mentioned in section one, the interpretation of a shunt infusion test is mainly based on the presence of an ICP waveform and whether it allows ICP to exceed the Critical shunt Pressure (CSP). The resistance to CSF outflow (Rout) should be as close to its manufactured and tested values (44).

In terms of follow up, we classified shunts as blocked (shunt revised with intraoperatively confirmed distal obstruction), borderline (not revised but underdraining as evidenced from symptoms, imaging and response to shunt

adjustment or revised but shunt was patent) and functioning (no revision, improvement at follow-up, alternative cause of symptoms identified), depending on whether the patient was revised and of the intra-operative revision findings. Children that were not surgically revised, received a clinical follow up in outpatient clinic at 3 and 6 months (or even longer, depending on their needs).

We compared the findings of intraoperative obstruction, functioning shunt on follow up and borderline functioning shunt with the results from CSF infusion tests and investigated the cut-off values and predictive values of CSF dynamics from shunt testing in vivo that corresponded to the state of the shunts in our paediatric cohort.

Statistical analysis

We checked for normal distribution. Non-parametric tests (Mann Whitney U and Kruskal-Wallis) or one-way ANOVA and t-test were used to compare differences between the different groups. All values are presented as mean \pm standard deviation unless stated otherwise. Finally, we performed a ROC analysis using the pROC package (325) in order to assess the accuracy of infusion tests in detecting malfunction and to calculate the cut-off values that describe malfunction for $ICP_{plateau}$, $AMP_{plateau}$, and R_{out} , $ICP_{plateau}-CSP$ and other parameters.

8.2.3 Results

During our set timeframe, 203 infusion tests had been performed (164 in Cambridge and 39 in Tübingen) on 166 unique children. Mean age was 8.05 ± 4.94 years, ranging from 1 month to 16 years. 52% (n= 86) were female and 48% (n= 80) male. 23 of the children had undergone two infusions on separate occasions, and 14 three or more.

The following valves had been implanted and tested with infusion: 51.7% Strata, 13.3% proGAV, 12.3% Hakim, 7.4% CSF flow control burr hole medium, 6.9% Strata NSC, 3.4% Delta, 1.5 % PaediGav, 1.5% CSF flow control valve contoured medium and 1% Sophysa Polaris. The detailed distribution of shunt valves according to each institution can be observed in **Table 8.2**.

Table 8.2. Shunt valve distribution according to institution.

Shunt Valve	Cambridge	Tübingen	Total
<u>CSF flow control valve</u>			
- burr hole medium pressure	15		15
- contoured medium pressure	3		3
<u>Delta Valve</u>	7		7
<u>Medos Hakim Progr. Valve</u>	16	9	25
<u>paediGAV</u>	1	2	3
<u>proGAV</u>	1	26	27
<u>Sophysa Polaris</u>		2	2
<u>Strata</u>	107		107
<u>Strata NSC</u>	14		14
<i>Total</i>	164	39	203

A flowchart of the patient classification based on follow-up and revision criteria is shown in **Figure 8.5**.

Functional shunts (Group A)

In 136 (67 %) cases the children hadn't required a revision and were doing well on follow-up with conservative management or different diagnosis. In all of them, the shunt had been reported as functional from the infusion test report. the $ICP_{plateau}$ was below the critical shunt pressure (CSP) with a mean difference to critical shunt pressure (ΔCSP) of -4.68 ± 4.07 mmHg $ICP_{baseline}$ was close to the expected operating ICP (ICP_{op}), thus ΔICP_{op} (deviation of baseline to operating ICP) was small with -1.15 ± 3.88 mmHg. ΔICP (the difference between $ICP_{baseline}$ and $ICP_{plateau}$) was 6.19 ± 3.35 mmHg. AMP at baseline was 0.49 ± 0.39 mmHg and Rout 4.42 ± 2.0 mmHg*min/ml.

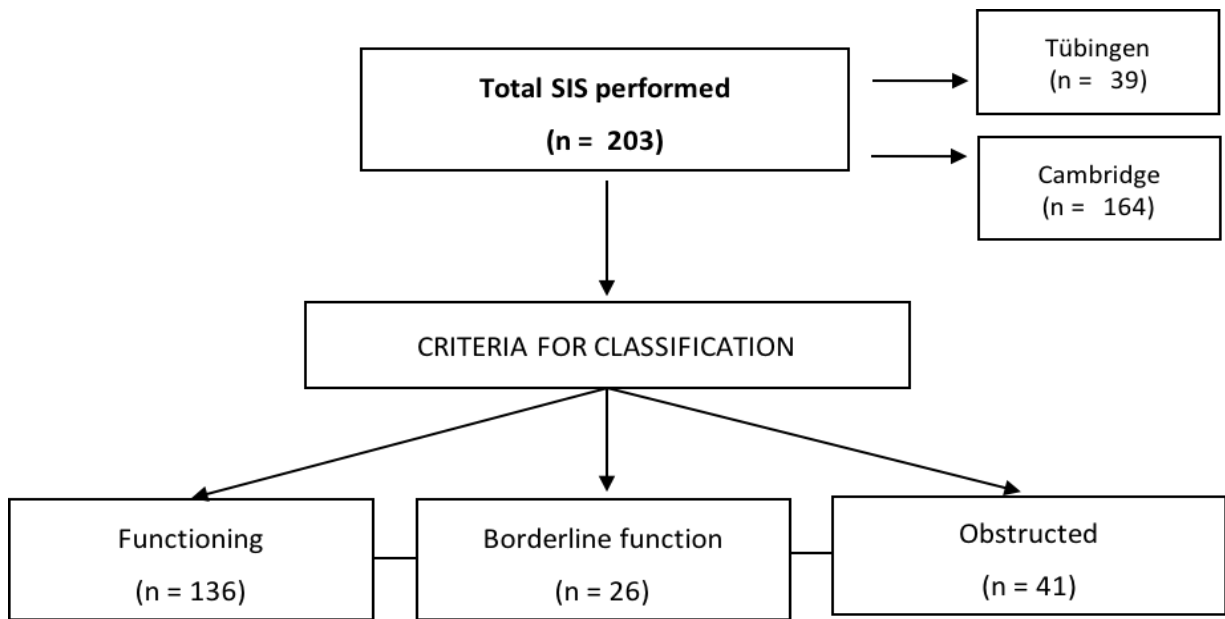


Figure 8.6 illustrates a clinical case of a patent shunt, performing within the expected parameters.

Figure 8.5. Flow diagram on the selection and categorisation of paediatric patients' shunt infusion studies. Group A included patients who didn't require revision and were still well on follow-up. Group B included patients whose shunt function appeared questionable and who required a shunt adjustment, but the shunt was not blocked in short-term follow up or revision. Group C included patients who underwent revision soon after the infusion and the shunt was confirmed to be obstructed intraoperatively.

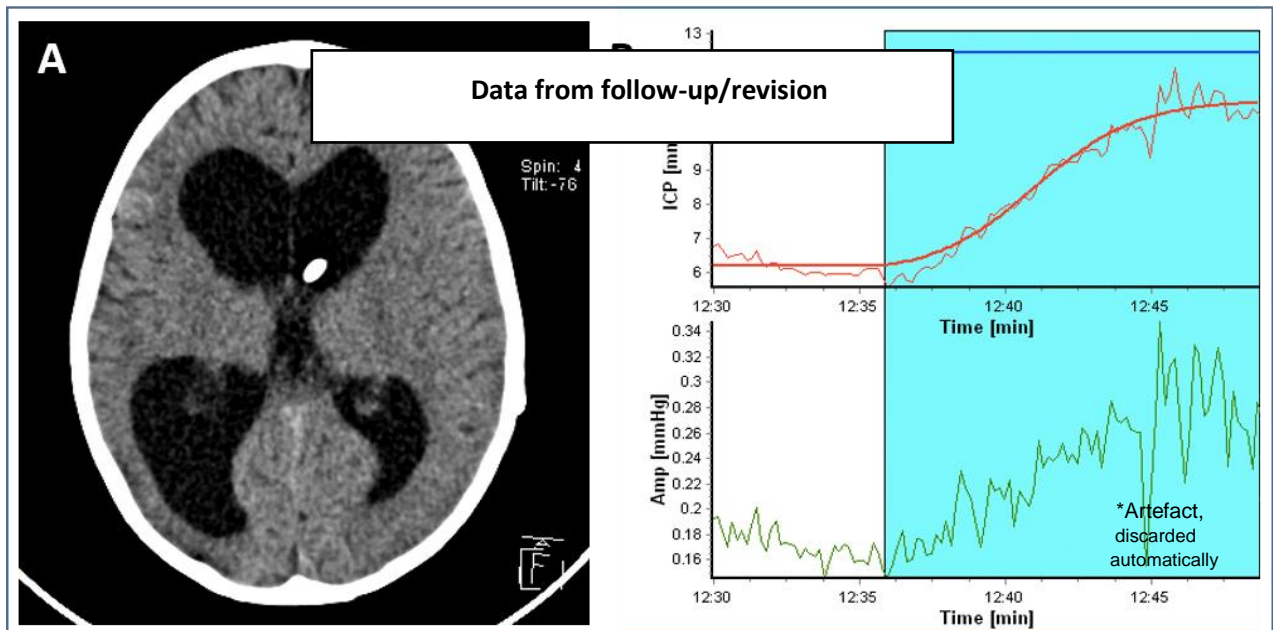


Figure 8.6. Shunt infusion study of a functioning shunt. A) CT-scan of a 4- years old child presenting with enlarged ventricles after VP-Shunt placement and valve replacement for a ProGav 4/29 (initially Hakim Medos 10) due to hydrocephalus after AVM-bleeding. Clinically they were improving and had no complains. **B)** Infusion test revealing a gradual increase of the ICP, with the plateau being reached below the shunt critical pressure

(upper panel); amplitude variation below 1mmHg (panel below) – indicating normal functioning shunt with adequate brain compliance. No VP-Shunt revision was performed and the child kept improving its clinical condition and development.

Borderline Shunts (Group B)

Twenty-six (12.8 %) SISs had borderline function and required adjustment. One child underwent shunt revision since the responsible consultant paediatric neurosurgeon decided on revision. In this case, the shunt was found not obstructed, but the child improved clinically on follow-up. The rest of the children had clinical signs that were indicative of underdrainage and shunt adjustment resulted to improvement at follow-up.

All parameters were significantly elevated compared to group A (see **Table 8.2**). The infusion report had detected underdrainage or severe underdrainage. $ICP_{plateau}$ was ≤ 5 mmHg above the critical shunt pressure, and ΔICP_{op} was 4.77 ± 3.87 mmHg. ΔICP ($ICP_{plateau}$ minus $ICP_{baseline}$) was 8.69 ± 3.29 mmHg, with $AMP_{baseline}$ 0.68 ± 0.47 mmHg and R_{out} 6.80 ± 2.67 mmHg*min/ml.

Obstructed shunts (Group C)

We placed 42 children (20.7 %) in this group, since a shunt obstruction was found at surgical revision, either of the valve or the distal catheter, with replacement of the respective non-functional part. **Figure 8.7** illustrates a case of distal obstruction.

All infusion parameters were significantly higher than both Group A and B. $ICP_{plateau}$ was above CSP on average by 13.97 ± 9.49 mmHg (significantly higher than in groups A & B, see Table 2). $ICP_{baseline}$ was not different to Group B, but significantly higher than Group A, as was ΔICP_{op} of 4.76 ± 5.82 mmHg.

In rare cases of occlusion, there was no real ICP plateau, as the pressure continued to rise to unsafe values (>40 mmHg), and 40mmHg was consider the plateau.

$AMP_{plateau}$ was 2.76 ± 2.04 mmHg. Increase in ICP during infusion was 18 ± 8 mmHg, and R_{out} 14.82 ± 6.39 mmHg*min/ml. (**Table 8.3**).

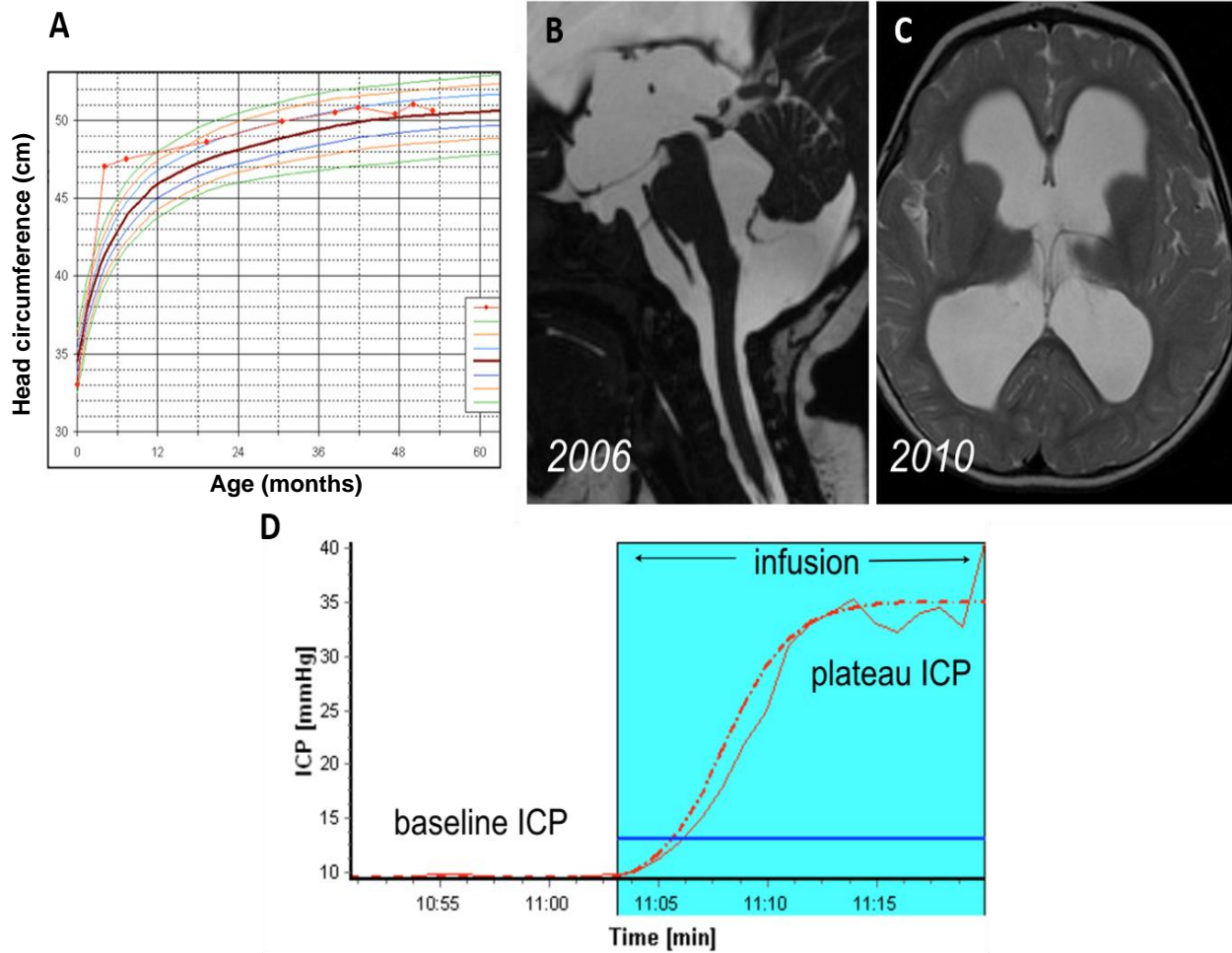


Figure 8.7. Shunt infusion study of a distally obstructed shunt. A) Head-circumference graph of 5-month-old child presenting with macrocephaly and diagnose of a Blake´s pouch (**B**). **C)** 4 years after VP-Shunt implantation, despite normalization of the head circumference, the ventricles remained enlarged and the child presented with developmental delay. **D)** Infusion test showed a significant increase of the ICP, reaching values of 35 mmHg and clearly above the shunt critical pressure (15 mmHg). The shunt was revised and during surgery, a kink of the connecting catheter between the burr-hole reservoir and valve was found which was invisible on the pre-operative skull X-ray. This explained the largely increased shunt resistance demonstrated by SIS.

Table 8.3. Results of cerebrospinal fluid dynamics as derived from the shunt infusion study in the 3 different groups. CSP: critical shunt pressure; **Rout:** resistance to CSF outflow; **ICP:** intracranial pressure; **AMP:** fundamental amplitude of ICP; **ΔICP:** ICP plateau - ICP baseline; **ΔAMP:** AMP plateau - AMP baseline; **ΔICPop:** ICP baseline-shunt operating ICP; **ΔCSP:** ICP plateau - shunt CSP.

	Functioning (Group A, N=136)	Borderline (Group B, N=26)	p-value (Group A&B)	Blocked (Group C; N=41)	p-value (Group B&C)	p-value (Group A&C)
Operating pressure [mmHg]	7.22 ± 2.07	6.95 ± 2.20	0.709	6.65 ± 2.33	0.572	0.7091
CSP [mmHg]	16.94 ± 2.77	16.67 ± 2.34	0.757	15.45 ± 3.18	0.053	0.0048
Shunt Rout [mmHg*min/ml]	3.20 ± 0.81	3.49 ± 0.82	0.014	3.49 ± 0.93	0.865	< 0.0001
ICP _{baseline} [mmHg]	6.07 ± 3.85	11.71 ± 4.47	< 0.0001	11.41 ± 5.89	0.430	< 0.0001
ICP _{plateau} [mmHg]	12.26 ± 4.31	20.40 ± 3.67	< 0.0001	29.42 ± 10.22	< 0.0001	< 0.0001
AMP _{baseline} [mmHg]	0.49 ± 0.39	0.68 ± 0.47	0.032	0.93 ± 0.61	0.045	< 0.0001
AMP _{plateau} [mmHg]	0.79 ± 0.62	1.17 ± 0.82	0.011	2.76 ± 2.04	0.0002	< 0.0001
Rout [mmHg*min/ml]	4.42 ± 2.00	6.80 ± 2.67	< 0.0001	14.82 ± 6.39	< 0.0001	< 0.0001
ΔICP [mmHg]	6.19 ± 3.35	8.69 ± 3.29	0.0002	18 ± 8	< 0.0001	< 0.0001
ΔAMP [mmHg]	0.3 ± 0.4	0.49 ± 0.56	0.0073	1.83 ± 1.8	< 0.0001	< 0.0001
ΔICP _{op} [mmHg]	-1.15 ± 3.88	4.77 ± 3.87	< 0.0001	4.76 ± 5.82	0.5701	< 0.0001
ΔCSP [mmHg]	-4.68 ± 4.07	3.73 ± 2.95	< 0.0001	13.97 ± 9.49	< 0.0001	< 0.0001

Cut-off values and ROC analysis

The cut-off values from the ROC analysis (group A versus Groups B& C -functioning versus malfunctioning shunts) were 11.74 mmHg for ICP plateau, 1.25 mmHg for AMP plateau, and 8.07 mmHg*min/mL for Rout. The accuracy of ICP_{plateau}, ICP_{plateau}-CSP and Rout was very high for separating functioning to malfunctioning shunts and are shown in **Figures 8.8 and 8.9.**

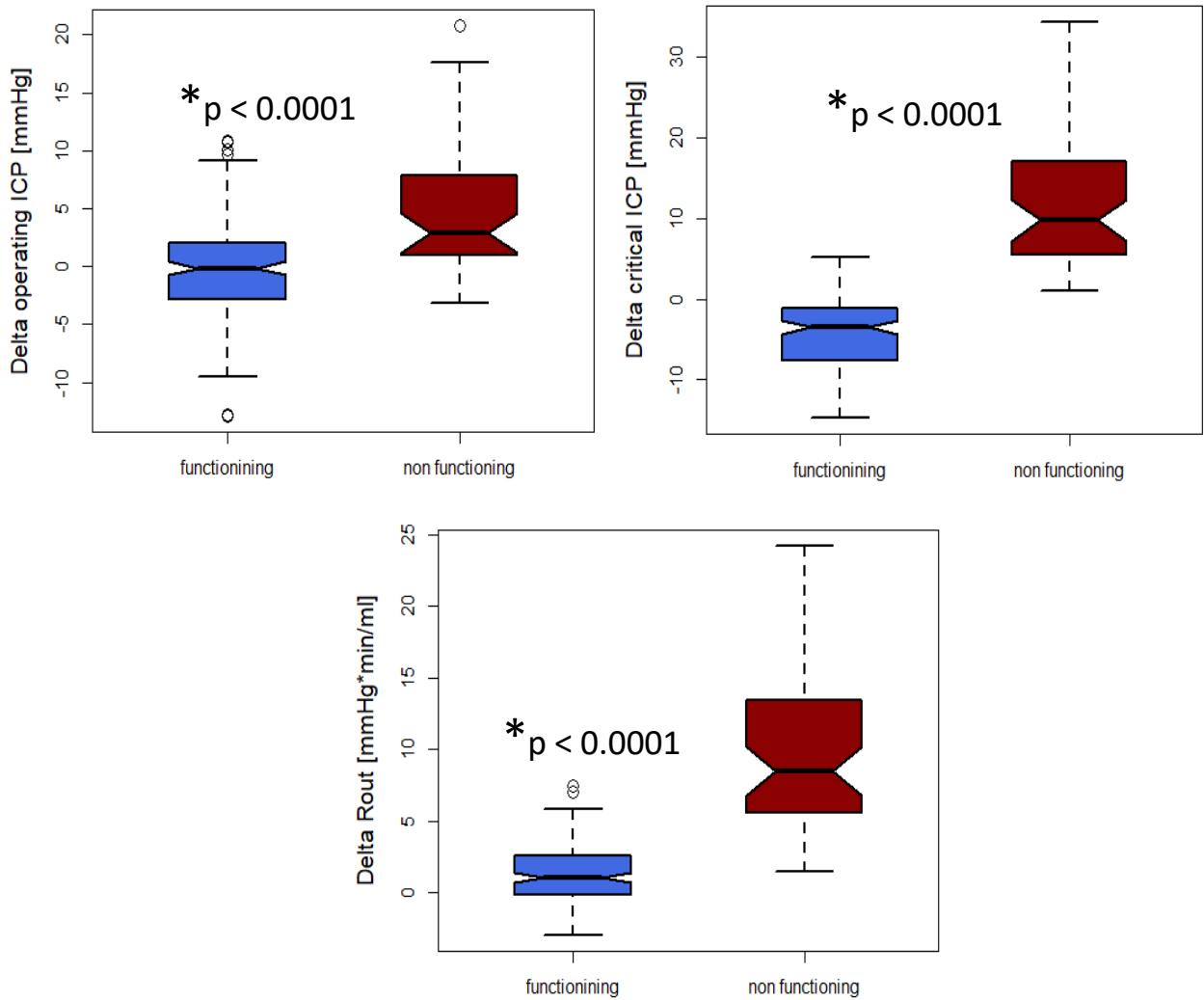


Figure 8.8. SIS results analysis between functional (Group A) and non-functional (Groups B&C) shunts. A) Delta operating ICP: $ICP_{baseline}$ - Shunt operating pressure. B) Delta critical ICP: Shunt critical pressure - $ICP_{plateau}$. C) Delta Rout: CSF resistance outflow - Shunt outflow (tested in Lab).

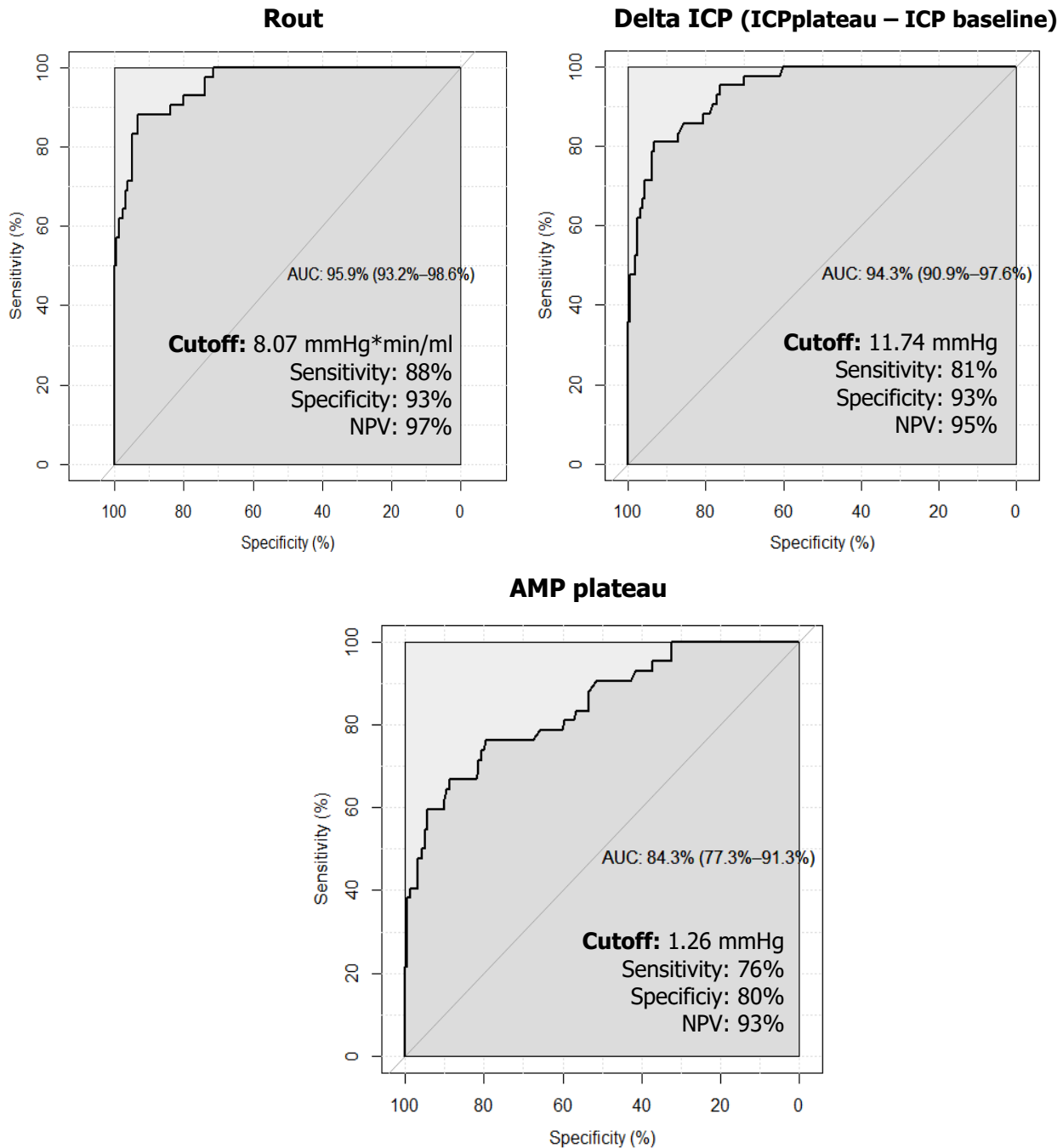


Figure 8.9. Receiver operating characteristics curves for Rout (left panel), delta ICP (middle) and AMP plateau (right panel) between functional and non-functional shunts. The respective cutoff-values, so as sensitivity, specificity, negative predictive value (NPV) and area under the curve (AUC) are given within the graphics.

Tübingen ventricular size analysis

We were able to obtain and analyse only the radiological and clinical follow-up data from the 30 children from Tübingen that had been subjected to 39 infusion tests. In Cambridge a vast majority of the CTs/MRIs was not accessible at the time of analysis due to some technical difficulties with the database the patient records were kept, as well as the lack of adequate follow-up documentation.

Clinical symptoms

Improvement was assessed based on clinical assessment by a paediatric neurologist, neurological development and feedback from the parents.

All 16 children with 19 infusion tests in Group A had remained stable or improved their neurological abilities according to their expected natural development during follow-up time, which was 33 ± 24 months. One child had a new infusion test showing obstruction at a later time point, after some new but inconclusive symptoms appeared.

Two of the three borderline children clinically after shunt adjustment (lower setting) and one child was monitored only and remained clinically stable.

10 of the 14 children (71%) with obstructed shunts that all underwent shunt revision improved in their clinical condition and neurological development at 6 months, while the remaining 4 children remained unchanged according to their previous status.

Radiological features

Radiological follow-up by MRI is usually undertaken and was available following in 37 of 39 infusion tests (95%), with a mean follow-up of 37 ± 29 months after the initial test.

In the Group A, 10/16 children (62%) had at last follow-up smaller and 5 unchanged ventricles (one child did not attend follow-up), with ΔFOHR and ΔEI (between last follow-up and pre-infusion) being 0.046 ± 0.0 ; $p=0.014$ and 0.037 ± 0.07 ; $p=0.029$ respectively.

The 14 children of Group C were submitted to 17 SIS and respective surgical revision due to shunt obstruction (3 children had 2 obstructions at different time points). 9 of

14 (64%) showed on last MRI follow-up after last revision smaller ventricles, and 5 children (31%) presented with unchanged ventricles. The Δ FOHR was 0.049 ± 0.097 ; $p=0.03$, and Δ EI 0.043 ± 0.097 ; $p=0.023$.

Numerical values of radiological features and statistical comparison between pre and post-infusion are shown in **Table 8.4**.

Table 8.4. Results of ventricle measurements on MRI of the 3 different groups in subgroup analysis from Tübingen (N=39). FOHR: frontal and occipital horn ratio; EI: Evan’s index; Δ : follow-up measurements – pre-infusion measurements. p-value: difference between pre-SIS and follow-up within group.

	Functioning (Group A; N=19)	p- value (A)	Borderline (Group B; N=4)	p-value (B)	Blocked (Group C; N=16)	p-value (C)
Follow-up MRI (months)	36.5 ± 26.19		50.33 ± 37.65		39.3 ± 33.8	
FOHR pre- infusion	0.49 ± 0.1		0.5 ± 0.11		0.46 ± 0.08	
FOHR follow-up	0.45 ± 0.1		0.43 ± 0.059		0.42 ± 0.062	
ΔFOHR	0.046 ± 0.08	0.014	0.073 ± 0.087	0.371	0.049 ± 0.097	0.03
Evans’ pre- infusion	0.37 ± 0.1		0.31 ± 0.11		0.38 ± 0.084	
Evans’ follow-up	0.34 ± 0.1		0.3 ± 0.07		0.33 ± 0.079	
ΔEvans’ index	0.037 ± 0.07	0.029	0.047 ± 0.063	0.25	0.043 ± 0.097	0.023

Complications observed

There were no complications associated with the infusion test, neither directly nor at long-term follow-up at 6 months, as well as no further records after that of a low-grade infection.

8.2.4 Discussion

We have presented a clinically-oriented, methodological, diagnostic and treatment approach using infusion tests for paediatric shunts that appear insidiously obstructed or are functioning, but the patients are symptomatic. Infusion tests can provide valuable and accurate, objective information in order to optimize the care of children with non-specific symptomatology and unchanged ventricles, or children with no symptoms and enlarging ventricles discovered in routine imaging. We have also for the first time reported quantitative thresholds that assist in differentiating between a patent and an obstructed distal catheter or valve, values that can be used to adapt and replicate our methodology with relative ease.

Regarding the shunt valves, in Cambridge there was a preference for Strata and CSF flow control burr hole valve, whereas proGAV and paediGAV were preferred in Tübingen. However, for Cambridge, burr hole valves are usually implanted in different centres. Nonetheless, we had selected the valves included in the study on the premises that they had similar shunt properties, and therefore would not influence our final analysis(44).

The patency of the proximal catheter is confirmed by visualisation and objective fast Fourier transformation analysis of the ICP pulse waveform, thus confirming communication with the ventricles. Even though gentle pressing on the pre-chamber with evident emptying and refilling can also indicate this patency, one should bear in mind that repetitive pre-chamber pumping may produce acute intracranial hypotension, dependent on the type of valve and as severe as -100mmHg, with all possible adverse consequences(326). Sometimes, partial obstruction of the proximal catheter can be suspected, when low AMP (< 0.5 mmHg) is detected, and/or the response to infusion is a decrease in AMP. Those cases had all been excluded from our cohort, and therefore there is no accounting for proximal obstruction at all.

The decision to perform shunt revision was based on infusion results in conjunction with the clinical symptoms and radiology, weighing down to the consultant's final opinion.

In section 6.1 and in the introduction, we have discussed the history and rationale of infusion tests, as well as the other methods used to assess shunt function and their limitations. We have also described how infusion tests constitute an important tool in the care of shunted patients, especially in avoiding revisions of patent shunts. With this article we have stressed their significance in the paediatric population in particular. Without the use of infusion tests, it is possible that 161/203 children (79%) would have been subjected to longer-term hospitalisation, invasive ICP monitoring, or even shunt surgery, without real justification, since their entire shunt system was unobstructed or slightly underperforming. Hence, infusion tests could support clinical decisions and can be easily performed in everyday neurosurgical care, with important implications.

Infusion test interpretation and accuracy

The methodology and clinical implications of shunt infusion studies have been reported extensively before, in mixed adult and paediatric populations. The understanding and performance of infusion studies can have some limitations and requires expertise when interpreting the results. We have therefore collected and retrospectively analysed data from two centres with a long-term experience in infusion studies.

Infusion rates were performed at both 1mL and 1.5mL per hour. Even though tests that were performed with infusion rates 1.5mL/h could implicate a higher plateau, all shunt critical pressure were adjusted to values previously calculated in laboratory settings(44,48).

As derived from shunt testing in vitro, $ICP_{baseline}$ and $ICP_{plateau}$ are expected to match the shunt operating pressure, ICP_{op} , and CSP accordingly (41,45). In order to translate those values from the laboratory to patients, the influence of the abdominal pressure (normally below 5 mmHg in non-obese children) is accounted for at around ± 5 mmHg

as the normal limits for ICP. A distal obstruction would therefore be predicted to cause an elevation $> 5\text{mmHg}$ above those pressure, which was the finding from our analysis. However, the baseline ICP, as derived from our ROC analysis, should not be used as a reliable predictor for distal shunt obstruction. As a result, baseline or steady-state values, especially with a manometer, should never be used for insidious shunt obstruction. Infusion or overnight ICP remain the most accurate methods for interrogating shunts.

Other parameters, such as $\text{AMP}_{\text{baseline}}$ and $\text{AMP}_{\text{plateau}}$ could also give some indication for malfunction, however they were not as reliable. AMP at baseline was lowest in the functional group, indicating that the intracranial compliance was normal and the intracranial compartment physiologically relaxed. Notably, while $\text{ICP}_{\text{baseline}}$ and its difference from ICP_{op} were not different between borderline and obstructed shunts, $\text{AMP}_{\text{baseline}}$ as a marker of compliance in the resting state was significantly higher in the obstructed shunts, indicating that compliance is more sensitive to insidious shunt underdrainage than pressure. Although it was increased in Groups B and even further increased in Group C, its low accuracy compared to Rout and $\text{ICP}_{\text{plateau}}$ could not justify its usage to detect shunt issues. Pathophysiologically though, it could indicate that shunt failure is associated with decrease of intracranial compliance and increased intracranial pulsatility. The compensatory reserve index RAP has previously been linked with imminent shunt failure (103). Increased Rout and pathological increase of ICP above CSP remain the most accurate descriptors of shunt malfunction, with thresholds of 1mmHg above CSFp and $4.5\text{ mmHg}\cdot\text{min/ml}$ above the shunt's inherent Rout respectively. Those thresholds alert to underdrainage, and a combination of increased Rout with further increased $\text{ICP}_{\text{plateau}}$ could differentiate clear obstruction.

Clinical safety

An internal audit performed between 2007 and 2009 (unpublished results) at the department of neurosurgery in Cambridge revealed a low rate $< 1\%$ of CSF infection following SISs if care is taken during the entire procedure – in particular what concerns skin disinfection and filling of the manometer lines and transducer(48). As

derived from section 6.1, we have also reported a 0% incidence of infection after shunt infusion tests in our series of 365 patients. This 0% infection rate was also replicated in our current study, therefore providing assurance that, when the appropriate standards are kept, infection risk could be practically eliminated.

Financial implications

We have not performed a health economics analysis on those patients, as it was not within the scope. Using the methodology, feasibility and safety data we provide here, perhaps a detailed evaluation of the overall financial benefit of infusion tests on the paediatric population might be of interest. Since saving shunt revisions early in life could prevent further revisions, perhaps the financial impact could be even more pronounced in young ages. Furthermore, a potential influence on developmental outcomes and continuity of care in this population could account for important financial benefits for the community, adding QALYs for the young, active population.

Tübingen sub-group analysis

All children in Tübingen were tested for suspicion of under-drainage or shunt blockage, as the presence of a gravitational ventriculostomy, protected them from developing over-drainage syndrome.

One third of the patients that had functioning shunts presented a low compliance. This can be in part explained through the contribution of the venous system and displaceable volume of venous blood. Even though the shunt is opened, a reduced venous outflow may increase the resistance parameters, therefore contributing for the hydrocephalus pathophysiology. Under the same principle, but in an opposite mechanism, increased venous outflow may compensate the higher intracranial pressure in non-functioning shunts, therefore explaining why 1/3 of the patients with non-functioning shunts showed a good compliance. Other adaptive mechanisms during brain development, or even the underlying disease that lead to hydrocephalus (e.g. children who suffered from post-haemorrhagic hydrocephalus with smaller brains) may also contribute to it.

Limitations

Our study, as a first of its kind, has been retrospective in nature. What is more, data collection involved two different centres with different standards of practice, with Cambridge showing a relatively low threshold for infusion tests whereas Tübingen a relatively higher one, although this has not been cross-checked with the centres' catchment areas, caseloads, and complexity of caseloads.

As far as other practice differences between the centres are concerned that could be raising questions on clinical implementation, children that are not cooperative do need to be sedated or studied under GA. This certainly brings in some additional "invasiveness", however, this is still drastically more invasive and more beneficial in the long-term compared to open shunt revision or routine insertion of ICP wires.

Unfortunately, an infusion test cannot differentiate between an obstruction within the valve or of the abdominal catheter, or in both, since it only detects increased Rout distally to the needles. If the valve is found unobstructed, then revision of the abdominal catheter can be performed without further concerns. On the other hand, if the flow through the valve is satisfactory, the abdominal catheter will most likely also be tested, to confirm or exclude the possibility that both the valve and the distal catheter could be blocked.

Finally, it is preferable to use a software (not necessarily ICM+) in order to continuously record ICP. The economic benefits associated with computerised infusion tests would significantly outweigh expenses related to software and expert expenses.

Conclusions

Shunt infusion tests are accurate, safe, feasible, minimally invasive and radiation free. They can be easily used for quantitative shunt assessment in children of all ages to exclude or confirm insidious shunt malfunction. They could be the gold standard for assessing complex hydrocephalus cases, when nothing else could direct management. If we consider the benefit versus the potential detrimental effects to the development and lifelong quality of such young children, infusion tests are an

important and currently unique tool for the paediatric neurosurgeon and perhaps even neurologist. Objectively and subjectively, a clinical and family-reported benefit, accompanied by radiological improvement has been preliminarily illustrated by the Tübingen cohort that should be followed by the larger cohorts in Cambridge and by prospective data.

After revealing several potential clinical, practical and outcome advantages, combined with the health economic advantages reported in section 8.1 and implied on this analysis, we suggest that shunt testing in vivo could become routine in neurosurgery units, especially centres specialising in hydrocephalus and complex cases.

CHAPTER 9

SLOW WAVES OF INTRACRANIAL PRESSURE

Influence of general anaesthesia on slow waves of ICP

The results presented in this section have been published in Acta Neurochirurgica Suppl:

Lalou A, Czosnyka Z, Lavinio A et al. Are slow waves of intracranial pressure suppressed by general anaesthesia? 2018; 126:129-132.

A previous version of the paper also exists in Neurological Research: Lalou, DA. Czosnyka, M. Donnelly, J., Lavinio, A. Pickard, JD. Garnett, M. Czosnyka Z, Lalou DA, Czosnyka M, Donnelly J, Lavinio A, Pickard JD, et al. Influence of general anaesthesia on slow waves of intracranial pressure. Neurol Res . 2016;38(7):587–92.

9.1 Introduction

Slow waves of ICP, also known as ‘b waves’, were first described by Lundberg in his 1960 dissertation (327) where he also named the previously discovered by Janny (328) plateau waves (A waves). They are observed as rhythmic fluctuations of ICP and are characterised by a low frequency of 0.3 to 4 cycles per minute (22,24,278,279,329). Unlike plateau waves, that have been shown to be caused by a drop in arterial blood pressure (MAP) that triggers a vasodilatory cascade, the physiological origin has not been definitively shown(22,23,329). During simultaneous recordings, slow wave oscillations appear concomitantly with those of CBF, which justifies the postulation that they are also vasogenic in origin, following the changes in cerebral blood volume caused by vasodilation and vasoconstriction (329–331). Besides this observed vasogenic correlation, other causations suggested have been a brainstem neuro pacemaker controlling cyclical electrical activity, as well as CO₂ changes during respiration have been implicated as causative agents(273,332) .

Plateau waves also usually last over 5-10 minutes (if uninterrupted by medical intervention) and ICP typically exceeds 40-50mmHg, whereas B-waves are short-lasting, and typically remain <40-50 mmHg) and constitute pathological events. On the contrary, slow waves of ICP have also been described in healthy individuals, and

the exact thresholds of frequency and magnitude that differentiate them with disease have yet to be quantified, especially in hydrocephalus(27,280). Hence, due to lack of a clear distinction between physiological and pathological waves, as well as uncertain clinical significance, diagnostic and prognostic exploration of b waves in hydrocephalus and TBI have nowadays obsolete. In TBI, the higher magnitude of B-waves has been associated with survival and low magnitude with a fatal outcome. However, they are no longer analysed towards this purpose and have since been replaced with different and more sophisticated methods of outcome classification and prognostication (220,256,258,260). In hydrocephalus, the magnitude (or amplitude) of B-waves has been shown to be inversely correlated with compensatory reserve and positively correlated with Rout(67) . Increased magnitude or frequency of slow waves, either during CSF infusion tests or from overnight ICP monitoring, has been contradictorily correlated with clinical improvement after shunting in normal pressure hydrocephalus (27,67,280). To the best of our knowledge, no specific numerical thresholds have been accepted for the frequency and magnitude of slow wave that described NPH or other CSF disorders.

GA is routinely used for ICP monitoring in TBI patients, as well as hydrocephalus patients that do not tolerate awake infusion tests, are agitated and difficult to comply, or for other clinical indications. Through our experience, we have macroscopically observed that slow waves are dampened or absent in patients studied under GA. Sleep studies have provided us with information on physiological frequency, magnitude, and the morphology or variation of B-waves during different sleep stages, however not during GA (22,332). We have hence aimed to quantitatively investigate the influence of GA on the magnitude of B-waves during wakefulness, by comparing awake and anaesthetised NPH patients undergoing infusion tests, as well as awake NPH patients with TBI long-term ICP recording.

9.2 Materials and methods

We formed two cohorts of 30 non-shunted patients each, undergoing computerised CSF infusion studies for possible NPH. Their clinical presentation was the usual for

NPH, and as has been described in our previous NPH cohorts used in this dissertation. A few patients overlap with those studied in previous chapters. Patients in GROUP A had undergone infusion tests awake, whilst GROUP B under GA. The later was used either because the patient was unable to fulfil the required 30 minutes to one hour of monitoring and stay still throughout the test, or as a perioperative technique of testing CSF dynamics followed by shunting within the same surgical session (24,110,233,333). GA was induced as per local standard protocol, using propofol, fentanyl and atracurium or vecuronium and maintained with either propofol infusion 3-6 mcg/ml alone or combined with remifentanil 0.05-0.2 mcg/kg/min (132,334–337). Central temperature and PaCO₂ levels were recorded and maintained stable at 36-37°C and 4.5-5.0 kPa respectively.

We expanded our study to ICP monitoring, using two further cohorts of 30 age-matched patients each, undergoing overnight ICP monitoring. GROUP C included naturally asleep patients investigated for hydrocephalus, with or without a shunt in place. GROUP D included the overnight part of the continuous monitoring of severe TBI patients. They were selected on the premises of having relative normotension (mean ICP < 18 mmHg), and during the first night of ICU stay, in order to eliminate the devastating effects of secondary insults (217,256,257). These patients were managed according to our Neurosciences Critical Care Unit (NCCU) protocol, which for an ICP <20mmHg without other evidence of evidently disturbed dynamics, consists of deep sedation with propofol and fentanyl or remifentanil, with or without neuromuscular blockade. We did not include patients with primary decompressive craniotomy. Body temperature and CO₂ levels were recorded and controlled at 36-37°C and 4.5-5.0 kPa, as part of standard clinical protocol and international guidelines(49).

Monitoring and use of recorded signals in TBI patients were approved by the relevant research ethics committee (29 REC 97/291).

Data analysis

ADL [author] removed artefacts manually in all groups prior to signal analysis and manually calculated slow wave magnitude [SLOW] using spectral analysis of the ICP signal recorded from the infusion tests and calculated as the root of the power of the signal in the frequency bandwidth 0.3 to 4 cycles/min (101,278,285). This calculation was imported to an automatic analysis profile in ICM+ in order to calculate SLOW from the longer recording in groups C&D. In Groups A&B, ICP required de-trending prior to calculation of slow wave magnitude. This was achieved with a moving average filter, enabling to efface the effect of a pronounced, artificial increase of slow wave amplitude due to fluid infusion.

Baseline ICP, Rout, elasticity and RAP were extracted as described in several previous chapters. Results are presented as mean \pm SEM. A one-way ANOVA was used to examine between group differences in examined parameters. Spearman rank correlation coefficient was used to examine the relationship between descriptors of slow waves and CSF compensatory parameters.

9.3 Results

The mean age was 73 ± 7 and 75 ± 8 years for Groups A& B respectively with a male to female ratio in both approximately 4:3. Illustrative cases of a conscious versus an anaesthetised possible NPH patients are presented in **Figure 9.1A and B**, respectively. Numerical results of slow waves and other infusion test parameters for the two groups are presented in **Table 9.1**.

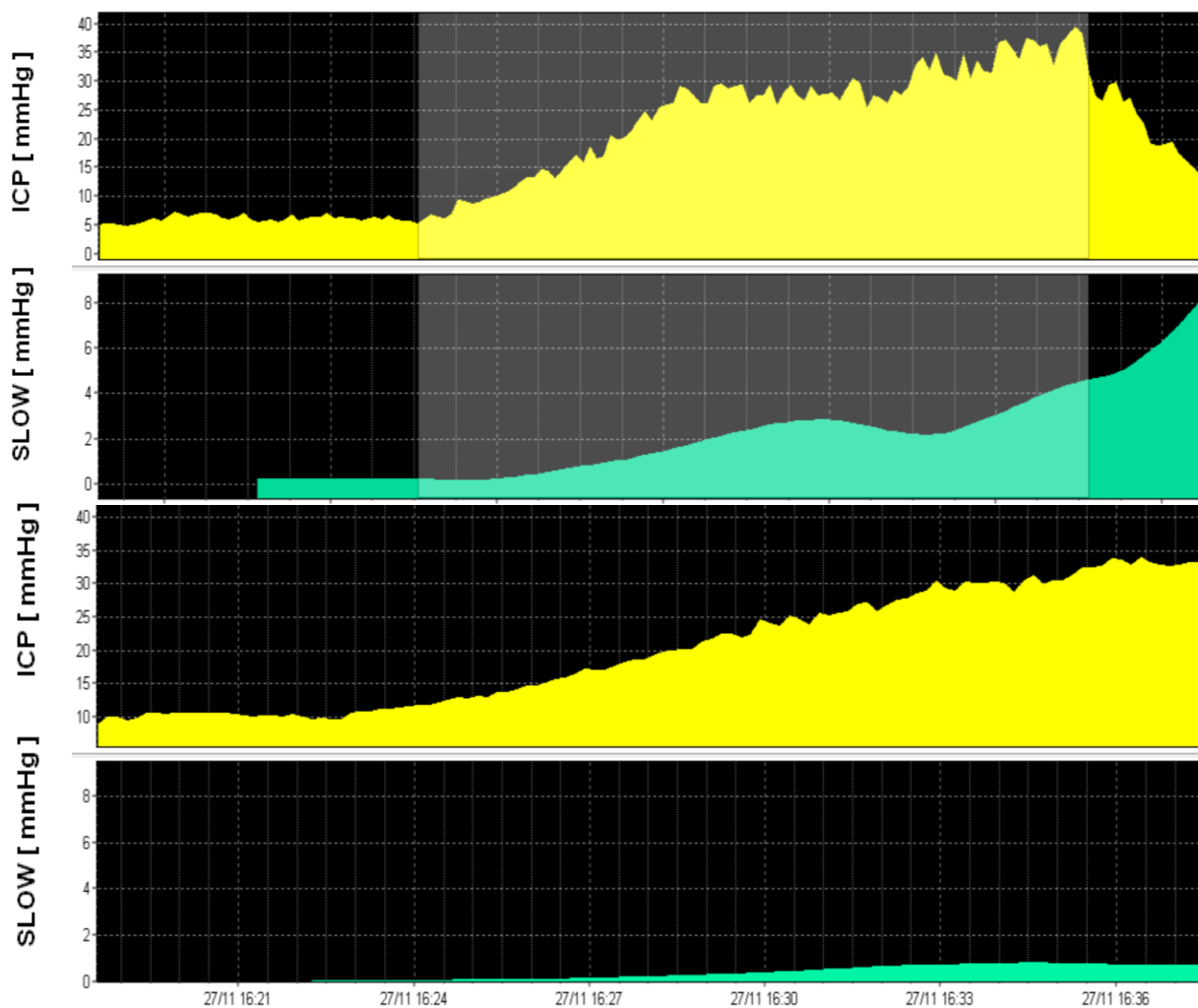


Figure 9.1: Influence of General Anaesthesia on slow waves of intracranial Pressure during infusion. Upper panel: Typical infusion study performed in conscious patient with ICP oscillations visible. Lower panel: patient under GA, ICP oscillations almost completely disappear. Slow: magnitude of slow waves

Table 9.1 Infusion test and slow wave analysis results from the first two groups; conscious patients with NPH (Group A) and under GA (Group B). *SLOW*: Slow wave magnitude

	Conscious (Group A)	Under GA (Group B)	p-value
Age [years]	73±7	75±8	
Male/female ratio	~4:3	~4:3	
SLOW [mm Hg]	0.23±0.16	0.15±0.11	<0.0023
SD of 10 sec averages of ICP [mm Hg]	1.41±0.24	0.61±0.28	<0.0001

	Conscious (Group A)	Under GA (Group B)	p-value
Baseline ICP [mm Hg]	9.56±4.1	5.04±3.87	NS
AMP [mm Hg]	1.82 ±1.7	1.91±1.41	NS
Rout [mm Hg/(ml/min)]	13.6±5.2	19.5±11.1	0.011
Elasticity [1/ml]	0.17±0.14	0.22±0.17	NS
Production of CSF [ml/min]	0.30±0.21	0.21±0.28	0.022

Mean age in Group C was 23±8 years and 29±7 years for Group D. Illustrative examples of an overnight monitoring recording in a naturally asleep, possible hydrocephalus patient versus a deeply sedated and ventilated patient are shown in Figure 9.2A and 2B, respectively. Numerical results from Groups C&D are presented in Table 9.2.

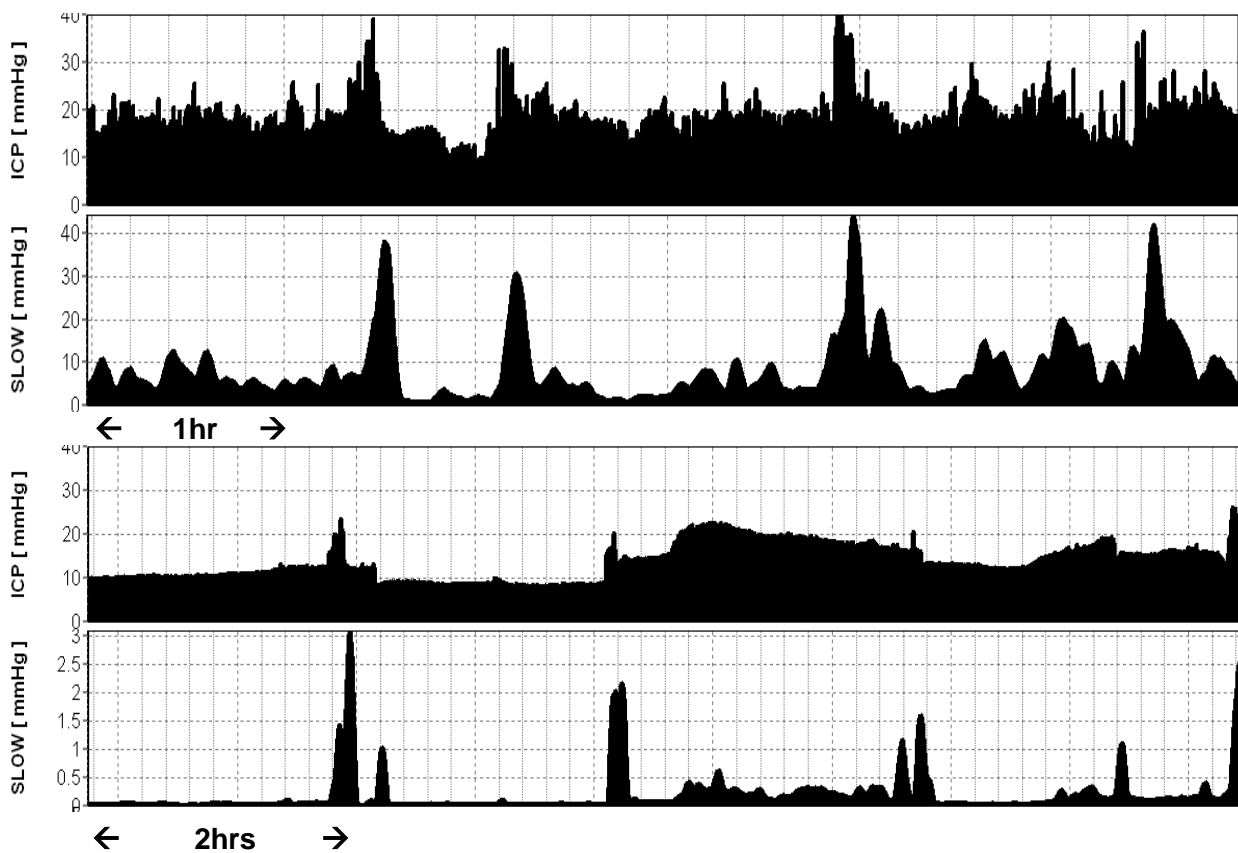


Figure 9.2 Influence of General Anaesthesia on slow waves of intracranial Pressure during overnight monitoring: Upper: Overnight ICP monitoring in conscious patient ICP= 17.5; slow= 4.2; Lower: monitoring of TBI patient ICP=13.5 , Slow=0.2

Table 9.2 CSF dynamics & slow wave analysis results from the second cohort groups (conscious patients with overnight ICP monitoring (Group C) & sedated TBI patients (Group D))

	Conscious (Group C)	Sedated (Group D)	p-value
Age [years]	23±8	29±8	
Male/Female ratio	~2:1	~2:1	
SLOW [mmHg]	0.196±0.13	0.11±0.091	0.0024
SD of thirty 10 sec averages of ICP [mm Hg]	1.42±0.64	0.71±0.42	<0.0001
Mean ICP [mmHg]	7.7±4.9	13.6±5.91	0.001
AMP [mmHg]	3.21±1.18	3.41±1.43	NS
RAP index	0.44±0.17	0.3±0.18	0.045

The average SLOW and SD of 10 sec-averaged ICP was significantly lower in the anaesthetised patients (Groups B and D) compared with the alert/naturally asleep patients (Groups A and C). In the infusion patients, there was no correlation between compensatory reserve and the power of slow waves. There was no significant correlation between power of slow waves and Rout or elasticity either. In group A only, the magnitude of B waves was positively correlated with baseline ICP (R=0.48; p=0.0067).

From the nature of measurement, there was a significant difference in the total duration of ICP monitoring between the infusion groups and the overnight ICP groups. There was no statistical difference between slow waves in Group A (baseline values, before start of infusion) and C, and respectively B and D (p>0.05).

9.4 Discussion

Our current findings are the first quantitative demonstration of the degree slow waves are suppressed by GA. They only represent a statistical estimate, and in order to assess the clinical utility and application of such a finding further studies are required.

It has been routine in our centre and many centres worldwide to anaesthetise animals and patients for ICP and CSF dynamics studies. Since different anaesthetic agents are available, their effects on ICP, CBF and metabolism are known and have been studied extensively. Propofol is among the most common agents used in brain injury and general anaesthesiology worldwide, and provides a flexible pharmacokinetic profile combined with a desired, profound suppression of cerebral metabolic rate, whilst preserving cerebral autoregulation (147,335,338). Fentanyl and remifentanyl are known as safe, however as they are adjunct agents, a detailed effect on intracranial dynamics has not been elucidated yet (334,338–340) and neuromuscular blockers are considered to have negligible effects (49).

Nonetheless, propofol-based anaesthesia appears to suppress slow waves by approximately 50% wakefulness or natural sleep, evident in both the average SLOW and 10 second SD of mean ICP, that were significantly lower in patients under GA than in those in fully conscious state. It would be difficult to hypothesise on the nature of this effect, as a combination of pharmacological, vascular and metabolic effects are related to the GA itself, on top of the influence of mechanical ventilation and relatively restricted changes CO₂(148,201,341). Baseline ICP is known to correlate with slow wave power, probably reflecting the fact that increased ICP is associated with poor intracranial compliance, which in turn increases pulsatile components of ICP and slow wave magnitude (114,330). However, from our current results, baseline ICP did not appear reduced by GA, and therefore slow waves are most likely not dependent on mean ICP under GA circumstances. On a similar note, intracranial elasticity, as a measure of compliance, did not differ between groups. Alternatively, slow wave changes could be linked with lower brain metabolism rate and CBF. Indeed, as there

is strong evidence that b-wave oscillations occur in response to those of MAP and/or cerebral oxygenation, changes in CaBV could account for those changes in magnitude (342–344). Finally, Rout was significantly higher in the GA group (group B). This could represent selection bias due to the fact that patients selected for GA present with more severe symptoms and are more likely to not cooperate or to be a candidate for shunting (280). Furthermore, there is no known physiological mechanism for GA to cause higher Rout, at least under stable haemodynamic conditions.

Separately to CaBV changes, arterial CO₂ could be one of the contributing factors to ICP fluctuations. The haemodynamic effects potentiated by the vasodilative properties of CO₂ are widely known under physiological circumstances. Under pathophysiological circumstances, such as sleep apnoea, changes in CO₂ and breathing patterns have been described in association with CBF and systemic MAP disturbances (90,345). A recent study has shown that hypocapnia also decreases the amplitude of slow waves in TBI patients (346). Whether relevant abnormal or mechanical ventilation changes could also apply to the detected differences is unknown. We have not performed such multimodal analyses for our current investigation. A further modality not monitored or interpreted on this paper is MAP slow wave power. As mentioned above on several occasions, slow waves in MAP are transmitted to the cerebral vasculature and, depending on the state of autoregulation, to ICP (256,271,347,348). Continuous monitoring of MAP intraoperatively, in order to determine an effect of GA on slow waves of MAP has not yet been attempted.

Regarding the innate complexities of TBI and the potential influence this could have on slow waves, those patients were carefully selected to fit the purpose of this study, by excluding anyone with ICP > 18 mmHg as well as beyond the first day of their admission. B waves are dampened or effaced in cases of an unreactive vascular bed, where a pressure-passive system suffers severe and steep rises in ICP. Therefore, in our selected patients, a lower slow wave magnitude cannot be directly attributed to the trauma more than the GA. Similarly, for our naturally asleep NPH patients, no significant effect of REM or non-REM sleep has been determined on the amplitude of b waves compared to wakefulness (22,90,349). Our study could not reveal a

pronounced effect of natural sleep on slow wave magnitude, as there was also no significant difference between Group A (daytime, awake) and Group C (night-time, asleep).

The global appeal slow waves have in disease has recently resurfaced due to the surge of research into the glymphatic system and the role that peaks of CSF production and ICP during slow-wave sleep have been postulated to have in clearing cerebral amyloid and therefore have been implicated in the pathogenesis of dementias. These reports have subsequently sparked new controversies in the field of CSF dynamics, redemonstrating the importance of investigating such important phenomena of the cerebral vasculature and fluid dynamics in relationship to natural sleep as well as induced sleep and pathophysiology.

There could be possible clinical implications of these reported findings. In the context of performing and interpreting ICP monitoring and CSF infusion test, it would be important to be aware of and consider the use and effect of GA, especially if slow waves consist part of the experimental or diagnostic/prognostic process. Alternative methods are taking over Rout and slow waves in identifying shunt responders and to indicate surgery in patients with a diagnosis of NPH. Despite this, ICP monitoring and infusion tests still provide objective assessment tools, and slow waves are yet to be rendered obsolete, especially since a threshold for their magnitude has not been described from a large enough cohort. Should this be attempted, the knowledge that slow waves are almost halved in magnitude by GA may prevent significant interpretation errors.

Limitations of the study

Our data is derived from an adequately powered cohort of unique individuals, and does not represent paired values within the same individuals, as attempting an experimental protocol of repeated infusion tests/ICP monitoring with and without GA on the same individuals would be harmful to the patients.

Since the overnight monitoring comparison group consisted of TBI patients, limitations arise from comparing different conditions, even though as mentioned above we tried to exclude most possible confounding parameters of disturbed CSF dynamics in those patients.

As this was a retrospective study reliant on monitoring performed for clinical reasons, CBF and/or metabolism were not assessed in any patient group and therefore cerebral vasodilation and CBF fluctuations cannot be confirmed with the current study. Similarly, MAP and PaCO₂ were not measured in order to address the aforementioned discussion points. It was not within the purpose of the study to compare CSF and slow wave dynamics with the use of different types of anaesthetics. Even though it is reasonable to assume that there may be a dose-dependent association between the depth of anaesthesia and the suppression of vasogenic ICP waves we are unable to explore this question with the dataset available.

Finally, previous studies have found that the amplitude of b waves probably increases during REM sleep, although results remain contradictory. In such case, REM sleep could account for another possible interpretation of the difference between Groups C and D. However, we could not monitor sleep phases in order to determine this.

Further studies need to be performed to confirm our findings, extend our speculations and provide practical information on how to interpret slow wave analysis derived from anaesthetised patients.

CHAPTER 10

CONCLUSIONS AND FUTURE DIRECTIONS

10.1 Conclusions

Through the works included in my dissertation, I have explored new insights into the clinical utility of CSF dynamics. I have highlighted how an understanding of the CSF and cerebral blood circulation could advance all combined pathways of pathophysiological knowledge, diagnosis and treatment of CSF disorders.

The main findings of each chapter and section are summarised in **Table 10.1**.

Table 10.1: Synopsis of the main findings per chapter of this dissertation.

Research question	Main findings	Section
Resistance to CSF outflow (Rout) in NPH	Significant correlation of Rout with age, as well as Rout with ICP baseline (derived from infusion tests). The later validates Davson's equation in NPH	5.1
	Rout and fundamental amplitude of ICP (AMP), as well as the slope of the AMP-ICP regression appear to be decreased in post-traumatic hydrocephalus versus idiopathic NPH	5.2
CSF dynamics in Pseudotumour cerebri syndrome (PTCS)	CSF pressure is coupled with sagittal sinus pressure in certain adults with PTCS. This coupling is resolved with CSF drainage.	6.1
	Increased CSFp with depleted compensatory reserve is characteristic in paediatric PTCS. However, there is heterogeneity in the elevation of CSFp and disturbance of CSF dynamics, as well as clinical presentation.	6.2
Value of shunt testing in vivo	Shunt testing in vivo, both for hydrocephalus and for PTCS and across all ages, is an accurate tool for diagnosing shunt malfunction.	7.1
	Unnecessary admissions, more invasive monitoring and operations can be avoided when infusion tests are used routinely, with significant cost-effectiveness	7.1
	In paediatric hydrocephalus, shunt infusion tests accurately reflect clinical follow-up and intraoperative shunt testing findings, and also contribute to saving unnecessary revisions in developing children.	7.2

Research question	Main findings	Section
Slow waves of ICP	Slow waves of ICP are most likely significantly suppressed by general anaesthesia, both in NPH and in TBI. Clinical and physiological applications of such a finding are awaited.	8
Autoregulation in NPH	A combination of arterial hypertension and impaired autoregulation is a negative predictive factor for shunt response.	9

Contributions to new knowledge

The new knowledge that is derived from my current work potentially is centred around paediatric PTCS and paediatric hydrocephalus, as we are one of the only centres performing infusion tests in such patients, and the safety as well as the utility of those procedures in the paediatric population has remained unknown. The financial impact of infusion tests has also not been demonstrated before, to the best of my knowledge, neither has the effect of GA on slow wave amplitude. The rest of my findings have mainly confirmed or expanded on previous work, I have therefore not broken academic ground with them but have to the existing pool of evidence in order to stimulate future leading-edge research.

Overall, I have attempted to revisit Rout. Using the recent findings that Rout could not predict outcome as reliably as first reported during the first works of Borgensen et al(67) and Boon et al(63) in the 1980s and 1990s, I have attempted to explain why Rout is lacking predictive value in NPH. As this is a multifactorial question, I have started by exploring which factors influence Rout, and have discovered that age, cerebral autoregulation, systemic arterial blood pressure and finally aetiology (TBI) are only a few of such factors. Perhaps this could be the beginning of understanding the variability and the limited predictive value of Rout.

In some cases of PTCS, a concomitant increase of CSFp and SSp can be seen during infusion, that results to Rout overestimation. The coupling is reversible with CSF

drainage. Increased CSFp (>20 or 15 mmHg) with depleted compensatory reserve can be identified in paediatric PTCS, albeit significant variability in several cases.

I have also managed to analyse large cohorts of shunted patients, including a two-centre paediatric study, to show the clinical value of shunt infusion tests; Shunt infusion tests contribute to avoiding long hospitalisations, surgeries for revising functional shunts, as well as being short-term and having practically zero complications.

Lastly, slow waves of intracranial pressure are of importance, as they carry information related to cerebral autoregulation. As they are suppressed by general anaesthesia, this could have an influence on to-date and future interpretation of slow waves in CSF disorders. PRx, calculated by slow waves of ICP and MAP, indicates disturbed global cerebral autoregulation in NPH and therefore used as a predictive parameter for shunting, combined with MAP as well as possible Rout.

10.2 Future directions

CSF dynamics in NPH

The puzzle of NPH in relationship with healthy ageing and other dementias is slow to unravel, unless a meticulous assembly of the cumulative knowledge acquired after many decades of research is performed. This should be used to design targeted research for further physiological understanding of cerebral circulation in physiological and pathophysiological ageing; Cerebral circulation per definition includes CSF, venous and arterial blood flow, and all relevant findings should be able to be translated to useful clinical information.

Given that a lot of centres have abandoned the clinical use of infusion tests, mainly due to limitations in shunt prognostication, there might be less opportunities to progress quickly in the field of testing CSF dynamics in NPH. However, there is a lot of information available to explore and validate a new reality for Rout: correction with age, association with depleted compensatory reserve and stiffer ageing brains to begin with. In addition, understanding of aetiology, comorbidities, vascular disease,

autoregulation, white matter hyperintensities and white matter tract distortion: all this information is readily available and requires proper testing and validation, since the next step should be adapting these findings clinically, after building the evidence for well-designed clinical trials.

Thorough mapping of a vascular disease morbidity score, together with imaging for CBF, white matter hyperintensities, white matter tracts with diffusion tensor imaging, and everything in the context of CSF circulation (with appropriate review of Rout) is required. In continuity with how all these are amenable or not to shunting or other treatment(s), the above appears as a step towards the right direction at this given moment. Post-shunting testing of CSF dynamics and cerebral circulation is vital and should not be neglected, especially in cases of no improvement.

CSF dynamics in PTCS

The coupling of CSFp and SSp could be used to explore therapeutic possibilities; it is likely that a resolution of the pathophysiological positive feedback loop between increased CSFp and SSp could correlate with resolution of clinical symptoms, as it is an interruption of the disease at its pathophysiological or pathogenetic process. A CSFp<20mmHg alone does not guarantee this uncoupling, and therefore adequate drainage to achieve reversal could be required. In cases of normal SSp, a different pathophysiological route has been considered(350), and it would be of significance to explore the same relationships between CSFp, SSp and compensatory reserve in different PTCS patients.

For paediatric patients specifically, a coupling between these two pressures has not been described yet, and the cohort of 31 patients I have currently reported remains small and heterogeneous. As more patients are being tested and further follow-up and treatment outcomes become available for our studied patients, the limitations of currently available clinical, imaging and CSF dynamics criteria should be weighed. In selected cases, further testing, perhaps with consideration of invasive with scope of non-invasive monitoring could be considered. ICP monitoring, together with SSp

continuous recording could be the start to enhance diagnosis of such patients, and the basis to build a non-invasive suite of tools for the paediatric and adult population.

Shunt testing in vivo

Testing the function of shunts with infusion tests presents with less challenges. On the contrary, an understanding of the entire cerebral circulation after shunting, especially in relationship with improvement and no improvement, poses similar challenges as a shunt-naïve brain. Firstly, the mere requirement that a shunt opens and closes as it is expected to, is difficult to ascertain. Shunt infusion tests are a very accurate and valuable tool to exclude obstruction, however the fine-tuning of CSF drainage through a shunt is a complicated process, with no objective tests on how to achieve this yet.

Further tools could assist in assembling the vignette of post-shunting circulation: concomitant assessment of the blood flow, as well as a combination of testing the presence of regular, spontaneous flow through the shunt combined with CSF infusion test to assure patency could show some promise. As NPH patients tend to gain only 1-2 quality life years, with obstruction of shunts being a rare issue compared to other age groups and types of hydrocephalus, it is a matter of wonder whether those patients are receiving adequate CSF drainage and have the right type of valve implanted for their needs.

No new devices could be required to monitor pressure and to flush the shunt system if infusion tests are available. There appear to add no new information to what is already available with infusion tests, besides increasing care costs and technical difficulties. Smarter approaches related to improving existing shunt valves or creating a single shunt valve could yield more effective results. At the same time, cogitation on the causes of shunt failure and the reasons behind deterioration of patients with patent shunts could easily reveal missing information that will assist in improving current care.

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