THE SEARCH FOR REVERSIBILITY OF
IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

ASPECTS ON INTRACRANIAL PRESSURE MEASUREMENTS AND ADVANCED MRI TECHNIQUES
IN COMBINATION WITH CSF VOLUME ALTERATION

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UMEÅ 2007
In honour of our Creator, Almighty God.
The physiological perfection, wealth of details and completeness of Your creations never stop to surprise me.

“Data collection without causal investigation usually does not constitute scientific research.”
“True scientific research always develops cause and effect relationships.”

“Most of the future has already happened. Thus, to shape it, affect it before present times”
Unknown
BACKGROUND: Idiopathic normal pressure hydrocephalus (INPH) is still a syndrome generating more questions than answers. Research today focuses mainly on two areas: understanding the pathophysiology and finding better methods to select patients benefiting from a shunt operation.

Even though the background of the disease remains unclear, there is wide agreement that there are two pillars of the disease concerning its pathophysiology: firstly, dysfunctional hydrodynamics of the CSF system and secondly, a periventricular chronic ischemia. Unfortunately, the causal effect between these entities remains unsolved, the solution most likely being the key to finally understand the disorder.

This thesis targets the aspect of finding better selection methods by investigating the measurability of intracranial pressure via lumbar space, and determining if intraparenchymal measurement of long-term ICP-oscillations (B-waves) could be replaced by short-term measurements of CSF pulse pressure waves via lumbar space. Furthermore, I look into the interaction between the CSF system and the parenchyma itself by investigating how the brain changes its cortical activity after long-term CSF drainage, and if there is any regress in the suggested ischemia after this intervention. Finally, I examine if the neuronal integrity in the INPH brain is impaired, and if this feature is relevant for the likeliness of improvement after CSF diversion.

METHODS: The comparisons of intracranial and lumbar pressure were made over a vast pressure interval using our unique CSF infusion technique, and it included ten INPH patients. Pressure was measured via lumbar space and in brain tissue, and the pressures were compared using a general linear model. Short-term lumbar pressure waves were quantified by determining the slope between CSF pulse pressure and mean pressure, defined as the relative pulse pressure coefficient (RPPC). The correlation between RPPC, B-waves, and CSF outflow resistance was investigated.

In a prospective study, functional MRI assessed brain activity before and after long-term drainage of 400 ml of CSF in eleven INPH patients. The functionalities tested included finger movement, memory, and attention. The results were benchmarked against the activity in ten healthy controls to identify the brain areas improving after drainage. The ischemia (Lactate) and neuronal integrity (NAA and Choline) were measured in a similar manner in 16 patients and 10 controls using proton MR
spectroscopy, and the improvement of the patients after CSF drainage was based on assessment of their gait.

RESULTS: There was excellent agreement between ICP measured in brain tissue and via lumbar space (regression coefficient = 0.98, absolute difference < 1 mm Hg). Adjusting for the separation distance between the measuring devices slightly worsened the agreement, indicating other factors influencing the measured difference as well. RPPC measured via lumbar space significantly correlated to the presence of B-waves, but did not correlate to outflow resistance.

In the prospective study, controls outperformed patients on clinical tests as well as tasks related to the experiments. Improved behaviour after CSF drainage was found for motor function only, and it was accompanied by increased activation in the supplementary motor area (SMA). No lactate was detected, either before or after CSF drainage. NAA was decreased in INPH patients compared to controls, and the NAA levels were higher in those patients improving after drainage.

CONCLUSIONS: ICP can be accurately measured via lumbar space in patients with communicating CSF systems. The close relation between RPPC and B-waves indicates that B-waves are primarily related to intracranial compliance, and that measurement of RPPC via lumbar space could possibly substitute B-wave assessment as selection method for finding suitable patients for shunt surgery.

Improvement in motor function after CSF drainage was associated to enhanced activity in SMA, supporting the involvement of the cortico-basal ganglia-thalamo-cortical loop in the pathophysiology of INPH. There was no evidence indicating a widespread low-graded ischemia in INPH; however, there was a neuronal dysfunction in frontal white matter as indicated by the reduced levels of NAA. In addition, the degree of neuronal dysfunction was related to the likeliness of improvement after CSF removal, higher NAA levels predisposing good response.
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ORIGINAL PAPERS


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**ABBREVIATIONS**

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
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<td>CBV</td>
<td>Cerebral Blood Volume</td>
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<td>CSF</td>
<td>Cerebrospinal Fluid</td>
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<td>fMRI</td>
<td>functional Magnetic Resonance Imaging</td>
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<td>1H MRS</td>
<td>proton Magnetic Resonance Spectroscopy</td>
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<td>IAHS</td>
<td>Idiopathic Adult Hydrocephalus Syndrome (=INPH)</td>
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<td>INPH</td>
<td>Idiopathic Normal Pressure Hydrocephalus</td>
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<tr>
<td>ICP</td>
<td>Intracranial Pressure</td>
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<tr>
<td>Liquor</td>
<td>CSF synonym</td>
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<tr>
<td>MMSE</td>
<td>Minimal Mental State Estimation</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>NAA</td>
<td>N-acetyl-aspartate</td>
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<tr>
<td>NPH</td>
<td>Normal Pressure Hydrocephalus</td>
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<tr>
<td>PVI</td>
<td>Pressure-Volume Index</td>
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<td>PWML</td>
<td>Periventricular White Matter Lesions</td>
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<td>RPPC</td>
<td>Relative Pulse Pressure Coefficient</td>
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<td>Rout</td>
<td>Outflow resistance</td>
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<td>SAS</td>
<td>Subarachnoidal Space</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<td>SE</td>
<td>Standard Error</td>
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<tr>
<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
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<td>TMT</td>
<td>Trail Making Test</td>
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<td>VPR</td>
<td>Volume-Pressure Response</td>
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<td>9-HPT</td>
<td>9-Hole-Peg-test</td>
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**BACKGROUND**

*Hydrocephalus and the CSF System: from discovery to modern time*

The designation Hydrocephalus comes from the Greek words \( \delta \varepsilon \alpha \rho \) (hydro) meaning water and \( \kappa e \phi a \lambda \eta \) (kefalé) meaning head,\(^{(1)}\) i.e. ‘water head’, a name in complete coherence with the essence of the disease – excessive fluid inside the cranium – but a most morbid designation when communicated to the general public.

Hydrocephalus is described in archaeology as far back as 10 000 years BC\(^{(2)}\); Pharaoh Ikhnaton (1388-1358 B.C.) being the most prominent person acquiring the condition.\(^{(3)}\) Later, Hippocrates (466-377 BC), who purportedly was the first person to name the disease, stated a few of the symptoms of the syndrome, implying brain melting as the root cause.\(^{(1)}\)

Next person providing information on hydrocephalus and CSF was Claudius Galen of Pergamon (130-200 AD). From animal dissections, he described the CSF as a “clear, watery liquid.” Furthermore, he discovered the foramen of Magendie and hypothesized the choroid plexus to be the production site of CSF.\(^{(4)}\)

As Antiquity passed into Middle Ages, medical wisdom and progress was gradually succeeded to Arab and Persian cultures,\(^{(1)}\) and the next time hydrocephalus is encountered we find ourselves in the Islamic caliphate of Cordoba, Spain. Here, another great contributor to the development of medicine and surgery, Abulkassim Al Zahrawi alias Abulcasis, lived from 936 to 1013. He suggested mechanical compression as an explanation to the cases of infantile hydrocephalus he encountered, and he also described how liquid flowed out as the skull was opened, seemingly as a therapeutic attempt.\(^{(5)}\)

In the transgression from Middle Ages to Modern Times, the medical centre of gravity shifted back to Europe, exemplified by the medical school in Salerno and universities of Padua and Montpellier.\(^{(1)}\) In 1510, Leonardo da Vinci made the first illustration of the ventricular system; an event made possible by the acceptance of dissection of human remains.\(^{(3)}\) A decade later, the cerebral aqueduct was described, but the outflows of the fourth ventricle remained unrecognised despite Galen’s earlier description of the foramen of Magendie.\(^{(1)}\)
Andreas Vesalius (1514-1564) first described the true concept of hydrocephalus, i.e. the accumulation of water inside the ventricles. He discovered the condition while performing a post-mortem examination on a two-year old girl with an enormously enlarged head, but without apparent neurological deficiencies when she was alive. In the coming centuries, several theories on CSF outflow were put forward. Richard Lower (1631-1691), a collaborator of Thomas Willis of Oxford, proved the cribriform plate to be watertight, instead suggesting that the clearance mechanism involved CSF resorption to the venous system. In 1701, Pacchioni (1665-1726) discovered the arachnoid granulations carrying his name, but associated them with secretion instead of absorption. Instead, he proposed “lymph nodes” to convey the “brain lymph” back to the venous system. In 1738, Fantoni revealed the correct function of the granulations.

Albrecht von Haller presented in 1747 the modern theory of CSF circulation, unfortunately without proof, and he also discovered the foramina of Luschka. Further examples of hydrocephalus found at autopsies were published in 1769 by Giovanni Battista Morgagni (1682-1771). More clinically interesting were the systematic neurological studies of hydrocephalic patients performed by Robert Whytt of Edinburgh (1714-1766), who in 1768 described the different courses the disease took depending on the status of the sutures.

In the nineteenth century, Francois Magendie (1783-1855), who rediscovered and named the foramen earlier observed by Galen, purported a reversed CSF circulation theory. According to his hypothesis, CSF was produced at the brain surface, flowed into the ventricles via his own foramen and was finally absorbed by the choroid plexus. Despite this faux pas in the theory building on CSF circulation, he contributed greatly to hydrocephalus research by suggesting occluded CSF circulation as a cause of the disease and performing the first CSF pressure measurement on a dog in 1841. Others providing pieces of the puzzle of the CSF system in those years were Luschka (1820-1875) and Bochdalek (1801-1883).

Ernst Axel Hendrik Key (1832-1901) and Magnus Gustav Retzius (1842-1919) of Sweden provided the decisive proof on the concept of CSF circulation in 1875. They provided irrevocable evidence for the “inside-production → ventricular-transport → outside-absorption” theory of CSF circulation; knowledge that modern science has little to add to. Continuing, Hilten in 1879 proved the occlusion theory to be accurate.
regarding the origin of hydrocephalus\(^{(1)}\); thus, completing the basic picture of the disease.

In the beginning of the twentieth century, Walter Dandy and Kenneth Blackfan of the Johns Hopkins Hospital of Baltimore created an animal model of hydrocephalus by blocking the aqueduct and foramina of Monroe on dogs.\(^{(8)}\) Furthermore, Dandy showed that removal of the choroid plexus before occlusion of the foramina prevented the development of hydrocephalus.\(^{(9)}\) Additional information on CSF outflow through the arachnoid villi was provided by Weed\(^{(10)}\) who also described aspects of the CSF and meninges.\(^{(11)}\)

In the fifties, sixties and seventies, a wealth of research on the physiology of the CSF system – including reasons for its failure – emanated. Pappenheimer performed his ingenious ventricular perfusion tests on goats,\(^{(12)}\) Welch investigated CSF secretion on rabbits\(^{(13)}\) while looking further into the function of the arachnoid villi on monkeys,\(^{(14,15)}\) and Davson experimented on CSF composition and turnover.\(^{(16,17)}\) Bering experimented on various grounds to why hydrocephalus develops.\(^{(18,19)}\) Additional information on turnover was provided by Sahar,\(^{(20)}\) who also looked into the significance of pressure to ventricular size and CSF production in cooperation with Hochwald.\(^{(21-23)}\) Several studies comprehending both the production and clearance of CSF were provided in the beginning of the seventies by Lorenzo,\(^{(24)}\) Cutler,\(^{(25)}\) and Davson.\(^{(26,27)}\) Finally, ways of manipulating the CSF system were described\(^{(28-32)}\) together with the hydrodynamic equations determining its behaviour during different circumstances.\(^{(33)}\)

During the last thirty years, the development of the research of hydrocephalus and intracranial CSF hydrodynamics has both deepened and widened. The differences between the subtypes of the disease have been outlined, and their different pathophysiology explored. The initial expectations attributed to the cure of hydrocephalus, i.e. the introduction of a shunt – basically a plastic tube from the beginning,\(^{(34,35)}\) was unfortunately not fulfilled as it was realised that all patients were not improved by the device. Consequently, finding appropriate patients for shunting has become a significant part of the research apart from understanding the pathophysiology.

Various methods to assess CSF hydrodynamics have been developed,\(^{(36)}\) where focus especially has been on outflow resistance,\(^{(37-40)}\) but in recent years, compliance and
the significance of pulse pressure have received more attention.\(^{(41-46)}\) Other hydrodynamic features have been targeted as well.\(^{(47)}\)

MRI and computer tomography have greatly contributed to the knowledge of hydrocephalus, including assessment of white matter lesions\(^{(48,49)}\) and CSF hydrodynamics.\(^{(50-52)}\) Also, MRI has contributed regarding animal models and hydrocephalus.\(^{(53,54)}\) Assessment of cerebral blood flow and blood volume using various techniques, especially SPECT, have also been of importance to increase our knowledge on the disease.\(^{(55)}\)

The search for exact methods to select patients for shunt operation is, of course, from a clinical perspective the most imperative. The methods have mostly been associated to assessing parameters believed to be associated to the CSF system,\(^{(56)}\) trying to find correct cut-offs for intervention. However, several neuropsychological test batteries have been tested as well.\(^{(57-61)}\) Lately, small-scale intervention in the form of long-term CSF drainage has been suggested as an accurate, although somewhat complicated, method to find patients suitable for shunting.\(^{(62)}\)

The shunt technique has developed as well. An important improvement was the antisiphon device,\(^{(63)}\) preventing excess drainage in the standing position. Another progress was the introduction of externally adjustable shunts using magnetism.\(^{(64)}\) This shunt can have its opening pressure changed from outside by applying a magnetic device. As facilitating and convenient the arrangement is for both patients and doctors, just as devastating is it for the application of advanced MRI techniques on shunted hydrocephalus patients.
Intracranial anatomical relationships

Meninges, subdural and subarchnoidal space, and dural venous sinuses

Three coverings, or meninges, are separating the surface of the brain from the cranial bones. These are, from inside and out, the pia mater, the arachnoid and the dura mater. The space between the pia mater and the arachnoid is designated the SAS, and it is filled with CSF. The thin pia mater is intimately attached to the winding surface of the brain, whereas the arachnoid bridges over the irregularities. In the SAS, the cerebral blood vessels and the cranial nerves lie. Fine connective tissue strands, trabeculae, connect the pia mater with the arachnoid.

Outside the arachnoid, and attached to the cranial bone, the dura mater lies. The space between these meninges is called the subdural space. This meninge is not as compliant as the other two. Two large dura sheets fold inwards and divide the cranial cavity into three compartments: tentorium cerebelli separating cerebrum from cerebellum, dividing the cavity into an infratentorial and supratentorial compartment, whereas falx cerebri further divides the supratentorial compartment into a right and left half.

The dura consists of two layers, and in between these layers the dural venous sinuses are found. These are chiselled cavities along the attachments of the dural folds, and they collect venous blood from the cerebral veins. The most important sinus is the superior sagittal sinus, running along the attachment of the falx cerebri.

In the spinal cord, the organisation of the meningeal layers is somewhat different. The dura mater is not attached to the bone, i.e. the vertebral column. Instead, the spinal dura mater forms a tubular sac that is attached to the bone only at the margin of foramen magnum and ends at the level of the second sacral vertebrae. Consequently, another space arises between the dura and the vertebral column, the extradural space. Here, plexus of veins are dispersed in adipose tissue. The spinal SAS looks similar to its cranial counterpart; however, the subdural space is more or less absent. The spinal SAS widens below the tail of the spinal cord, forming the lumbar cistern, where CSF can be obtained by inserting a needle between the lower lumbar vertebrae.
Arterial supply and venous drainage of the brain and spinal cord

Two pairs of arteries supply the brain: the internal carotids and the vertebrais. The carotid arteries enter the skull through the carotid canals, whereas the vertebrales ascend through the cervical vertebrae and enter the cranial cavity through the foramen magnum. After entrance, the vertebral arteries combine, forming the basilar artery. It gives off branches supplying the cerebellum, the brainstem, and the deep middle and posterior part of the cerebrum. The internal carotids divide into the middle and anterior cerebral arteries, supplying the lateral and medial part of the hemispheres. There are also small arteries connecting the carotid and the vertebral/basilar system, forming the circle of Willis, rendering it possible to redistribute blood in case of obstruction.

Branches from the vertebral arteries supply the rostral part of the spinal cord, whereas the radicular arteries supply the rest. These are smaller segmental branches coming more or less directly from the aorta, entering the spinal canal through the intervertebral foramina.

The venous drainage of the brain is somewhat unconventional. The venous vessels start deep into the parenchyma and gradually combine to form larger cerebral veins on the surface of the brain. They empty into the dural venous sinuses via so-called bridging veins. The sinuses are lined with endothelium, but lack a smooth muscle layer, and can subsequently not change their cross section. No valves are present either.

The majorities of the cerebral veins lie on the convexity of the brain and drain into the superior sagittal sinus (Fig 1 and 2). From there, blood passes several other sinuses on its way down to the final common outflow, the jugular vein, which leaves the cranial cavity through the jugular foramen. Venous blood originating from deep middle parts of the cerebrum drain into inferior sinuses that also finally emanate in the jugular vein. The ventral brain surface drains into basal sinuses that in part drain into venous plexus of the spinal cord; a drainage path shared with the cerebellum. Veins draining the spinal cord are distributed similarly to the spinal arteries.

The ventricular system, the subarachnoid space and CSF

There are two anatomically separated spaces where CSF is to be found: firstly, inside the parenchyma, making up the ventricular system of the brain and the central canal
of the spinal cord and secondly, between the two innermost meningeal layers, in the SAS.

The ventricular system consists of four ventricles and their connections. Two lateral ventricles are situated in the left and right hemispheres of the cerebrum, and they communicate with the third ventricle in the midbrain through the foramina of Monroe. The cerebral aqueduct connects the third and fourth ventricle; the latter laying sandwiched between the brain stem and cerebellum. A narrow caudal continuation forms the central canal. The ventricular system is lined with a thin layer of ependymal cells. In the roof of the ventricles, this layer is thickened and highly vascularised and invaginates into the ventricles. This structure is called the choroid plexus, and it is considered to be the CSF production site. The CSF circulates between the ventricular system and the SAS via the lateral (foramina of Luschka) and median (foramen of Magendie) apertures of the fourth ventricle. Here, CSF can move between the ventricular system and the SAS.

Important features of the SAS are the arachnoid villi. They are numerous at those parts of the arachnoid lying just below the dural sinuses, and they also protrude into the sinuses, forming the recycling station for CSF to the venous system. At the superior sagittal sinus the concentration of villi is so appreciable that visible granulations are formed.

Hence, CSF net flow is directed from the production sites in the roof of the ventricles, via the foramina of Monroe, cerebral aqueduct and apertures of the fourth ventricle, towards the SAS and its associated arachnoid villi where CSF is reabsorbed to the blood circulation. However, the real fluid motion is pulsating due to the perpetual pressure variations caused by the heartbeat and respiration, and also other non-continuous events such as talking, coughing and sneezing.

Intracranial physiology and haemodynamics

The CSF

CSF is a clear and colourless liquid. Compared to plasma, the concentration of potassium and glucose is lower, sodium is about equal, and chloride is higher. CSF also contains metabolites produced in the brain, indicating that in addition to supporting and protecting the brain, the liquid serves the purpose to clear the brain
from metabolic debris. The total CSF volume in human is suggested to vary between 125 and 170 ml, but even vaster intervals are have been purported.

**CSF production and outflow**

The bulk production of CSF takes place in the choroid plexus of the lateral ventricles, but other sites are involved as well. The exact mechanism is not completely understood but the main hypothesis involves initial filtration into the ependymal cells from the capillaries, and thereafter an osmotic pressure, maintained by the active exchange of different ions over the cellular membrane, drives fluid into the ventricles.

The most salient feature when reviewing numbers on CSF production is the variation in units rather than data. Figures translated to a common unit show that 500 ml per 24 hours is a good rule of thumb, but both more and less have been reported. Most importantly, the formation rate of liquor is non-pressure dependent within normal physiological conditions.

CSF is chiefly absorbed into the superior sagittal sinus. Other resorption sites exist as well, although they are not as contributive in comparison. For instance, spinal SAS villi, capillaries in the meninges, and along the exiting cranial and spinal nerves. The ependyma of the ventricles and even the choroid plexus have also been suggested as outflow sites. Recent studies have demonstrated that especially spinal resorption seems to be more important than anticipated.

On a microscopic level, the outflow mechanism in the villi is equivocal. Both a closed system, where a membrane separates the CSF and sinus blood, and an open system involving a series of tubules within the villi with free communication in both directions, have been proposed. In addition, a theory suggesting that vacuoles transport CSF in the arachnoid cell has been put forward. A completely different absorption mechanism, where the uptake takes place via the brain extracellular space, has also been proposed, but has yet failed to put the “arachnoid villi-theory” out of the market.

Despite this controversy, the one-way valve characteristic of the outflow mechanism, involving a linear pressure dependent outflow and no inflow, is widely accepted. Normal transvillius pressure is 3-4 mm Hg, and standard values for
outflow resistance are below 10 mm Hg·min/ml.\textsuperscript{(70)} Sometimes, the notion outflow conductance, i.e. the inverse of the resistance, is used when discussing CSF outflow.

The fact that day production is up to five times greater than total CSF volume indicates how sensitive the system is to any impairment of the flow, whether it is increased secretion, obstruction of circulation, or reduced absorption capability. Any influence on these features will have impact on CSF volume, leading to changes in the equilibrium of the system.

**Intracranial pressure-volume relationship and compliance**

ICP is the physiologic final common path for several influences on the brain, and it must be controlled within certain limits for the brain to perform adequately. The dependence of ICP on intracranial volume is a key to understand intracranial physiology.\textsuperscript{(77-86)}

The exact definition of ICP is not as unambiguous as one might think as it can be measured by several methods at several locations.\textsuperscript{(87,88)} Golden standard is considered the ventricular fluid pressure,\textsuperscript{(89)} which can be interpreted as the global ICP provided that all relevant gradients between tissue and liquor, and different compartments, have smoothly levelled out. This presupposes an unimpaired connection between the cranial and spinal SAS as well.\textsuperscript{(73)} This view seems reasonable from a physical point of view, especially during conventional circumstances, but the theory is challenged when various intracranial conditions come into play, for instance a tumour or a haematoma.\textsuperscript{(90)}

As a matter of fact, but for sound reasons, the global ICP theory has not been put to the test in healthy humans, in particular not when it comes to measuring intraparenchymal ICP via lumbar space.

ICP in healthy people varies between individuals. In a horizontal position, levels from zero to 20 mm Hg are referred to, and short-term ICP variations are well tolerated due to compensatory mechanisms. Prolonged raised ICP above acceptable limits might lead to dangerous and possible life-threatening situations.\textsuperscript{(65,67,68,72,91)}

The axiom on intracranial pressure-volume relations is the *Monroe-Kellie doctrine*.\textsuperscript{(67,68,70,73,74,92)} It states that the cranial bone is entirely rigid without any capability of distension, and subsequently the total cranial volume always remains constant. Hence, the volume of one entity in the cranial cavity can only change provided the other contents change to the same extent. The contents in this context are brain
tissue, blood volume, and CSF. Total intracranial volume varies from 1600 to 1900 ml and the approximate distribution between tissue, blood and CSF is 6:1:1.\(^{(65,71,73)}\) This fundamental doctrine – stipulating that intracranial volume is constant – is actually in complete contradiction to the widely used concept of "intracranial pressure-volume dependence".\(^{(77,79,80,82,93,94)}\) What is actually meant by the pressure-volume relationship is that ICP depends on those volumes in the skull that can redistribute outside the cranial cavity, i.e. CSF and blood.

The everyday – or more accurately every second – application of the doctrine occurs when the heart delivers fresh, oxygenated blood in a pulsatory manner to the brain. When the blood bolus reaches the cerebral arteries in the SAS, CSF is pushed aside, diverting liquor out of the cranial cavity into the spinal lumbar sac. At the same time, CSF compresses the cerebral veins, pushing venous blood into the dural sinuses. However, this redistribution procedure takes some time and before equilibrium is restored, there is a short moment of increased ICP. This pressure rise is often designated the pulse pressure, or pulse wave, amplitude,\(^{(92,94)}\) and its size depends on intracranial and spinal compliance,\(^{(85)}\) also referred to by its inverse, elastance. Compliance, in turn, depends on the tone of the cerebral vascular vessels\(^{(85)}\) and the stretchability of the lumbar sac. Thus, the higher the intracranial tension, the higher the pulse pressure required making room for the incoming blood entity.\(^{(95)}\) The proportion between these two ways to handle excess intracranial volumes varies,\(^{(79)}\) and probably depends on current ICP. For instance, higher ICP increases venous outflow resistance by compressing the bridging veins, raising the price on blood redistribution.\(^{(96)}\) When the entire blood bolus has passed the cerebral vascular system, room is made for the CSF to return from the spinal to the cranial space, and equilibrium is restored. A simplified model of the interaction between the intracranial blood and CSF compartments is shown in Fig. 1.
Figure 1
Simplified model illustrating the interaction between CBF, CBV, and CSF circulation. Note that the option of artificially infusing/withdrawning CSF to/from the CSF compartment also is included.

Due to the fast course of events of the pulse flow, it is assumed that the CSF outflow mechanism has no time to kick in and assist in the accommodation process of the incoming blood volume. However, this changes during artificial large volume injections, or continuous infusion, of CSF into the CSF system; a procedure applied when measuring certain parameters of the CSF system. Physiologically, the outflow mechanism obviously comes into play during CSF clearance, but it is also engaged during slow blood volume oscillations.

ICP is commonly claimed to increase exponentially with volume. This assertion is in a sense true, but does not entirely capture the complexity of the issue. For a start – and as have been stated earlier – intracranial volume is constant and pressure rises are related to the state of the intracranial and spinal compensatory mechanisms available. Also, it is argued that ICP increases exponentially with CSF volume. However, this is still not entirely on the money, as the precise volume of the CSF system at a certain time is difficult to determine. What we do know on the other hand is that provided the volume injection is given fast enough, as explained earlier, CSF outflow has no time to occur, and the pressure rise strictly depends on the compliance available and the inserted volume. This relation is essentially linear; however, as compliance is a function of pressure, differentiating and integrating...
this equation yields an exponential relation between pressure and the injected volume.\(^{(92)}\) Thus, after pruning the initial statement on intracranial pressure-volume relations, we end up with an exponential relation between pressure and CSF volume increase determined solely by intracranial and spinal compliance, provided CSF no outflow occurs.\(^{(92)}\)

Looking into CBV oscillations, the same principles apply: the pressure response to short-term pulsations is shaped by the available compliance only.\(^{(98,99)}\) However, as the introduced volumes in these cases are unknown, it is difficult to verify de facto that the compliance is “the same” as when corresponding CSF volumes are injected. Yet, the pressure response to blood pulsations does provide vital information on intracranial environment as it reflects the physiological load on the brain in each heartbeat. The load is the product of compliance and injected volume and subsequently represents the stress subjected to the brain every time a blood bolus reaches intracranial space. Scaling the load with pressure, a pressure-independent load parameter arises.\(^{(100)}\) This parameter is an individual characteristic of the interaction between CBF dynamics and intracranial-spinal compliance, and its consistency over large pressure ranges reflects the continuous efforts of the body to keep CBF constant.\(^{(85)}\) If this parameter is zero or negative at high pressures, it would indicate that blood flow autoregulation is exhausted, implying that further pressure rise will impede CBF.\(^{(95)}\)

**Quantification of outflow resistance, CSF production and compliance**

Measurement of outflow resistance is based on the well-founded assumption of a linear dependence of outflow on pressure, and there are several approaches at hand. However, all methods are infusion tests, meaning that they are all based on infusion of mock CSF via a syringe into the CSF system.

The constant infusion method is based on finding the equilibrium pressure, i.e. the pressure where a certain constant infusion rate is balanced by an equal outflow.\(^{(28,36,101-103)}\) The outflow resistance is calculated as the ratio between the pressure increase at flow equilibrium and the infusion rate. In contrast, the constant pressure method measures the required inflow to keep pressure constant at several pre-set levels.\(^{(29,30,63)}\) The slope of the regression line between inflow and pressure determines the outflow resistance. A third method includes bolus injections into the
CSF system, assessing the time until pressure returns to equilibrium.\textsuperscript{(33,62,104,105)} This relaxation time depends both on outflow resistance and compliance.

CSF production can be determined by withdrawing CSF from the CSF system, lowering ICP below the dural venous pressure, assuring that no outflow occurs. The removed CSF then corresponds to the production. CSF production has also been assessed using MRI flow sequencing of the cerebral aqueduct.\textsuperscript{(106,107)} However, the use of CSF production as a diagnostic tool remains undetermined and therefore not much attention is paid to this aspect of CSF hydrodynamics.

The VPR\textsuperscript{(108-111)} was initially described as a method to assess compliance, measuring the pressure response to a rapid addition or removal of small volumes of saline. However, that procedure was disadvantageous, because of the non-linear pressure-volume relationship. Conversely, PVI\textsuperscript{(79)} is a non-pressure dependent index that is derived from transforming the exponential pressure-volume curve to a semilogarithmic linear relation. PVI is defined as the slope of the linear relationship. Normally, 5 – 10 ml of saline are added within 2 – 10 s to determine PVI,\textsuperscript{(36)} and standard PVI values are 25 ml (the volume required to tenfold the pressure) or above in adults, when fast bolus methods are applied.\textsuperscript{(33,104)} Using slower infusion methods yields different values.\textsuperscript{(36)}

Determination of the aforementioned pressure-independent load parameter\textsuperscript{(98)} – reflecting individual stress on the brain from the incoming blood boluses – requires access to the pressure amplitude over a vast pressure interval. Suggestively, this is sampled during the relaxation phase of an infusion test, i.e. the phase when infusion is halted at the maximum pressure level and the pressure returns to its resting value.

**Cerebral blood flow, cerebral blood volume, autoregulation, and ICP**

CBF amounts to 750 – 1000 ml per minute, and the carotid system provides the bulk.\textsuperscript{(112)} CBV ranges from 60 to 200 ml, where two thirds are accommodated in the veins and the rest on the arterial side.\textsuperscript{(73)}

To optimise CBF over time and space, it must continuously be monitored. Increased activity in a certain part of the brain immediately results in raised perfusion to meet the new metabolic demands. Different tissues also have different needs, reflected in grey matter having greater flow per unit mass than white matter (75-80 ml/100 g/minute in grey matter, whereas white matter suffices with one third of that). The
The purpose of the autoregulation is to guarantee that blood flow through the brain always is adapted to its demands.\(^\text{(73)}\)

Flow magnitude is determined by the ratio of cerebral perfusion pressure and vascular resistance. Cerebral perfusion pressure is approximately the difference between the systemic arterial pressure and the outflow pressure in the large veins, which basically equals ICP.\(^\text{(97)}\) The autoregulation of the intracranial vessels ensures a stable CBF over a wide range of cerebral perfusion pressure and outside this range flow becomes passively dependent on cerebral perfusion pressure.\(^\text{(73)}\) Sufficient flow is sustained by regulating the cross-section of the brain arterioles, and the stimuli causing constriction or relaxation are of two major types: changes in pressure, and changes in the concentration of gases and ions.\(^\text{(65)}\)

The arterioles of the brain react promptly to changes in blood pressure. A lowering causes dilation whereas a rise causes constriction. Thus, CBF is kept constant over a wide range of mean arterial pressures, from 60 up to 150 mm Hg. Above and below these limits, blood flow to the brain becomes a linear function of blood pressure.\(^\text{(112)}\)

Carbon dioxide and oxygen also greatly influence the flux of blood through the brain. A rise in carbon dioxide causes a swift dilation of the cerebral arteries with a subsequent increase in flow. The direct effect on the arterioles is believed to be regulated by the pH-value, and, as hydrogen ions are a by-product from the metabolism of the neurons, increased neuronal activity generates increased flow, maintaining neuronal efficiency.\(^\text{(65)}\) The brain utilizes an almost constant amount of oxygen over time.\(^\text{(65)}\) If any insufficiency arises, the lowered concentration in arterial oxygen causes a vasodilatation of the vessels, but the effect is less pronounced compared to carbon dioxide.\(^\text{(112)}\) The effect of oxygen on the cerebral vessels is much the same as it is on vessels in other parts of the body.\(^\text{(65)}\)

The relation between the vascular components and ICP is not entirely understood. Mathematical models\(^\text{(113-115)}\) have contributed to the apprehension of this very complex interaction, but quite a few issues still remain unclear.

The underlying question is that of cause and effect. For instance, CBV is determined by CBF, the size of the cerebral vascular system and by the resistance to venous outflow. Thus, increasing CBF yields larger CBV, which certainly affects both ICP and CSF volume, but on the other hand the opposite is true as well, as increased ICP will
render in efforts to push cerebral venous blood out from brain, of which success depends on the venous outflow resistance. The ultimate purpose of these complicated physiological feedback mechanisms are of course to preserve adequate CBF.\textsuperscript{(73)}

Subdivision of ICP into a vascular and a CSF component has been proposed as a way of describing these interactions and has been evaluated in head injury. One third of the ICP rise was then attributed to CSF and the remainder to the vascular side.\textsuperscript{(116)} Nevertheless, intracranial hypertension results from the interaction of many factors, and further research to identify these factors and their mutual dependence is vital for a deeper understanding of the issue.\textsuperscript{(73)} The reasoning considering subdivision of the origin of ICP is similar to the aforementioned approach regarding compliance.

\textit{Hydrocephalus}

\textbf{Classification}

During the twentieth century, the classification of hydrocephalus evolved parallel to the increased understanding of the disease. If necessary, the resolution of the subdivisions can be quite high, much thanks to modern imaging technique.\textsuperscript{(117)} In most cases, however, it is sufficient to divide the disorder in two basic categories: \textit{non-communicating} and \textit{communicating}. The former designation describes a rather straightforward, but possibly life threatening, condition, where the interference lies within the ventricular system, for example a tumour compressing the cerebral aqueduct. The latter refers to circumstances where the communication between the ventricles and the SAS is still intact, implying a less obvious cause of the condition.\textsuperscript{(72)}

\textbf{Normal pressure hydrocephalus}

In 1965, Adams reported on a special clinical example of communicating hydrocephalus in elderly.\textsuperscript{(118)} The patients had severely widened ventricles, with Evans index\textsuperscript{(119)} far exceeding normal limits. However, there was no significant raise in ICP, which singled out this state of hydrocephalus from others. Those affected carried gait impairment as the most apparent clinical feature. Also, the state was not acute, but insidious. It was hypothesized that the disorder was caused by malabsorption of CSF in the arachnoidal villi.

Later, it was discovered that NPH could be further subdivided based on the aetiology of the disease. One form is apparently associated to prior intracranial complaints, such as meningitis or traumatic brain injury.\textsuperscript{(70)} This type is commonly designated
secondary NPH. In the other kind, however, no such associative event can be identified and the aetiology remains unknown. Consequently, the condition is designated idiopathic NPH. INPH patients are generally older than patients suffering from the secondary type.\(^{(120)}\) The idiopathic group accounts for between one and two thirds of all NPH cases.\(^{(70,72)}\) Unfortunately, the groups are not always kept apart when reporting studies on the disease, a fact that must be kept in mind when dealing with clinical and other data. Still, many of the clinical features are the same, but regarding figures on CSF hydrodynamics, MRI and outcome after treatment, not to mention epidemiology, it is important not mixing the two categories.

As time went by, it was also discovered that the significance of the “normal pressure” was to a sense exaggerated, and other names for the condition evolved. Examples are adult hydrocephalus syndrome (AHS),\(^{(68)}\) adult chronic hydrocephalus,\(^{(121)}\) and arrested hydrocephalus.\(^{(122)}\) However, none of them has so far put the initial designation out of the market.

*Idiopathic normal pressure hydrocephalus*

**Epidemiology**

The epidemiology of INPH is not well known due to inconsistent criteria over time and mixed up figures with the secondary form of the disease. It is appreciated that up to 5% of all cases of dementia are attributed NPH regardless of subdivision, and it is mostly contracted by people in their sixth or seventh decade.\(^{(120)}\) Men and women are equally affected.\(^{(72)}\) In Sweden, between three and six shunt operations in adults per 100 000 people are performed every year and 30% of these relates to INPH.\(^{(123)}\) In a recent study targeting assisted-care and assisted-living facilities, 9-14% of 147 patients were assessed to suffer from INPH depending on criteria.\(^{(124)}\)

**Clinical symptoms**

The symptoms following INPH are a typical triad: imbalance and/or gait disturbance, mental impairment and urinary incontinence, but all of them are not necessarily present.\(^{(120,125,126)}\) However, gait or balance impairment is often considered a compulsory sign for taking the INPH diagnosis into account, and it is often the debut symptom.\(^{(127)}\) The gait of INPH patients is described as hypokinetic-rigid,\(^{(128)}\) but it is sometimes referred to as a frontal gait.\(^{(129)}\) It bears resemblance to other subcortical conditions like PD and Binzwhangers disease.\(^{(130,131)}\) Cognitive decline is commonly
associated to memory to begin with, but the dysfunction may later become more widespread, affecting other cognitive functionalities as well. Another common complaint from the patients is on tiredness and sometimes disturbed sleeping rhythm. Incontinence is often the last debuting symptom, and its severity can vary from occasional urgency to complete loss of bladder control.

**Pathophysiology**

The pathophysiology of INPH remains an enigma. However, there is today wide agreement that some kind of subcortical chronic ischaemia is involved with a two-folded background: altered CSF hydrodynamics in combination with cerebral vascular disease. Unfortunately though, what is the chicken and what is the egg of these two is not entirely clear. Furthermore, the details of each entity are not established either. Regarding CSF hydrodynamics, the theory has involved increased resistance to CSF outflow; a hypothesis supported by mere facts. However, this theory is not undisputed, and it has not been explicitly proven. During the first years of the present millennium, several theories on compliance and pulse pressure have come into focus when explaining the malfunctioning CSF hydrodynamics associated with the genesis of the disease. The constant pulsatory pumping on the ventricular walls possibly wear them out, changing the viscoelastic properties of the parenchyma, finally causing ventricular dilation. This course of action has also been indicated in mathematical models. From that perspective, the increased CSF outflow resistance might just be a side effect. Nonetheless, this parameter is of paramount interest as it is the parameter that is decreased in order to cure the disease. Another interesting aspect of outflow resistance is that it is higher in secondary than idiopathic INPH.

Evidence for a vascular component in INPH consists of the white matter lesions commonly encountered on MRI images and evidence of cerebrovascular disease. Mostly, the white matter lesions are periventricular, but they can be found in the deep white matter as well. Also, in some cases they are absent. Yet, exactly what white matter lesions are is still not entirely elucidated, even though they are widely present in patients with Binzwanger’s disease, indicating vascular origin. However, nothing excludes them from being caused by the failing hydrodynamic system itself. CBF, especially in frontal regions, is also reduced in INPH. Similarly, periventricular blood flow in white matter is impaired and so is
energy metabolism. More interesting though, periventricular blood flow and metabolism alter when the CSF system is subjected to CSF volume alterations.

Other theories are speculated upon as well: a congenital hydrocephalus associated to enlarged head circumference, mechanical compression of the brain by the ventricles, ventricular reflux and periventricular CSF absorption, reduced CSF turnover impairing clearance of toxic debris, and increased pulse pressure amplitudes hammering the periventricular region. A spinal aetiology has also been proposed.

**Diagnostic tests**

The diagnostic tests have two purposes: to confirm the suspected diagnosis and investigate if the patient would benefit from treatment. Unfortunately, the conclusions from the investigations are sometimes intermingled, meaning that test results indicating good outcome after intervention are at the same time taken as pretext for the diagnosis or vice versa. This should be avoided in order not to compromise data from the different investigations.

The primary purpose of the inclusion tests is to distinguish INPH from important differential diagnoses such as Alzheimer’s disease, Binzwangers disease (SAE) and Parkinson disease. The tests can be subdivided into imaging techniques, clinical tests, hydrodynamic and blood flow tests, and CSF drainage tests.

**Imaging techniques**

**Computed tomography**

This is usually the first step taken when INPH is suspected. The evidence primarily searched for are dilated lateral ventricles, preferably with Evans index exceeding 0.3. Further including findings are an enlarged third ventricle and absence of cortical atrophy. Low attenuation of periventricular areas, indicating white matter lesions, also point in the direction of NPH.

**Magnetic resonance imaging**

MRI is considered the best technique to evaluate presumed INPH. It allows for exact assessment of the extent and severity of white matter lesions, especially by using FLAIR sequences. However, as white matter lesions are present in Binzwangers disease as well, carefulness is necessary regarding any decisive conclusions. Also, the
technique allows for assessment of the volume of the hippocampal body, a structure often atrophied in Alzheimer’s disease. In INPH, the same structure might be shrunk as well due to the dilation of the temporal horns, not atrophy. Of course, cortical atrophy can be estimated as well. In addition, MRI renders it possible to track the flow velocity through the cerebral aqueduct; a parameter usually increased in INPH. It has also been suggested as a selecting parameter for successful shunt operations, but results on this issue are still inconclusive.

The application of MRI on INPH is today rather limited. There are several subtechniques of MRI that are of great interest to look further into the suggested ischemic part of the INPH pathophysiology and possibly also can be used to select patients for shunting. These techniques include fMRI and 1H MRS. fMRI is a high-resolution method taking advantage of the momentary redistribution between oxygenated and deoxygenated haemoglobin occurring in cortical areas during neuronal activation. The locally increased blood flow is likely related to increased energy utilization at the synapses. This physiological entity can be used to visualise areas in the INPH brain that are active during certain stimuli, for instance limb movement, indicating if microlevel blood flow is compromised. 1H MRS can target the ischemia and its possible consequences. It assesses metabolic ratios in the brain, including NAA, lactate and choline. By measuring these entities, the severity of the suggested ischemia can be investigated and also if it has affected the integrity of the neurons.

Clinical tests

Neuropsychological assessment

The Mini mental state estimation is frequently used to scan the mental functions, but it is not exclusive in any way. Other more specific tests are used to track frontal and subcortical functions. The Trail making and Stroop tests are good examples. However, these tests can only provide a crude classification of subcortical and cortical mental deficits, and further differentiation demands additional tests. The tests are also good for follow-up after intervention, or to follow the development in cases where decision on treatment is ambiguous.
Motor function assessment

Targeting gait and imbalance impairment, the primary symptoms of INPH, is probably the most important aspect when it comes to diagnosing INPH, selecting patients for shunt surgery, and performing follow-ups. Some kind of gait or imbalance problems is more or less a prerequisite for the INPH diagnosis to come into play. The tests include assessing walking speed and step frequency over distances like 10 or 25 meters. Additional investigations include video recording, where a more detailed evaluation of the patient’s gait and balance is possible. It involves raising and seating, walking and turning, and various balance tests. Unfortunately, there is still no universal scale to evaluate the video recording, making comparison between studies dubious. Also, the evaluation is subjective, even though excellent inter-agreement between neurologists has been demonstrated.

Another motor function that research has started to target is the hand and finger motor performance. It has been demonstrated that this motor functioning is impaired as well in INPH, and that there might be dysfunctions in sensory feedback in INPH, contributing to the motor deficits. A common test investigating this function is the peg-board test.

CSF hydrodynamics and cerebral blood flow tests

B-wave examination

This examination involves analysis of the presence of slow and rhythmic oscillations in ICP during 24 hours. The waves last for 0.5-2 minutes with amplitude from discernable to 50 mm Hg. The genesis of them is not fully understood, and their relation to other intracranial parameters is not clear. However, there is evidence that they reflect cerebral arterial blood volume oscillations. Also, they are present in healthy people as well. Nevertheless, this examination has been proposed to be a useful method in predicting good outcome after shunt surgery. The interpretation of the waves used to be done visually by a clinician, but modern computer technology and signal analysis have made it possible to objectively estimate the B-wave content in an ICP recording. The investigation also makes it possible to estimate mean ICP, but its value is questionable, as the position of the patient’s head may vary. The investigation is invasive, requiring neurosurgery to insert the intraparenchymal ICP probe, followed by 24 h supervision on an intensive care unit.
Infusion tests

Several hydrodynamic parameters can be estimated using this investigation and there are quite a few procedures to assess them, as described earlier. However, the basic principle includes insertion of a needle into the SAS with the purpose of infusing or withdrawing liquid, at the same time monitoring the pressure. Depending on which procedure that is chosen, the investigation time varies from one to several hours.\(^{(36)}\) The patient is lying motionless in the lateral recumbent or supine position during the entire investigation, making the procedure a bit stressful. In addition, the insertion of lumbar needles is painful, further implicating that there are ethical aspects to address as well. Patients sometimes suffer from headache after the investigation and there is also the possibility of an infection or a subdural haematoma even though these risks are minimal. The primary target parameter is CSF outflow resistance,\(^{(178)}\) and the value of this parameter is used both for diagnosis and selection of shunt candidates.\(^{(37,127)}\) Other assessable parameters include CSF opening pressure, compliance, the aforementioned load parameter\(^{(100)}\) and CSF production. From these figures the dural venous pressure can be calculated as well.

Measurement of cerebral blood flow and metabolism

Most measurements of cerebral blood flow on NPH patients have been performed by SPECT, and there are indications that CBF in frontal regions is reduced.\(^{(55)}\) Furthermore, studies of CBF and metabolism with positron emission tomography and microdialysis have revealed decreased CBF and metabolism in periventricular areas.\(^{(152,153)}\) However, the methods have yet to work their way into common clinical use in INPH diagnosing, as the methods are highly complex. Also, results from CBF studies are difficult to interpret since the techniques vary and results are not consistent.\(^{(120)}\) Thus, as of now, they do not provide additional decisive information on either diagnosis or possible success after treatment.

CSF drainage tests

The foundation of these tests is to mimic the cure of INPH, i.e. continuous CSF drainage provided by the insertion of a shunt. Hence, they are not diagnostic methods, but selection methods to pick suitable patients for surgery. The idea is that if patients improve after the test, it seems likely that they would improve after a shunt
operation as well. The clinical features tested are commonly gait and balance, as cognition and incontinence seems to need more time before improvement occurs.\(^{(40)}\)

There are two forms of drainage tests: a short-term and a long-term. The short-term test is commonly called a CSF tap test and involves removal of 50 ml liquor by a lumbar puncture followed by observation of any clinical improvements during the coming hours.\(^{(179)}\) The other test is referred to as continuous external lumbar drainage (ELD) and involves drainage of 100-200 ml CSF on a daily basis for 3-5 days.\(^{(62,180-183)}\) The patient is subjected to insertion of a catheter into lumbar space, and thereafter the patient is drained of a certain amount of CSF every day. When the investigation is finished, the catheter is extirpated. The method is associated to infection risks\(^{(120)}\) and the catheter might cause root pain. Poor flow and “post-lumbar” headache might also throw spanners into the works.

**Treatment**

There is today only one viable option to treat INPH, and that is to provide the patients with a shunt. Improvement after shunting considering gait, mental capacity and continence varies between 50 and 75 % and can in some cases be pronounced.\(^{(184)}\) Still, improvement rates are a function of time and progress is not always persistent.\(^{(185)}\) The operations are not without risks of complications, subdural haematomas (2-17%), infections (3-6%) and seizures (3-11%) serving as examples.\(^{(184)}\) This fact underlines the importance of a careful selection of patients for surgical treatment and close postoperative follow-ups. Also, complications might arise after a seemingly straightforward recovery, for instance due to shunt failure.\(^{(185)}\) Assessment of shunt function a few months after the operation is standard procedure during follow-ups at the Hydrocephalus centre in Umeå, and it is accomplished by again subjecting the patient to an infusion test.\(^{(143)}\)

Apart from searching for the true pathophysiology of INPH, finding the 100% accurate method to select patients for surgery is what science struggles for. None of the investigations accounted for can in a single case predict the effect of treatment. As is the case with diagnosing INPH, several results from different examinations – all pointing in the same direction – preferably ought to be at hand before neurosurgery is recommended. Unfortunately, all tests are not available everywhere, implying that some neurological specialist have to make do without the entire picture when deciding on surgery. There are, however, a few indicators that are found to be of
better prognostic value than others.\textsuperscript{(56,127)}\textsuperscript{(120)} Still, one must be aware that these indicators are perishable, and the incessant flow of new research brings fresh indicators into play, making the previous ones obsolete.

Today, there is great, but not decisive, support for ELD as the most selective method to find patients benefiting from shunt surgery.\textsuperscript{(56)} It has high positive predictive value and good sensitivity. Still, the method demands several days of care at a neurological ward, and it is not without risks for the patient. Second in line is measurement of CSF outflow resistance.\textsuperscript{(37,40,56)} The exact limit of the cut-off resistance is not entirely agreed on, but patients with high resistance certainly stand a very good chance to improve.\textsuperscript{(186)} Unfortunately, the method is not spread over the world, and it demands specific technical equipment, knowledge and staff. Still, the method carries the advantage of providing fairly reliable answers in a relatively short time. The short-time CSF drainage test, i.e. the CSF tap test,\textsuperscript{(179)} also has good positive predictability, but the sensitivity is worse.\textsuperscript{(40,56)} Its advantage is that it can be performed at any centre without any specific preconditions. B-waves have also been claimed to be a good tool to select shunt candidates,\textsuperscript{(120,177)} but results are inconclusive.\textsuperscript{(187)} Also, this method is both complicated and demanding in resources.

Other more general factors that are claimed to predispose good outcome are little, or a short history of, mental impairment and absence of substantial white matter lesions,\textsuperscript{(120)} although the support for the claims on white matter lesions is week.\textsuperscript{(146)} Furthermore, in the case of severe white matter lesions, the diagnosis Binzwangers disease must be considered as well. Moreover, there is support for that patients having the full triad regarding symptoms have less chance of improving from shunting.\textsuperscript{(62)} The age of the patient does not seem to influence outcome.\textsuperscript{(120)}

It must be remembered that all methods are not available everywhere and that different methods are weighted differently depending on the experience of the attending team of neurologists/neurosurgeons. This sometimes makes it difficult to compare and evaluate results on INPH shunt surgery from different centres over the world. Thus, there is great need to incorporate evidence-based medicine into all aspects of INPH research.
INTRODUCTION

The pathophysiology of INPH,\(^{118}\) also designated IAHS,\(^{40}\) is still shrouded in mystery. Nevertheless, it is well known that the condition can be reversed by a shunt operation, making CSF flow out from the cranium, relieving the patients of their symptoms.\(^{185}\) However, the exact events completing this relief is not clear. Several hypotheses have been purported, but so far, none of them has put the other out of the market. One suggested mechanism involves the reversal of a chronic subcortical ischemia,\(^{127}\) transferring the CSF drainage into better working conditions for the brain. The ischemia might be related to cerebrovascular disease\(^{147-149}\); however, its precise connection to the malfunctioning CSF system – as expressed by the finding of modestly raised ICP, increased CSF outflow resistance \(R_{\text{out}}\)\(^{40}\) and presence of abnormal B-wave patterns\(^{188}\) – in terms of cause-and-effect is unclear.\(^{134}\)

Subcortical involvement – possibly in interaction with frontal areas\(^{55}\) – is confirmed by the cardinal symptoms of the condition: imbalance, gait disturbance, incontinence and cognitive decline. Furthermore, periventricular white matter lesions are common,\(^{150}\) and these regions have been demonstrated to show impaired blood flow and energy metabolism.\(^{152,153}\) These regions also react to short-term CSF volume changes,\(^{154,155}\) further supporting the presence of a reversible chronic ischemia in INPH. Still, there is great need for further knowledge on what happens in the INPH brain after long-term drainage, especially regarding the suggested ischemia, but also in terms of how the revival is expressed in the working brain.

Clinical improvement occurs in 70% of INPH patients after shunt surgery\(^{185}\). This demonstrates the difficulties in selecting appropriate patients. Decisions on shunting is based on several investigations,\(^{120}\) including determination of the functionality of the CSF system. This involves assessing hydrodynamic parameters like ICP, \(R_{\text{out}}\) and elastance, but also includes estimation of the presence of slow and rhythmic oscillations in ICP, so called B-waves,\(^{173}\) likely arising from CBV oscillations.\(^{174}\)

\(R_{\text{out}}\) and elastance is assessed by studying the pressure-infusion curve,\(^{28,29,79}\) while other techniques use the pulsating intracranial blood volume to assess how ICP is influenced by the combined effect of elastance and volume change.\(^{86,98}\) To capture the B-wave content, a probe must be surgically inserted in the parenchyma, after which a long-term pressure ICP registration takes place. Today, there are objective
methods to analyse the investigation.\(^{(47)}\) Unfortunately, the interactions between these different entities are still uncovered, as the methods assessing them have not been appropriately compared. In particular, this pertains to the aspect of correct ICP measurement via lumbar space, as this procedure commonly is the basis for calculating the hydrodynamic parameters.\(^{(178)}\)

The lumbar puncture technique was first encountered in 1891,\(^{(189)}\) and as long as the CSF system is fully communicating, it seems likely that the technique accurately assesses ICP.\(^{(190)}\) Consequently, this supposition laid the foundation for the lumbar infusion tests to determine intracranial hydrodynamics.\(^{(28,29)}\) However, ICP is not a straight-forward concept.\(^{(88)}\) Golden standard is ventricular CSF pressure accessed by a ventricular catheter;\(^{(173)}\) today however, the application of brain tissue sensors increases, for instance when measuring intracranial B-waves. This development redefines the ICP standard. Thus, apart from investigating how intracranial B-waves relate to the CSF hydrodynamic parameters, and if the examination could possibly be substituted by a simpler method, it is important to verify that the pressure assessment during the lumbar infusion test de facto measures an ICP similar to the one in brain tissue. I investigate both these aspects in study I and II, measuring and comparing ICP in brain tissue and via lumbar space, determining the relation between the ICP-derived CSF hydrodynamic parameters.

To address what happens in the INPH brain after long-term CSF drainage, I combine, in turn, \(^{1}\)H MRS\(^{(167,168)}\) (Paper 3) and fMRI\(^{(165)}\) (Paper 4) with long-term external lumbar drainage (ELD) – an excellent method to simulate shunting\(^{(56)}\) – to investigate the impact by CSF removal on the subcortical ischemia and cortical activity. I also explore the influence of the suppression on neuronal integrity, and if this effect is relevant for improvement of gait after ELD, providing further insight into understanding what distinguishes responders from non-responders after CSF drainage.\(^{(56,184,191)}\)

\(^1\)H MRS targeted compounds like NAA, choline and lactate, markers for neuronal density, membrane and myelin integrity, and ischemia,\(^{(169)}\) whereas the fMRI experiments targeted motor and cognitive functions: finger tapping (motor function), face-name encoding and retrieval (memory), and the Stroop test (motor reaction time and attention).
AIMS

To establish the absolute and relative relationship between ICP measured in brain tissue and CSF pressure measured via lumbar space.

To determine the effect from the infusion pump and the significance of the level difference between the measurement positions, for the brain tissue ICP – CSF pressure relationship.

To ascertain how intracranial B-wave content in INPH patients is related to $R_{out}$ and RPPC; a parameter derived from the CSF pulse pressure method.

To investigate if the levels of the markers NAA, Cho, and Lac in frontal white matter differ between INPH patients and healthy controls.

To investigate if CSF drainage can revoke the suggested chronic ischemia in INPH patients.

To investigate if INPH patients responding to CSF drainage – defined as improvement in gait – have different marker levels than non-responders.

To determine which brain areas in INPH patients – relevant for the fMRI experiments according to brain activation in healthy controls – show enhanced activation after long-term CSF drainage in conjunction with improved behavioural performance.
METHODS

Clinical material

The clinical material is presented in Table 1. All INPH patients suffered from imbalance and/or gait disturbance, and several of them had memory deficiencies and incontinence as well. Radiological examination showed a communicating hydrocephalus with Evan’s index\(^{119}\) exceeding 0.3 without severe white matter lesions or extensive cortical atrophy.\(^{127}\) Controls outperformed patients on all clinical tests (MMSE\(^{61}\), TMT\(^{57,58}\) and 9-HPT\(^{192}\)). Two patients were unable to perform the fMRI investigation before ELD. Irretrievable fMRI data and patients terminating their ELD explain the drop-off.

Table 1

<table>
<thead>
<tr>
<th>STUDY</th>
<th>ICP comparison, B-waves and CSF hydrodynamics (Study 1 &amp; 2)</th>
<th>(^1)H MRS and fMRI (Study 3 &amp; 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td></td>
</tr>
<tr>
<td>Group size</td>
<td>10</td>
<td>18 (16)**</td>
</tr>
<tr>
<td>Male/Female (%)</td>
<td>80/20</td>
<td>66/33 (69/31)**</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.4</td>
<td>73.7 (73.4)**</td>
</tr>
<tr>
<td>Group size after ELD*</td>
<td></td>
<td>16 (11)**</td>
</tr>
</tbody>
</table>

*Only included as controls in the Stroop test of the fMRI study
**The numbers in the paranthesises refer to the fMRI study
#Pertains only to the patients of the \(^1\)H MRS and fMRI studies

Controls were recruited by advertising in the local newspaper. They were confirmed healthy to participate by a medical examination and questionnaire, and from inspection of the clinical MR images taken in connection with the \(^1\)H MRS/fMRI acquisitions. Written consent was obtained from all participants, controls and patients, and, if necessary, their relatives. The local ethics committee approved the studies. (Paper 3 and 4)
**ICP measurements and the lumbar infusion test**

**Assessment of B-waves**

An intraparenchymal catheter tip sensor was inserted into the brain tissue close to the frontal horn of the right ventricle, after which a 24 h ICP registration commenced. The B-waves were revealed using a computer algorithm for individual wave analysis and the B-wave percentage (B%) was calculated as the accumulated time with intervals defined as B-waves divided by total time.\(^{(47)}\)

**Infusion test set-up and parallel measurement of ICP**

Right after finishing the B-wave examination and with the brain tissue sensor still measuring ICP, two needles were inserted into the lumbar SAS. One needle was used for data acquisition and the other for CSF volume alteration. The CSF pressure was measured via lumbar space by a transducer at the level of the cranial sagittal center, defined as the midpoint between the highest and lowest point of the head in the supine position.\(^{(Paper 1)}\) The vertical separation distance \( (D_{\text{Sep}}) \) between the sampling positions was measured from radiological scans, and translated to its corresponding pressure difference \( (P_{\text{Sep}}) \).\(^{(Paper 1)}\) The set-up of the ICP measurement is shown in Fig. 2.

![Figure 2](image)

The set-up of the ICP measurement\(^{(63)}\) and the internal relationship between the measurement positions. The brain tissue sensor measuring brain tissue ICP \( (\text{ICP}_{BT}) \) had its tip (T) located in the anterior roof of the right ventricle. The lumbar space transducer measuring lumbar space ICP \( (\text{ICP}_{LS}) \) was zeroed at the level of the cranial sagittal center (CSC), defined as the midpoint between the highest (A) and lowest (B) points of the head in the supine position. The vertical separation distance \( (D_{\text{Sep}}) \) between the measurement positions was defined as the vertical distance between point T and CSC. The figure was originally published in Paper 1.
Pressure manipulation and data sampling

Two or three pressure levels above resting pressure were applied to the CSF space (Fig 7), while recording the corresponding rate of artificial CSF inflow. When the last level was finished, the pump was stopped, and ICP returned to its resting value. Before the examination was finished, a CSF drain was performed.\(^\text{(Paper 1)}\)

Comparisons of ICP, determination of R\(_{\text{out}}\) and RPPC

To compare the pressures, the investigation was divided into three stages, Halt, Infusion and Drain, depending on the pump action (Fig. 3). Each stage was then divided into one-minute intervals and for each interval, the mean for brain tissue ICP and lumbar space ICP was calculated (Paper 1).

To determine R\(_{\text{out}}\), the corresponding flows/pressures for each level were plotted, and the slope, equal to the inverse of R\(_{\text{out}}\), was determined by linear regression.

The basic principle of the CSF pulse pressure method is to measure the pulsatory ICP amplitudes at different ICP.\(^\text{98}\) RPPC was defined as the slope of the ICP amplitude – mean plot, and data were sampled during the relaxation phase of the infusion test (Fig. 3).
Figure 3

The pressure manipulation during the lumbar infusion test. On the y-axis, ICP is represented by brain tissue ICP (ICP\textsuperscript{BT}). The curve was divided into three stages: Halt, Infusion and Drain. During Halt the pump was at rest and it included two parts: Halt\textsubscript{1} corresponding to the measurement of resting pressure and Halt\textsubscript{2} to the pressure relaxation from the top level. The Infusion stage was characterized by net CSF inflow raising the pressure and the Drain stage by net outflow lowering it. The relaxation phase – used by the CSF pulse pressure method to determine RPPC – consists of the first 10 minutes of Halt\textsubscript{2}. The figure was originally published in Paper 1.

Statistics regarding the ICP comparison, B-waves, R\textsubscript{out} and RPPC

The indirect lumbar space ICP (ICP\textsubscript{LS}) and the direct brain tissue ICP (ICP\textsubscript{BT}) were compared by paired t-tests and a Bland-Altman plot\textsuperscript{(193)}. In addition, the data were analysed using a general linear model (GLM) (Paper 1):

\[
\text{ICP}_{\text{LS}} - P_{\text{Sep}} = k \cdot \text{ICP}_{\text{BT}} + m_{\text{Pump}} + m_{\text{Patient}} \quad (1)
\]

The left side of the equation represents lumbar space ICP adjusted for the pressure difference due to the vertical separation distance between the measurement positions. Using analysis of variance, we tested if lumbar space ICP:

- linearly co-varied with ICP in brain tissue (k\cdot\text{ICP}_{\text{BT}})
- was influenced by the pump action (m_{\text{Pump}})
- was affected by individual offsets (m_{\text{Patient}}) other than vertical separation distances
B-wave percentage (B%), outflow resistance ($R_{out}$) and RPPC were compared using simple and multiple linear regression. The level of significance was set at 0.05.

**Gait assessment, 1H MRS, fMRI and long-term CSF drainage**

**Long-term external lumbar drainage (ELD) of CSF**

The patients were subjected to a three-day ELD as a supplemental test to predict the benefit of a shunt operation.\(^{(56)}\) Approximately 25 ml CSF, but sometimes less, was drained from the CSF system by an ELD device connected to a catheter inserted into the lumbar space. During the entire investigation, the patients received preventive antibiotics. To investigate if the ELD affected ventricular size, the pre- and post-ELD Evans indices\(^{(119)}\) were compared from the MRI images.\(\text{(Paper 3 and 4)}\)

**Gait assessment and definition of improved gait**

The patients’ gait was evaluated by video recording before and after ELD, and their performances were assessed on a scale developed from the gait and balance scale of Tinetti\(^{(194)}\) in order to suit hydrocephalus patients.\(\text{(Paper 3)}\) The adapted scale ranges from zero to 8 and has excellent interobserver reliability.\(^{(170)}\) The score was based on assessment of step length, steadiness of a 10 m walk, and turning.

To be classified as “improved” following ELD, patients were required to increase their score one point or more. Patients having a full score pre-ELD were evaluated using improvement in gait velocity.\(\text{(Paper 3)}\)

**fMRI protocols**

The *finger tapping* protocol had a 30 s block design, and the performance was evaluated by counting the total number of taps for each hand. The *face-name encoding and retrieval* protocol had a similar design, where the performance was evaluated by determining the number of correctly retrieved names (max = 36).

The *Stroop* test\(^{(60)}\) protocol was event-related, and it included 24 words of each category, neutral, congruent and incongruent. The performance was evaluated regarding both reaction time and attention. Reaction time was defined as the absolute time from when the word appeared until the subject answered. Attention included the number of adequately answered word colors (max = 24 in each category), and the difference in reaction time between incongruent and congruent word responses.\(\text{(Paper 4)}\)
Statistical comparisons on behavioural data were made using non-parametric Mann-Whitney and Wilcoxon signed ranks tests. The statistical significance level was set at 0.05.

MRI, ¹H MRS and fMRI image acquisition

The scanning was conducted on a Philips Intera 1.5 T whole body MR scanner. The MRI protocol included, apart from the ¹H MRS and fMRI sequences, clinical T₁ and T₂ weighted sequences used for estimating Evans index, and the degree of PWML according to the four-degree scale of Fazeka. After finishing the ELD on the third day, the patients repeated the MRI investigation.

The ¹H MRS protocol included a point resolved spectroscopy (PRESS) sequence with an echo time of 136 ms, chosen with the purpose of detecting the double-inverted lactate signal at this echo time. The volume of interest (VOI) was 30*20*12 mm, equal to 7200 mm³, and positioned in the frontal white matter without extension into the ventricle. The resulting signal from the VOI was exported to a PC and analysed by the Java-based software jMRUI version 2.1.

fMRI data were acquired by sampling the blood oxygen level dependent (BOLD) signal stimulated by a T₂*-weighted, single shot, gradient echo, echo planar imaging (EPI) sequence. The images were converted to analyze format using the software MRIcro.

¹H MRS and fMRI signal analysis

jMRUI analysed the ¹H MRS signal in the time domain and quantified the peak areas from the signals NAA, choline (Cho), lactate (Lac) and creatine (Cr). The following ratios were calculated: NAA/Cr, Cho/Cr and Lac/Cr. The use of creatine as reference is standard procedure. When calculating the NAA/Cr and Cho/Cr ratios for the individual patient, the average value of the pre- and post-ELD ¹H MRS measurements were used as CSF drainage does not alter these markers. (Paper 3)

Correlations and group based differences between clinical variables, video recording scores, ¹H MRS ratios, Evans indices and PWML degrees were investigated using non-parametric statistics. Statistical significance was set at 0.05.
fMRI image analysis was performed in SPM2 implemented in Matlab®, directed by an in-house developed software designated DataZ, and the pre-processing steps included slice timing correction, realignment, unwarping, normalisation to an EPI template, and smoothing.\(^{(201)}\) Single subject statistical contrasts regarding brain activation were set up using the general linear model. For the finger tapping and face-name memory protocols, regressors were modeled as fixed response waveforms, whereas event related regressors were used for the Stroop protocol. Statistical parametric maps (SPMs) were generated using \(t\)-statistics to find areas activated according to the models, and group results were disclosed using random effects analyses. The following regressor contrasts were applied: left/right-hand versus rest, encoding/retrieval versus baseline, the “push time” events for each hand, and incongruent versus congruent items.\(^{(201)}\)

Statistical significance levels were set at \(p = 0.05\) (FDR-corrected\(^{(202)}\)) for within-groups analyses and \(p = 0.005\) (uncorrected) for between-group analyses. Minimum required spatial cluster extent was 20 voxels and relevant regions for improvement in the INPH brain were defined as territories with increasing activation after ELD that overlapped areas activated in controls or were in contiguous proximity to those areas. Co-ordinates were given according to the reference system automated anatomical labelling (aal).\(^{(201)}\)
RESULTS

*Brain tissue and lumbar space ICP, B-waves, Rout and RPPC*

The overall average difference between ICP_{LS} and ICP_{BT} was -0.75 mm Hg (SD = 2.10). The individual average differences were similar, but the standard deviations were smaller. In two patients, the differences exceeded 3 mm Hg. (Paper 1)

The Bland-Altman plot (Fig. 4) looks homogenous without any relevant bias. The span holding 95% of the pressure differences was -5.1 to +2.6 mm Hg, and individual data were collected around the individual averages rather than scattered all over the 95% span.

![Bland-Altman plot](image)

*Bland-Altman plot of pressure difference (y-axis) versus mean, (x-axis). The digits in the plot represent data from that specific patient (1 – 10). The solid line indicates the total average difference, whereas the dotted lines frame the interval holding 95% of the sampled pressure differences. The figure was originally published in Paper 1.*

The coefficient of determination was 0.996 for the GLM and all three included parameters had significant effects on ICP_{LS}. The regression coefficient k was 0.98 [0.97, 0.99] and the pump influence was small in comparison. Accounting for the vertical separation distances generally gave worse agreement (more negative
differences than the measured values) between brain tissue and lumbar space ICP, except for patient no. 9 and 10, where the separation distance perfectly fitted to explain the measured differences.

The relationship between B% and RPPC shows a highly significant correlation (Fig. 5). No other significant correlations were found, and $R_{out}$ did not contribute significantly to explain the B% in addition to RPPC. Nine out of ten patients improved after shunting.

![Plot of B wave presence (B%) versus Relative Pulse Pressure Coefficient (RPPC). The correlation equation reads $B\% = 81 \times R_{PPC} - 0.8$ (R=0.91, p<0.001, N=10). The figure was originally published in Paper 2.](image-url)

**Figure 5**

Plot of B wave presence (B%) versus Relative Pulse Pressure Coefficient (RPPC). The correlation equation reads $B\% = 81 \times R_{PPC} - 0.8$ (R=0.91, p<0.001, N=10). The figure was originally published in Paper 2.
\(^{1}\)H MRS, clinical and gait data, fMRI and behavioural data before and after long-term CSF drainage

Clinical tests, \(^{1}\)H MRS, ELD and drain volume, Evans index and gait improvement

The clinical tests scores did not correlate to \(^{1}\)H MRS ratios and the \(^{1}\)H MRS ratios did not change from CSF drainage.

Sixteen patients were drained of approximately 400 ml, and half of them improved their gait after ELD. No differences in CSF volume and Evans index were observed between the groups, and Evans index did not change significantly after drainage in either group.

Mean NAA/Cr ratio was significantly reduced in INPH patients compared to controls (p= 0.02) and patients improving following ELD had significantly higher NAA/Cr ratios than those who did not (p= 0.01). No significant differences were found for Cho/Cr. In no single case was a lactate signal detected.

NAA/Cr correlated almost to the video recording score post-ELD. There were no other significant relations between PWML, \(^{1}\)H MRS ratios, Evans index, video recording scores and improvement.

fMRI, ELD and drain volume and Evans index

Eleven patients were analysed both before and after ELD; the same eleven patients in all three protocols. Their drain volume was 400 ml. No change in Evans index was observed after ELD.

Behavioural data of the fMRI experiment

Motor functioning: Controls significantly outperformed INPH patients. Significant changes after ELD were observed in right-hand finger tapping (p= 0.02) and for right- and left-hand Stroop reaction times (p= 0.01). There was a tendency for improved left-hand finger tapping (up 21%, p = 0.12).

Cognitive functioning: Controls performed significantly better than patients on all cognitive tests. However, INPH patients did not improve after CSF drainage on these tests, and consequently brain activity for the cognitive measures was not considered.
**Brain activation – motor functioning**

The supplementary motor area (SMA) showed consistent enhanced activation across tasks where patients improved in motor performance after ELD. Additionally, a small cluster of two voxels in left SMA enhanced its post-ELD activation in left-hand finger tapping – where performance had a tendency to improve (p= 0.12). In addition, less consistent condition-specific changes were noted after ELD in parietal and occipetal cortex (two protocols), precuneus (one protocol), cerebellum (one protocol) and the precentral gyrus (one protocol).


**DISCUSSION**

The studies included in this thesis are unique in several perspectives. For a start, this is the first study on man where ICP methodically has been measured in brain tissue and via lumbar space in patients with confirmed communicating CSF systems. (Paper 1) The results confirm the accurateness of the lumbar technique, assuring that the lumbar infusion test indeed measures adequate ICP values, paving the way for correct assessment of the CSF hydrodynamic parameters; a most essential aspect when searching for INPH patients where symptom reversibility after shunting is likely.

Another selection method to find reversible INPH patients is the assessment of intracranial B-waves,\(^{(188,203,204)}\) despite their unknown relation to CSF hydrodynamic parameters like elastance, outflow resistance and RPPC; parameters whose role in intracranial hydrodynamics is well established. The strong connection found between the presence of intracranially measured B-waves and the RPPC measured via lumbar space is a novelty. It indicates not only that the complex and lengthy intracranial B-wave assessment can be replaced by a simple measurement of the CSF pulse pressure during a lumbar infusion test, it also speaks in favour of B-waves primarily reflecting intracranial compliance, not outflow conductance.

Understanding how the malfunctions of the CSF system in INPH patients – definitely including increased CSF outflow resistance,\(^{(40)}\) and possibly changes in elastance and RPPC as well – are transferred to the brain parenchyma and cause underperformance in brain functions is a mystery. However, as this process already has occurred when encountering the patients, focus is on understanding how the process is reversed when draining fluid from the CSF system.

From this perspective, the studies on INPH patients where \(^1\)H MRS and fMRI have been combined with long-term ELD are novel and important approaches regarding INPH pathophysiology. They complement earlier works demonstrating altered subcortical blood flow and energy metabolism after CSF volume alteration,\(^{(154,155)}\) indicating the reversion of a chronic ischemia as the reason for improvement after CSF drainage. However, \(^1\)HMRS could not confirm the presence of such a chronic ischemia, nor could it detect its reduction after drainage. Subsequently, its role in regard to brain tissue revival in INPH patients after CSF removal remains unclear. Nevertheless, there was evidence for pathological effects on neurons in frontal areas.
of INPH patients. This aspect was further underlined by the fact that patients improving their gait were less affected than those not improving.

The fMRI study gave further support for the specific importance of frontal areas\(^{(55)}\) in INPH. The supplementary motor area (SMA) was found to enhance its activity in conjunction with improved motor functioning of the hand. This supports the view of INPH as a hypokinetic condition caused by malfunction in cortico-basal ganglia-thalamo-cortical circuits\(^{(172,205,206)}\), fibres travelling in close relation to the ventricles. This anatomical relationship might explain why motor function seems more likely to initially improve after CSF diversion\(^{(191)}\) and that it commonly is the first symptom to appear.

The enhanced activity in the SMA, indicating revival of the aforementioned functional loop, in combination with the absence of a general chronic ischemia in frontal white matter, could suggest that the indicated periventricular chronic ischemia\(^{(127,152,153)}\) is confined to the ventricular rim. Thus, it might still be the entity that is reversed by drainage. Possibly, other mechanisms are responsible for the general negative effect on neuronal integrity in subcortical white matter.

Combining these facts, an interesting theory would be that the reversal of the neuronal suppression, which still might be caused by a chronic ischemia close to the ventricles, is a necessary, but not sufficient, criterion for the CSF drainage to have effect. For sustained effect, the level of general permanent neuronal damage – possibly caused by other mechanisms than the periventricular chronic ischemia – must not have gone too far. In that case, shunting is futile.

If future studies would support this hypothesis on the course of events occurring in the INPH brain after CSF drainage, the approach on why and when an INPH patient is shunted might need to be revised. Early intervention becomes essential in order to reverse the symptoms, suggesting that when deciding on surgery, different weighing between the present quality of life and the risks of the operation might be needed.

**ICP in brain tissue and measured via lumbar space**

ICP-comparing studies are mostly conducted on animals or trauma patients having spontaneous ICP variations and analysed using simple linear regression. In contrast, we have analysed patients with open CSF systems, lying completely still in a horizontal position on their back, utilising our unique infusion apparatus and
technique for pressure control. It includes frequent and evenly distributed data sampling over a generous pressure and time range, from zero to 50 mm Hg during two hours, consisting of several constant pressure levels of 10 minutes or more. The data were applied to a general linear model, which by design correctly determines the regression coefficient (slope) and provides individual offsets.

**Comparison of the measured ICP values**

The average difference in ICP readings are of no clinical importance and the Bland-Altman plot (Fig. 4) further supports the applicability of the lumbar puncture technique. Similar or worse results are found in many studies of parallel ICP measurement.\(^{207-216}\) The span of the observed 95% pressure difference interval was mainly due to the variation in individual average differences, not individual variations spread all over the span, an observation shared by others.\(^{210,211}\)

**Relative pressure comparison, pump impact and individual offsets**

The slope value of 0.98 assures that intraparenchymal pressure changes are measured just as well via lumbar space. Other parallel ICP measurements show high correlations and for the most part a slope close to unity\(^{207,208,211,213,217-223}\); however, the variation is unexpectedly large.

Level differences between the sites of ICP measurement have earlier been suggested to justify disagreements between ICP readings.\(^{216,218,220,221}\) In the present investigation, the individual offsets were mostly larger than the individual differences, suggesting that accounting for level differences between measurement positions mostly worsens the agreement between the two ICP measurement methods, as outlined in Fig. 6. Still, the offsets are no extremes in comparison.\(^{208,210,211,220,221}\) Therefore, additional explanations must be provided to account for the individual offsets. One possible factor is drift of the brain tissue sensor or lumbar space transducer or both.

The lumbar infusion test was conducted about 24 hours after insertion of the brain tissue sensor. In clinical tests, the 24 hour drift of the brain tissue sensor has been reported to be positive, approximately 1 mm Hg, with single maximum absolute drifts from 1 to 9 mm Hg after up to nine days.\(^{210,213,215,216}\) Long-term drifts must be considered seeing that drift magnitude does not depend on time.\(^{213}\) The lumbar space transducer was referenced to air and calibrated at the start of the infusion test.
For that reason, it should have no drift. Thus, as explained in Fig. 6, the average positive drift of the brain tissue sensor together with a few extreme drift values fit well to explain a major part of the individual offsets, but not all. This observation has been reported by others as well.\(^{(208,210)}\) Accordingly, yet another explanatory factor is needed to make ends meet. A possible candidate is compartment gradients, a physiologic reality that has been suggested before.\(^{(90)}\)

![Figure 6](image)

Illustration explaining the relations between ICP differences, the hydrostatic effect from \(D_{\text{Sep}}\), drifts and compartment gradients. The patient lies supine on the bunk with the nose in the front direction. A) According to this study, the \(\text{ICP}_{\text{BT}}\) measured in the frontal brain tissue is approximately 1 mm Hg above \(\text{ICP}_{\text{LS}}\), i.e. the ventricular pressure, referenced to CSC. B) Adjusting for \(D_{\text{Sep}}\) results in most cases in increased disagreement between the ICP methods. This is manifested by a majority of the individual offsets being larger than the individual measured differences. At the reference level, brain tissue ICP is approximately 2 mm Hg above \(\text{ICP}_{\text{LS}}\). C) The result of subtracting an assumed average 1 mm Hg drift from the ICP measured in brain tissue, still leaves approximately an unexplained difference of 1 mm Hg.
Compartment gradients

In communicating hydrocephalus, the theory of a higher CSF pressure inside the ventricular wall than outside has been disproved.\textsuperscript{(224)} Instead, simulations have suggested a theory including lower ICP in brain tissue than the surrounding CSF.\textsuperscript{(141,142,225)} However, the difference is required to be rather small.\textsuperscript{(140)} Others consider this theory refuted as well.\textsuperscript{(226)} In contrast, this investigation indicates the opposite; ICP in brain tissue might be higher than CSF pressure. Such a gradient would perfectly step in where drift left off explaining the individual offsets, as described in Fig. 6. Whether or not the gradient is associated to INPH remains to explore. However, similar gradients have been suggested to be linked to white matter oedema in humans,\textsuperscript{(209)} a phenomenon related to INPH,\textsuperscript{(227)} but the gradients have also been demonstrated on healthy animals.\textsuperscript{(228)}

Clinical applicability

The core of the lumbar puncture technique to assess ICP is unconditional pressure transmission along the cranio-spinal axis. That has been verified to a satisfying degree. Lumbar CSF pressure measurements were almost of the same quality as absolute ICP measurement in brain tissue and the small differences found were most likely not related to the technique itself. The excellent statistical agreement between the ICP assessment methods compared in our study gives prominence to the Codman Microsensor\textsuperscript{TM} as well.

Complete pressure conveyance, without any pump influence, is the stipulation for correct estimation of baseline ICP, CSF outflow resistance, compliance, and RPPC in hydrocephalus patients when using the lumbar infusion test. All these aspects have been corroborated, further supporting the clinical applicability of the test.\textsuperscript{(229)} Still, the application does not stop here, but pertains to all neurological condition where ICP assessment is needed, provided the CSF systems are fully communicating.

B-waves and CSF hydrodynamics

RPPC, $R_{\text{out}}$, elastance and B-waves

RPPC is not the same as elastance; an aspect that most likely explains why earlier studies have not found correlations between B-waves and elastance.\textsuperscript{(230-232)} Elastance determines the relation between pressure and volume increase,\textsuperscript{(79)} whereas the RPPC is derived from the joint effect of elastance and pulsatory blood volume changes.\textsuperscript{(98)}
Subsequently, it describes the total stress imposed on the brain and CSF system by the pulsating blood flow.

The correlation between B-waves and RPPC was highly significant, and $R_{out}$ did not contribute to explain the variation in B-waves. This supports that the RPPC alone is the parameter most correctly describing the B-wave presence. Still, others have not been able to corroborate this finding; however, this might be due to differences in the methods to assess B-waves.

There was no significant correlation between B-waves and $R_{out}$. In literature, great variation in correlation coefficients between B-waves and $R_{out}$ are found, and the ambiguities might depend on methodological issues concerning measurement of $R_{out}$ and B-waves.

**Why do RPPC correlate to B-waves?**

The coupling between B-waves and RPPC can be explained by incorporating blood volume oscillations to the model of the CSF system, and apply standard current circuit analysis. Pulse waves and B-waves origin from intracranial blood volume oscillations that are imposed on the CSF system. The CSF system can either store these extra volumes or redirect them into the dural venous system; the cause of action depending on the wavelength of the blood oscillation, ICP, elastance and $R_{out}$. By applying common numbers in the context of INPH, it can be demonstrated that it is storage, not absorption, that is the method of choice regarding both pulse waves and B-waves, despite their different wavelength. Thus, B-waves and RPPC seem to reflect the same functionality of the CSF-system.

**B-waves role when selecting INPH patients for shunt surgery**

About 70% of INPH patients improve after shunt surgery. Thus, the 90% improvement rate found in this material speaks in favour of a correct diagnosis. Still, there was no difference in the B-wave presence between improved and non-improved patients. However, the number of patients was small, making conclusions uncertain. The role of B-wave analysis in finding patients improving after shunting is disputed, some considering its usefulness confirmed, while others disagree. This puts B-wave analysis together with several other methods trying to forecast the benefit of a shunt operation in a general case of INPH.
Subcortical ischemia, neuronal integrity, cortical activation, improvement, and long-term CSF drainage

Lactate and the subcortical ischemia

The absent lactate signals indicate that lactate levels in frontal white matter of INPH patients are below 1 mM, corroborating findings in lateral periventricular white matter. Thus, nothing points in the direction of a widespread subcortical chronic ischemia in INPH. Possibly, the lactate levels indicated by microdialysis are confined to the areas closest to the ventricle, just as is the case with the reduced blood flow.

NAA, neuronal integrity and gait improvement

The reduced NAA levels in INPH patients are similar to those found in Alzheimer’s disease. NAA is primarily found in neurons and it is considered to reflect neuronal integrity. Thus, reduced levels suggest neuronal dysfunction, agreeing with observations of axonal degeneration in INPH patients. The higher NAA levels in patients improving their gait further supports this perspective. Similarly, high NAA levels forecast improvement after shunting in secondary NPH. Thus, a reversible neuronal suppression is probably not the only factor impeding INPH brain function; a neuronal deficiency seems to be present as well.

White matter lesions demonstrate low levels of NAA and impeded energy metabolism. However, we did not find a correlation between PWMLs and NAA. Still, PWMLs are less present in lateral periventricular regions; a fact possibly explaining why reduced NAA levels have not been found in those territories.

Cortical activation and improved finger motor functioning

INPH is considered a hypokinetic-rigid or frontal gait disorder – explaining why gait is the motor function most studied – and it carries similarities with subcortical disorders like Parkinson’s and Binzwangers disease. The improved finger motor function shows that gait is not the only motor activity improving after CSF drainage in INPH, corroborating earlier findings.

The finding of increased SMA activity in protocols where finger motor function improved post-drainage back the hypokinetic view of INPH, involving failure in the cortico-basal ganglia-thalamo-cortical circuits, especially frontal
Malfunction in this system has been suggested in Parkinson (256-258) and Binzwanger patients (205,259) as well, further supporting similar pathophysiological target areas, although with completely different backgrounds.

The reversal mechanism in INPH after CSF drainage remains a mystery. Possibly, the recovery is associated with reversing the suggested chronic ischemia (127); however, as the 1H MRS study refutes any widespread subcortical ischemia involving increased lactate levels, this can only apply to pathways running to and from SMA in close proximity to the ventricles. In addition, the ischemia might only involve increased lactate/pyruvate ratios. (260) Still, there might be a completely different and undiscovered mechanism responsible for the recovery. Regardless of which, the revocation renders in normalized SMA signalling, improving the planning process vital for correct motor function.

Enhanced activation after CSF drainage was also found in the precentral gyrus and cerebellum. The observation on the precentral gyrus might be related to improved communication through the corticospinal tract running relatively close to the ventricles. However, it was only observed in one condition, compared to three for SMA, indicating that improvement in finger motor function is primarily related to enhanced activation in SMA. Nothing indicates direct involvement of cerebellum in the pathology of INPH. Probably, it is recovery of suppressed fibres travelling through the periventricular zones – for instance the widely projecting cortico-cerebello-thalamo-cortical pathway (261) – that accounts for the improved activity in cerebellum.

There was enhancement after CSF drainage in parietal cortex in two of the motor protocols, and this region, (262-264) as well as precuneus, (265,266) is important for several indirect sensory aspects regarding movement. Fascinatingly, problems with force scaling has been observed in both INPH (172) and Parkinson patients. (267-269) Hence, the dysfunctional motor planning process in INPH might not be a sole motor problem, but include malfunction in the incorporation of sensory feedback as well; a process requiring intact sensory systems. (270) However, INPH patients do not generally suffer from a malfunctions in the peripheral sensory system. Also, primary sensory input do not terminate in SMA. (256) A probable explanation is that sensory feedback is not properly integrated in the basal ganglia-thalamo-cortical circuit, (268,269,271) projecting
to both frontal and parietal areas.\(^{(26)}\) Also, there might be disturbances in circuits directly connecting parietal cortex and SMA.

**Long-term CSF drainage**

Shunting and long-term CSF drainage are not the same; however, there are similarities regarding improvement in INPH patients,\(^{(56,62,183)}\) and we drained similar volumes to other studies.\(^{(62,180-183)}\) In the \(^1\)H MRS study, the similarities in drain volumes and Evans indices between patients improving and not improving their gait after CSF removal further support the relevance of the groupings’ different NAA levels. Similarly, in the fMRI study, the unchanged Evans index after ELD assures that enhancements after drainage are accurate, and not attributed to anatomical mismatch due to post-ELD reshaping of the brains.
CONCLUSIONS

Changes in brain tissue ICP can be assessed with excellent accurateness by measuring CSF pressure via lumbar space in patients with communicating CSF systems.

The observed absolute pressure difference between ICP measured via lumbar space and in brain tissue is below 1 mm Hg. Variation is due to static pressure differences between the sensors and drift of the sensors; however, the presence of a small compartment gradient is not excluded.

The action from the infusion pump does not impair the accurateness of ICP recording via lumbar space.

The presence of long-term ICP waves, so called B-waves, primarily correlates to the compliance related parameter RPPC of the CSF system, not outflow resistance.

Invasive over-night measurements of ICP B-waves in order to select INPH patients for shunt surgery can possibly be substituted by short-term measurements of RPPC via lumbar space.

Frontal white matter in INPH patients suffers from reduced levels of NAA, indicating neuronal dysfunction.

INPH patients improving after CSF drainage have higher levels of NAA in frontal white matter than non-improving patients, indicating that enough functional neurons are a prerequisite for good outcome after CSF removal.

There are no widely increased levels of lactate in the frontal INPH brain, suggesting that the demonstrated subcortical chronic ischemia of INPH is confined to the ventricular rim. It could not be determined if the CSF drainage reduced the suggested ischemia.

Improvement in motor function after CSF drainage is associated with enhanced activation in the supplementary motor area. This observation is consistent with INPH being a disorder related to suppression of periventricular cortico-basal ganglia-thalamo-cortical pathways with special attention to frontal areas, and that this axonal restrain is caused by a disturbed CSF dynamics that can be restored by CSF removal.
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