The adjustable shunt valve in the treatment of adult hydrocephalus

Effect on complications, intracranial pressure and clinical symptoms

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To my beloved wife Johanna

and to our wonderful sons Valter and Viktor

ABSTRACT

Background: Hydrocephalus causes impaired gait, balance, cognition and continence, all of which can be reversed by shunt treatment. Adjustable valves are commonly used in the shunt treatment of hydrocephalus but randomized controlled trials (RCT) are scarce. The aim of the present thesis was to evaluate adjustable valves in the treatment of hydrocephalus.

Patients and Methods: In Study I, 450 hydrocephalus patients undergoing primary shunt insertion were followed over 10 years to investigate the short-term perioperative risk factors of shunt surgery. In Study II the relationship between intracranial pressure (ICP) and ICP wave amplitude (AMP), valve settings and body positions were studied in 15 hydrocephalus patients. During the shunt operation an intraparenchymatous ICP-sensor was simultaneously inserted and ICP/AMP analyzed with the shunt ligated and when opened at different opening pressures and body positions. A double-centered RCT was conducted in studies III and IV, including 68 patients with iNPH. The patients received a ventricular shunt and were randomized into two groups; in one group (20-4) the valve was initially set to 20 cm H_2O and gradually reduced to 4 cm H_2O over the course of the 6 month study period. In the other group (12), the valve setting was kept at a medium level of 12 cm H_2O during the whole study period. In study III the time to and type of complications and overdrainage symptoms were recorded. In Study IV clinical variables were continuously compared between the two groups.

Results: In total, 538 patients were included and the six month shunt revision rate was 19 %. Fifty-four percent of the patients received adjustable valves. Both adjustable valves and right frontal placement of the shunt were associated with a lower shunt revision rate, but not independently. ICP and AMP decreased significantly when the shunt was opened but the difference in ICP between the highest and lowest valve settings (*in vivo*) was smaller than previous measurements *in vitro*. Gradual reduction of the valve setting from 20 to 4 cm H_2O neither improved clinical outcome nor the complication rate, compared to a fixed valve setting at 12 cm H_2O. The clinical improvement was seen within 3 months postoperatively.

Conclusions: Gradual reduction of the valve setting from a high to a low level neither improved the clinical outcome nor the complication rate, compared to a fixed valve setting at medium level. The pressure window in an adjustable valve is narrower *in vivo* than *in vitro*. ICP in the upright position is significantly different from the supine position. Right frontal shunt placement and the use of adjustable valves were associated with a lower shunt revision rate, but a coincidence of these two variables was found.

Key words: *Hydrocephalus, Shunt surgery, Shunt complications, Intracranial pressure, Pressure hydrocephalus.* ISBN 978-91-637-5698-6.

SAMMANFATTNING PÅ SVENSKA

Hydrocefalus orsakas av en ökad mängd hjärnvätska (likvor), vilket orsakar gång- och balanssvårigheter, kognitiv svikt och urininkontinens. Sjukdomen behandlas med att avleda likvor genom att operera in en shunt, bestående av två slangar sammankopplade med en ventil, placerad strax under huden. Den ena slangen går från hjärnans hålrum till ventilen och den andra går från ventilen till bukhålan. Ventilen är avsedd att reglera dräneringen av likvor, genom ett mekaniskt motstånd, för att förhindra över- och underdränering. Justerbara ventiler möjliggör ändring av ventilmotståndet efter shuntoperationen med hjälp av en magnet som placeras utifrån över huden som täcker shuntventilen. Justerbara shuntar används idag rutinmässigt vid behandling av hydrocefalus men betydelsen har inte utvärderats i randomiserade kliniska prövningar. Syftet med denna avhandling är därför att utvärdera betydelsen av justerbara shuntar vid behandling av hydrocefalus.

I avhandlingen ingår sammanlagt 538 patienter. I den första studien utvärderas perioperativa riskfaktorer vid shuntbehandling av hydrocefalus genom att analysera data i shuntprotokoll som samlats in vid operation av 450 hydrocefaluspatienter under 10 år på neurokirurgen Sahlgrenska universitetssjukhuset. I den andra studien mättes det intrakraniella trycket (ICP) när shunten var stängd och när den öppnades vid olika öppningstryck och kroppslägen. Studien genomfördes i samarbete med Umeå universitet.

I en dubbelblind randomiserad klinisk prövning delades 68 patienter in i två grupper där ventilmotståndet i den ena gruppen gradvis sänktes från en hög till en låg nivå medan ventilmotståndet i den andra gruppen behölls konstant på medelnivå. Shuntkomplikationer (tredje studien) och klinisk effekt (fjärde studien) jämfördes mellan de båda grupperna. Studien genomfördes i samarbete med Oslo universitetssjukhus.

Avhandlingen visar att gradvis sänkning av öppningstrycket från en hög till en låg nivå varken påverkar komplikationsfrekvensen eller den kliniska effekten av shuntbehandling, jämfört med ett fast öppningstryck på medelnivå. Shuntens placering frontalt höger och justerbara ventiler var förknippade med en lägre reoperationsfrekvens, men då en samvariation av dessa variabler påvisades, behövs kontrollerade studier för att undersöka detta mera specifikt. Vid kliniskt bruk påverkas medelvärdet av ICP inte lika uttalat av öppningstrycket som påvisats vid laboratorietest. ICP vid upprätt kroppsläge skiljer sig påtagligt från liggande kroppsläge.

ABBREVIATIONS

AD	Alzheimer's disease
CSF	Cerebrospinal fluid
CT	Computer tomography
DP	Differential pressure
ETV	Endoscopic third ventriculostomy
FDA	Food and drug administration
GF	Gauge factor
ICP	Intracranial pressure
iNPH	Idiopathic normal pressure hydrocephalus
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
NFL	Neurofilament light protein
NPH	Normal pressure hydrocephalus
PET	Positron emission tomography
PL	Performance level
RCT	Randomized controlled trial
SD	Standard deviation
SDH	Subdural hematoma
SDS	Standardized score
sNPH	Secondary normal pressure hydrocephalus
SPECT	Single photon emission computed tomography
SSCD	Somnolence spoor coma disorder
tSDS	Total standardized score
VA	Ventriculoatrial
VP	Ventriculoperitoneal

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I.   Farahmand D, Hilmarsson H, Högfeldt M, Tisell M.
        Perioperative risk factors for short term shunt revisions in adult
        hydrocephalus patients.
        Journal of Neurology, Neurosurgery and Psychiatry, 2009.
        80(11): p. 1248-53.

II.   Farahmand D, Qvarlander S, Malm J, Wikkelsö C, Eklund A,
        Tisell M.
        Intracranial pressure in hydrocephalus: Impact of shunt
        adjustments and body positions.
        Submitted to Journal of Neurology, Neurosurgery and
        Psychiatry, 2014.

III.   Sæhle T, Farahmand D, Tisell M, Eide PK, Wikkelsö C.
        A randomized controlled double-center trial on shunt
        complications in idiopathic Normal Pressure Hydrocephalus
        treated with gradually reduced or "fixed" pressure valve settings.
        In revision, Journal of Neurosurgery, 2014.

IV.   Farahmand D, Sæhle T, Eide PK, Tisell M, Hellström P,
        Wikkelsö C.
        A double-blind randomized trial on the clinical effect of different
        shunt valve settings in idiopathic normal pressure hydrocephalus.
        Submitted to Journal of Neurosurgery, 2014.

CONTENTS

1 INTRODUCTION

1.1 History

The present understanding and treatment of hydrocephalus is based on a long scientific tradition.

In 1669 Nicolaus Steno presented the first truly scientific description of hydrocephalus in his study "On a Calf with Hydrocephalus" [162]. Hippocrates (460-370 B.C.) is usually considered the first to have performed drainage of cerebrospinal fluid (CSF) by puncture of a dilated ventricle through the open fontanel of a child [14]. His work was later quoted by Robert Whytt in 1768 as a proposed treatment by making a perforation in the upper part of the cranium, although it still remains unclear whether the ventricle was punctured or if only the subarachnoid space was drained. Whytt was the first to describe hydrocephalus as a human disease, illustrated by cases of tuberculous meningitis, but he was concerned about the high morbidity and mortality associated with ventricular drainage. The need for a closed CSF drainage system became obvious [60,226].

Improved understanding of the CSF anatomy was achieved by the work of Magendie (1738-1855), who described the outlet of the fourth ventricle [60]. In 1876 the Swedish neuroanatomists Retzius and Key published what was perhaps the most important neuroanatomical work of the nineteenth century, in which they described the correct CSF flow pathway by dye injection techniques [110]. In 1949 Russell published an encyclopedia of hydrocephalus specimens, which contributed to an improved understanding of the disease [190].

During the twentieth century several attempts were made to treat hydrocephalus including CSF drainage by vein grafts from the ventricle to the sagittal sinus (Payr, 1908) as well as from the lumbar subarachnoid space by means of a cannula through a lumbar vertebral body to the peritoneal/retroperitoneal space (Cushing, 1908) [161] and bilateral plexectomy (Dandy, 1918).

Further advances in the treatment of hydrocephalus recognized the necessity of a one-way valve mechanism and the use of synthetic materials in CSF diversion [60]. In 1939 Torkildsen described a surgical procedure for CSF deviation with shunting through a tube from the lateral ventricle to the cisterna magna [216], with an initial perioperative mortality of almost half of

the patients [60]. Various CSF diversion procedures to the ureter, jugular vein, thoracic duct, heart, pleural space, gall bladder, fallopian tube, ileum, and salivary ducts were also attempted [145]. The treatment of obstructive hydrocephalus by third ventriculostomy was first described by Dandy using a subfrontal, and later a subtemporal, approach. Ventriculoscopy was proposed in 1923 and the technique has been further developed during recent decades to improve outcome [58,211].

In 1952 Nulsen and Spitz implanted the first shunt with a ball and spring mechanism to drain CSF from the lateral ventricle to the jugular vein [154], and in 1966 Raimondi and Matsumoto introduced the ventriculo-peritoneal shunt [180]. Pudenz contributed greatly to the technical advances in modern valve technology by producing a one-way slit valve made of silicone [170]. In 1973 Hakim proposed the use of a shunt with an adjustable differential pressure (DP) valve [90].

1.2 The CSF physiology and anatomy

CSF is clear and colorless fluid with a slightly higher density than water [128]. The majority of the CSF (80 %) is thought to be made in the epithelial cells of the choroid plexus by an active transport of sodium, from the blood to the ventricles of the brain, creating an osmotic gradient, which drives the secretion of water into the cerebral ventricles. The remaining CSF is formed by trans-ependymal bulk flow from the brain parenchyma to the ventricles [148,167]. The choroid plexus is located in the bodies and temporal horns of the lateral ventricles, posterior roof of the third ventricle, the inferior medullary velum, and the roof and lateral recesses of the fourth ventricle. The intracranial and spinal CSF compartments are connected from the fourth ventricle to the cisterna magna and the basal cisterns through the foramina of Luschka, and into the central canal through the foramen of Magendie. Figure 1 shows the anatomy of the cerebral ventricles and CSF cisterns.

Figure 1. *Anatomy of the cerebral ventricles and cerebrospinal fluid cisterns illustrated by a mid-sagittal T2 weighted magnetic resonance image of a 90- year-old male included in study II. Anterior is left in the image.*
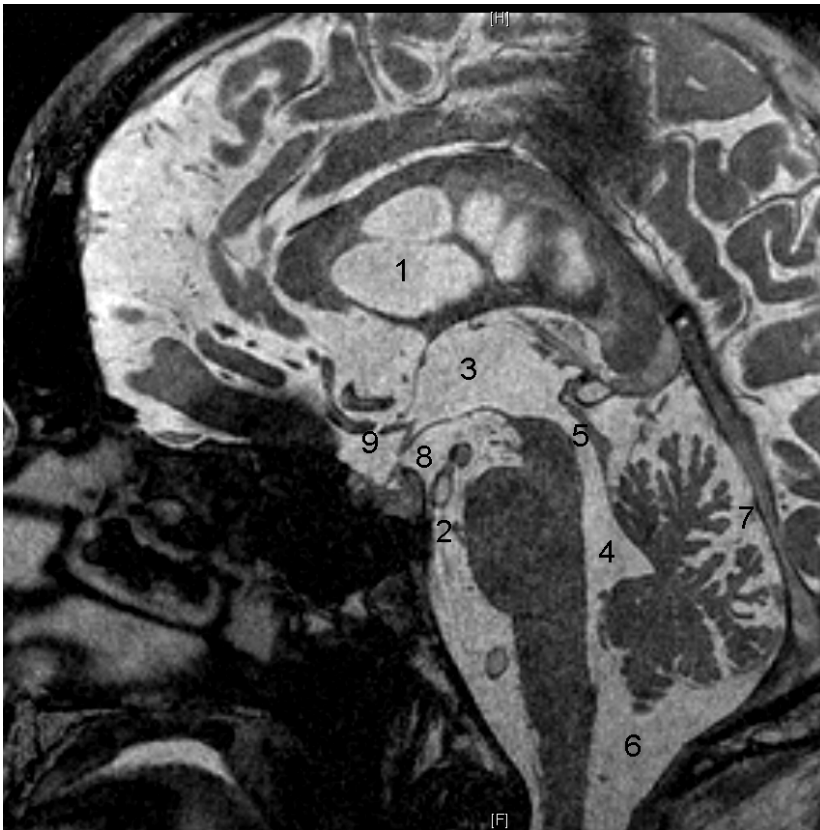
1 = lateral ventricle. 2 = prepontine cistern. 3 = third ventricle. 4 = fourth ventricle. 5 = cerebral aqueduct. 6 = cisterna magna. 7 = cerebellar cistern. 8 = interpeduncular cistern. 9 = chiasmatic cistern.

The CSF glucose level is about half that of blood and the protein content is very low. It has the same osmolality and sodium ion concentration as plasma, while the potassium and calcium ion concentrations are lower and the chloride ion concentration higher than in plasma [188].

The CSF formation rate is 20-40 ml/h [41,42,73,84,144,152,189], normally balanced by CSF absorption through the arachnoid villi and venous blood [53]. Night time production of CSF is approximately double that produced in the day [152]. The mean total intracranial volume of CSF in healthy, elderly individuals is approximately 105-146 ml [13,87], of which 15-77 ml is contained in the ventricles [7].

Aquaporin 1, a water channel highly expressed on the cell plasma membrane of the choroid plexus epithelial cells, is likely to facilitate CSF secretion into the ventricles [16,157,159]. Aquaporin 4 seems to play an important role in the absorption of CSF [27,77], which is believed to occur primarily through arachnoid granulations into the venous sinuses. In addition, other routes of CSF absorption have been suggested, such as perivenular CSF flow into the cervical lymphatics and transependymal flow into the brain parenchyma, have been proposed [64,159,166], as well as a significant spinal CSF absorption [63].

1.3 Hydrocephalus

1.3.1 Definition

Hydrocephalus has been defined as increased production and/or decreased absorption of CSF [132,179]. Based on the resistance levels of the CSF circulation, it has also been defined as an active distension of the ventricular system related to inadequate passage of CSF from its point of production within the ventricular system to its point of absorption into the systemic circulation [185].

1.3.2 Etiology and classification

Adult hydrocephalus is often classified as communicating (80 %) or non-communicating (20 %) [211]. The most common form of communicating hydrocephalus is idipopathic normal pressure hydrocephalus (iNPH). Secondary normal pressure hydrocephalus (sNPH) can be caused by subarachnoid haemorrhage, trauma, congenital factors, cerebral tumors and central nervous system infections [76,107]. Non-communicating hydrocephalus is most commonly caused by aqueductal stenosis due to tumors, cysts, and vascular malformations in the posterior fossa, but can also be congenital or due to infection or trauma.

Dandy classified hydrocephalus as internal where the cerebral ventricles were dilated, and external where the subarachnoid spaces were dilated [49,50,52]. Adult hydrocephalus is mostly internal and associated with an enlarged ventricular system [179].

1.3.3 Epidemiology

The total incidence of surgical treatment for adult hydrocephalus in Sweden has been reported to be 3.4 per 100 000 inhabitants and year [213]. The most common type of adult hydrocephalus is iNPH. Several studies show an

incidence of iNPH between 1.1-5.5 per 100 000 adults [39,112,117,213,223], but exploratory population studies in Norway an Japan indicate a pronounced under treatment of the disease [39,99,207]. There is no sex difference in the incidence of hydrocephalus [186].

1.3.4 Clinical symptoms and pathophysiology

The classical triad of hydrocephalus symptoms includes gait and balance disturbance, cognitive impairment, and urinary incontinence. All three components need not be present for a diagnosis of iNPH [186], although they are found in the majority of patients [113]. Previous studies have revealed similar symptomatology in adult patients with communicating and chronic obstructive (aqueductal stenosis) hydrocephalus [94,130,211,214].

Although early descriptions emphasized cognitive symptoms as the initial clinical manifestation of iNPH, most studies indicate that gait disturbance may be the earliest [78,113,156,186,198]. However, because cognitive symptoms of iNPH can be subtle and may go undetected without formal testing, it has not been determined which symptoms appear first. The characteristic gait disturbance in iNPH is often described as broad-based, short-stepped, magnetic, apractic and hypokinetic [75,186,205]. With disease progression, patients experience difficulties turning in place, requiring multiple steps [186]. Computerized analysis of the gait of iNPH patients revealed reduced walking speed, step height, and impaired counter rotation of the shoulders relative to the pelvis when walking [186]. In addition, slowness of upper and lower extremities is common in hydrocephalus [29,153]. Balance disturbance is a common symptom and can be measured with a force plate [30,43,202].

The focal origin of the gait and balance disturbances in hydrocephalus is not well understood. It has been suggested that the gait disturbance is caused by ventricular enlargement that compresses the upper motor neuron fibers passing through the medial portion of the corona radiata [186], although a study on the neurophysiologic pathway that measured motor evoked responses did not show any involvement of the pyramidal tract [19]. Impaired blood flow to the thalamus, basal ganglia and head of the caudate nucleus has also been mentioned in the pathophysiology of hydrocephalus [158]. The balance disturbance in iNPH is believed to be partly caused by disturbed subjective visual vertical in pitch due to dysfunction of certain visual centers in the brain stem [228].

Most neuropsychological domains can be affected in iNPH [95,147]. The cognitive impairment in hydrocephalus mainly consists of frontal lobe executive functions, such as impairment in tasks that require reasoning, anticipation, goal establishment, strategy formation, and error monitoring [64,102,155]. Impairment of memory and learning is commonly found in hydrocephalus [95,101], as well as constructional apraxia [89]. In addition, psychomotor speed, attention and concentration are impaired [95,101,210]. The Mini-Mental State Examination (MMSE, [79]) score in hydrocephalus patients is often about 25 [95,97,210]. Impaired wakefulness is a common feature and has been referred to as a constituent of a somnolence-sopor-coma disorder (SSCD) [125,129,219]. The focal origin of the SSCD may lie in ascending reticular activation system impairment, involving neuronal circuits from the brain stem to the thalamus or hippocampus [124,219]. The visuospatial impairment can be of occipitotemporal origin and caused by ventricular distension impairing neuronal circuits in this region [210].

Urinary incontinence is the least well explained symptom of hydrocephalus. In the early stages of the disease common symptoms are increased frequency and urgency [186] but with disease progression incontinence becomes worse [11,183,186,198] and can result in a complete loss of urinary control. In rare cases patients may also have fecal incontinence [186]. The pathophysiology of urge incontinence is believed to be myogenic or neurogenic [224], where the latter seems consistent with hydrocephalus. The focal cerebral origins may include the pontine micturition center, the medullary raphe nucleus (serotoninergic neurons), the locus ceruleus (noradrenergic neurons), and the periaqueductal grey [54]. The voluntary control of micturition in humans is believed to be dependent on connections between the frontal cortex and hypothalamus as well as between the brain stem and spinal cord (primarily the sacral parasympathetic nucleus and the sphincter motor nucleus (Onuf's nucleus)) [54,192]. Continence is normally maintained by the detrusor-sphincter reflex but on initiation of micturition, the reflex is inhibited by the brain stem micturition center in pons, facilitating voiding. In hydrocephalus the urinary dysfunction is believed to be primarily associated with frontal executive functions [186,193,195]. The involvement of other cerebral centers in urinary incontinence caused by hydrocephalus is poorly studied.

Clinical symptoms of increased ICP often include headache (worst in the morning), nausea, vomiting, and/or blurred vision. Neuroophtalomologic evaluation often reveals papilledema and/or ocular palsies. A severe increase in ICP leads to altered consciousness. After clinical assessment, further evaluation by means of supplementary tests is often indicated to determine the cause of the symptoms [62]. Increased ICP is often associated with obstructive hydrocephalus and sNPH, while the ICP in iNPH patients is considered to be lower [23].

1.3.5 Neuropathology and CSF biochemistry

Neuropathological studies of humans and animals suggest the presence of periventricular gliosis, axonal stretching, and axonal and secondary myelin damage through a combination of ischemic and mechanical effects [55]. Postmortem human biopsy studies of adult hydrocephalus patients have mainly shown vascular changes and Alzheimer disease (AD) pathology, but no pathological changes specific to idiopathic or secondary hydrocephalus [3,20,57].

Increased levels of neurofilament light protein (NFL) and reduced levels of the Alzheimer-associated form of amyloid b (Ab42) have been found in CSF in iNPH, AD, and Binswanger disease [104,160,172,208,218,220]. The CSF findings in iNPH have been suggested to be a sign of reduced periventricular metabolism, major periventricular degeneration, and absence of major cortical degeneration [104].

1.3.6 Imaging

Pneumoencephalography was introduced by Dandy in 1919 and is performed by replacing CSF by air through lumbar puncture [51]. In 1942 Evans described pneumoencephalography as a tool for the diagnosis of hydrocephalus by measuring the ratio between the air filled space (ventricular size) and the cranial diameter, which was defined as the Evans ratio [74]. An Evans ratio above 0.3 was considered a sign of ventriculomegaly [74].

Radionuclide cisternography for the diagnosis of hydrocephalus was introduced in the 1960s and involves injecting a radionuclide into the lumbar CSF followed by serial imaging of the brain. The major finding consistent with communicating hydrocephalus is early ventricular reflux of the radionuclide, which persists over time [17,93,201,209].

In 1956 Löfgren described the use of cerebral angiography in the diagnosis of hydrocephalus [131]. At that time it was a useful tool for differentiating

between aqueductal stenosis and infratentorial tumor as the cause of obstructive hydrocephalus.

After the introduction of computer tomography (CT) in the diagnosis of hydrocephalus [122] the use of the radiological methods described above decreased, although radionuclide cisternography is still employed in certain cases. While CT remains the first step in the radiological evaluation of hydrocephalus, magnetic resonance imaging (MRI) has several diagnostic advantages compared to CT. MRI can show signs of communicating hydrocephalus as the presence of an aqueductal flow void (a signal artefact) [5,38], decreased callosal angle [103,196] and decreased diameter of the corpus callosum in sagittal views [37]. Both CT and MRI often reveal an increased Evans index (>0.3) and effaced sulci at the high cerebral convexities [186].

Single photon emission computed tomography (SPECT) [86,123,222], positron emission tomography (PET) [115,158], and transcranial doppler ultrasonography [61,181] studies have all demonstrated cerebral blood flow abnormalities in chronic hydrocephalus, but none of these methods are currently used in the routine diagnostic evaluation of hydrocephalus.

1.3.7 CSF dynamics

Historically, the term "normal-pressure" is due to the fact that lumbar puncture opening pressures were not elevated in patients with NPH [2,91]. Although an increased intracranial pressure (ICP) should raise the suspicion of secondary hydrocephalus [140], an increased ICP wave amplitude (AMP) has been described in iNPH [67].

The normal lumbar CSF pressure range has been reported to be 4-14 mm Hg, when measured by lumbar puncture in the supine position [4,31,85,136]. In NPH, lumbar CSF pressures are slightly elevated (4-18 mmHg), but overlaps the range of pressures observed in normal subjects [186]. Lumbar CSF pressure is a good estimate of ICP in the supine position [127], but a slight attenuation in the lumbar AMP has been shown compared to intracranial AMP registration [21].

AMP in iNPH patients is elevated preoperatively and decreases after shunting [45,69,71,173]. ICP monitoring has been supposed to be of predictive value in the diagnosis of NPH [70,177] and for the evaluation of shunt malfunction [90].

Resistance to CSF absorption or outflow (R_{out}) can be determined by a lumbar infusion test. R_{out} is measured as the increase in pressure after infusion of liquid at a certain rate (mmHg/ml/min). It is believed to reflect the CSF absorption capacity and to be increased in hydrocephalus patients before shunting. In the infusion test a lumbar puncture is performed by inserting two needles; one to measure the pressure and the other to infuse or withdraw liquid [8,106,173]. Conductance ($1/R_{out}$) can be determined as the slope of a linear regression of pressure and flow at each pressure level [8-10,72,73]. Although different infusion methods can be used to measure R_{out} and conductance, a good concordance between the three most common infusion methods (constant flow infusion [44,100,109], bolus infusion [142] and constant pressure infusion [9,72,73]) has been demonstrated [206]. High values of R_{out} correlate with good clinical outcome but many shutresponders have normal values, why one should not rely only on R_{out} for selecting shunt patients [12,106,137,229]. It can however be a useful shunt function diagnostic test [139,164].

1.3.8 Treatment

The shunt operation
Shunting of the CSF from the ventricular system to the peritoneum or the right atrium is the primary treatment for hydrocephalic adults with communicating hydrocephalus and might also be secondary treatment for those patients with non-communicating hydrocephalus who do not improve after ETV [211].

A shunt operation is normally carried out when the patient is under general anesthesia and in the supine position. In our institution, a short (about 5 cm) sharp cutaneous incision is performed between the right arcus and the umbilicus, and blunt dissections are made through the subcutaneous tissue, anterior rectus sheath, rectus muscle, posterior rectus sheath, and transverse fascia to open the peritoneum. A tunneling instrument is inserted under the anterior rectus sheath and tunneling performed subcutaneously in the cranial direction, until the level behind the ear, where the tip of the tunneling instrument is extracted through an accessory incision. A small arcuate incision is made parasagittally and in front of the coronal suture on the right side. A small tunneling instrument is inserted from here to the accessory incision. A burr hole is made and the dura mater opened into the subarachnoid space. The pia mater is then opened and a ventricular catheter inserted pointing to the foramen of Monro. The surgical gloves are changed before the shunt is tested to prevent bacterial colonization when handling the shunt. After testing the shunt, the distal end of the abdominal catheter is attached to the tunneling instruments. Pulling out the tunneling instruments

allows the shunt system to be placed subcutaneously. The distal catheter is placed into the abdominal cavity. The wounds are then closed by suturing.

Alternatively, the distal shunt catheter can be inserted into the right atrium of the heart by puncturing the right internal jugular vein, resulting in a ventriculoatrial (VA) shunt.

Shunt insertion can also be carried out by placement of a lumboperitoneal shunt, draining CSF from the lumbar subarachnoid space into the abdominal cavity [28].

Alternative treatments

Endoscopic third ventriculostomy (ETV) is often the primary treatment for obstructive hydrocephalus, however a few studies have shown a beneficial effect for the treatment of communicating hydrocephalus [82,165].

Plexus coagulation is another described treatment but it is more invasive than shunt surgery and when evaluating the patients postoperatively, shunting may still be required [151].

At present there is no approved pharmacologic treatment for hydrocephalus [6,64].

1.3.9 Outcome after shunt surgery

Clinical improvement rates after shunt insertion have been reported to be 50-90 % [105,113,138,143,212,215,230]. In a systematic review study the one-year improvement rate from 1990 to 2012 was about 80 % in comparison with the period 1970 to 1990, when it was around 50 % [215].

Table 1 presents a summary of some of the most commonly used outcome scales. There are, however, several difficulties involved in evaluating outcome after shunt surgery. Firstly, the selection criteria for shunt treatment in hydrocephalus patients differ between studies. Secondly, there is no common outcome scale for postoperative assessment. Furthermore, as complications are relatively common, there is no general consensus about the inclusion of complications in the long-term postoperative outcome assessment. However, a strength is that various outcome scales have demonstrated significant improvement after shunt surgery. In addition, improved self-reported functional and social outcome has been found postoperatively in hydrocephalus patients [40,212].

Table 1. *Outcome scales for adult hydrocephalus. The presence of separate grading scales for each domain is specified.*

Outcome scales for iNPH	Year	Gait/balance domain	Dementia domain	Urgency domain
iNPH scale [98]	2012	yes	yes	yes
iNPH grading scale [118]	2007	yes	yes	yes
NPH grading scale [65]	2006	yes	yes	yes
NPH scale [125]	2004	yes	no	yes
Dutch NPH scale [33]	1997	yes	yes	no
Krauss scale [116]	1996	yes	yes	yes
Kiefer scale [146]	1994	yes	yes	yes
Black scale [25]	1980	no	no	no
Stein & Langfitt Scale [204]	1974	no	no	no
Rankin scale [182]	1957	no	no	no

Long term outcomes (3-5 years) indicated variable improvement rates compared to short-term outcome and a total mortality rate of 27-57% [105,114,138,149,171,178,197].

1.3.10 Complications after shunt surgery

Shunt revisions have been reported in 16-53 % of patients with adult hydrocephalus (Table 2). The main complications are mechanical shunt obstruction, overdrainage and infection. Subdural hematoma (SDH) occurs in up to 28 % of patients after shunt insertion [22,25,36,125,163,194]. The reported shunt infection rate is 3-15 % [18,26,34,59,83,119,125,200]. The location of the ventricular catheter [217], the experience of the surgeon [34,83,200], and previous shunt surgery [169] are variables that have been associated with the risk of shunt malfunction. No randomized controlled trials have assessed the shunt revision rate comparing fixed and adjustable shunt valves [23,231].

Table 2. *Shunt revision rates in adult hydrocephalus patients, as reported in selected previous studies.*

Author	Year	Study design	Number of patients	Shunt revision rate (%)
Present thesis	*2014*	*Prospective*	*527*	*19*
Reddy [184]	2013	Retrospective	710	33
Pujari [171]	2008	Retrospective	55	53
Ringel [187]	2005	Retrospective	407	25
Lam [121]	1997	Retrospective	128	41
Borgbjerg [35]	1995	Retrospective	884	45
Vanneste [223]	1992	Retrospective	166	28
Larsson [125]	1991	Prospective	74	50
Puca [169]	1991	Retrospective	356	29
Benzel [22]	1990	Retrospective	37	16
Greenberg [88]	1977	Retrospective	73	33
Udvarhelyi [221]	1974	Retrospective	55	44

1.4 Intracranial pressure and CSF flow

1.4.1 Pressure and siphoning

Pressure (P) is the force (F) per unit area (A).

$$P = F / A, \text{ where } F = \rho\, g\, V => F = \rho\, g\, h\, A.$$

$$\rho = \text{density}, g = \text{force of gravity}, V = \text{volume}, h = \text{height}$$

$$\text{Thus, } P = \rho\, g\, h\, A / A \implies P = \rho\, g\, h.$$

The pressure of a liquid is directly proportional to its height above the measuring point (Figure 2). In VP-shunt treatment, the vertical height between the proximal point of drainage (the lateral ventricle) and the distal point of drainage (abdomen) determines the amount of CSF siphoning due to gravity.

Figure 2. *The pressure (relative to atmospheric pressure (p = 0 mm Hg)) at the bottom of a vertically oriented container is dependent on the height (h) of the fluid above the measuring point.*
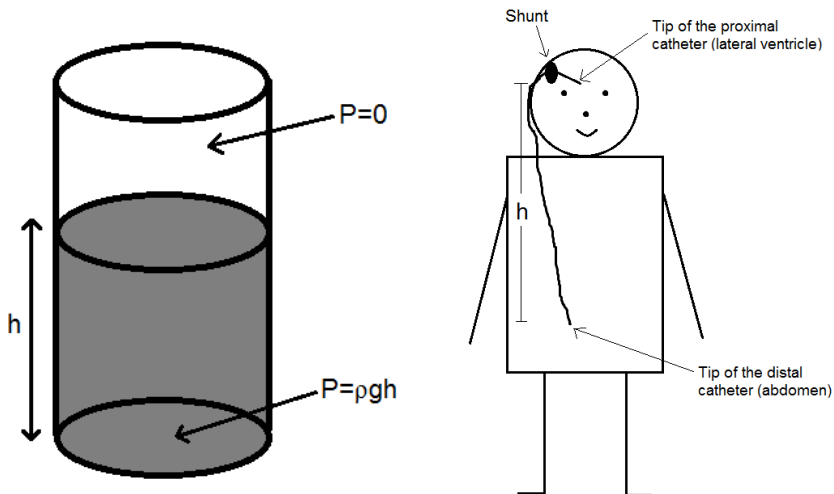
1.4.2 Flow

Flow (Q) is the volume of fluid (V) that passes a point per unit of time (t), $Q = V / t$. Flow can be laminar or turbulent (Figure 3a and 3b). CSF flow in a shunt catheter is probably laminar where, due to friction, the fluid velocity is highest at the center and slower near the edges of the catheter, due to friction. Flow through the narrow orifices of a shunt valve is probably turbulent, causing increased resistance in the shunt system.

Laminar flow is described by Poiseuille's law (Figure 3a). The flow is thus highly dependent on the radius (fourth power) of a catheter. When the radius and viscosity are constant as in a CSF shunt system, the relationship between flow and resistance can be described as

$$Q = \Delta P / l$$

where ΔP is the differential pressure between two compartments and l is the length of the horizontally oriented container. Thus, in a shunt system the horizontal flow is inversely proportional to the length of the catheter.

Figure 3. *Illustration of a) laminar and b) turbulent flow.*

a) Laminar flow, described by Poiseuille's law: $Q = \Delta P \, \pi \, r^4 / (8 \, \eta \, l)$.
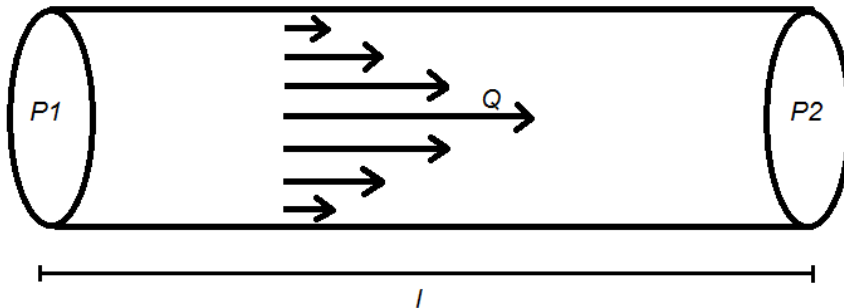

b) Turbulent flow.

1.4.3 Monro- Kellie doctrine

In 1783 Alexander Monro presented his findings that the brain is incompressible, has a rigid encasement and contains a constant blood volume where the volume of the arterial blood supply should be equal to that of the volume of the venous blood drainage. His findings were later supported by George Kellie and together they constitute the Monro-Kellie doctrine, later modified by Harvey Cushing by incorporating the importance of the CSF volume. Cushing therefore refined the Monro-Kellie doctrine (Figure 4) as we know it today, stating that expansion of any one of the intracranial compartments (brain tissue, blood and CSF) causes a rise in ICP if the volume of the other two remains constant. In hydrocephalus an excessive CSF volume exists, often in combination with an enlarged ventricular system [176].

Figure 4. *The relationship between intracranial pressure (ICP) and intracranial volume (brain tissue, blood and cerebrospinal fluid) known as the Monro-Kellie doctrine.*
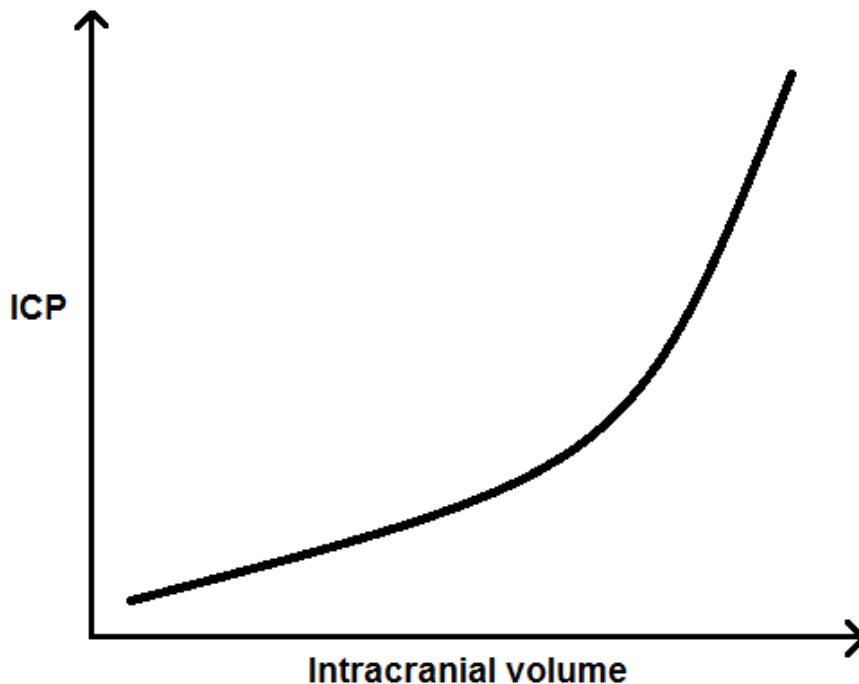
1.5 ICP monitoring techniques

ICP can be measured using various monitoring techniques including external ventricular drainage (EVD) and microtransducers [47,176]. Lumbar puncture pressure is an indirect measurement of ICP. EVD for intraventricular pressure monitoring was first described in the clinical setting by Lundberg in 1960 [134]. It contains an intraventricular catheter connected to an external strain gauge sensor that transmits the fluid pressure at the ventricular catheter tip relative to the level of the sensor. It has the benefit of a lower rate of zero drift [68] but carries a relatively high risk of infection (9 %) [133]. The most common types of microtransducer for ICP monitoring in the clinical context are strain gauge, fiberoptic and pneumatic sensors.

Strain gauge sensors

Strain is defined as deformation of a material due to applied forces that changes the geometry of a material. The generation of an electric charge when a material is subjected to stress causes movement of electrical charges to the surface of the material, known as the piezoelectric effect, originally discovered in quartz by the Curie brothers [108]. The change in electric charge caused by deformation can then be measured (voltage) by electrodes on the surface of the material to estimate the level of the applied pressure. The gauge factor (GF) is specific to each material and determined by the relative change in resistance ($\Delta R/R$) in relation to the relative change in the length of the material after application of strain ($\Delta L/L$) [80]:

$$GF = (\Delta R/R) \ / \ (\Delta L/L)$$

Due to the absence of creep or hysteresis and the superior elastic characteristics of silicone, intracranial pressure sensors are often fabricated by implanting resistors into the silicone to register pressure. The electrical signal is then conducted through a wire to an external device where the analogue to digital conversion (ADC) takes place to display the pressure curve [80].

Strain gauge sensors require calibration with zeroing either before (Codman, Johnson and Johnson Raynham, Massachusetts, USA[®]) or after (Raumedic AG[®], Münchberg, Germany) insertion.

Fiberoptic and pneumatic sensors

The Camino (Camino Laboratories, San Diego, California, USA[®]) system uses a fiberoptic sensor. Fiberoptic devices, such as the Camino ICP Monitor, transmit light via a fiber optic cable towards a displaceable mirror. ICP

changes will move the mirror, and the differences in the intensity of the reflected light are translated to an ICP value [176]. The Spiegelberg® (Spiegelberg GmbH & Co. KG, Hamburg, Germany) system is a pneumatic sensor that uses an air-filled balloon catheter connected to a monitor containing a strain gauge sensor to measure ICP and that continuously performs automatic zeroing in situ. However, it has a low sampling frequency [46,68], making it less favorable for measuring ICP wave amplitudes.

1.6 Shunt valve mechanisms

Most modern shunts include valves designed to drain a controlled amount of CSF and only permit one-directional flow from the CSF compartment to the target point. The three most common shunt valve mechanisms in the treatment of hydrocephalus are DP valves, flow regulated valves, and slit valves. The DP valve has a ball in a cone mechanism where the opening pressure is regulated by the tension of a spring (Figure 5). This valve has only two states; closed and open. It opens when the inlet pressure overcomes the resistance of the spring pressing on the ball to keep the valve closed. Flow regulated valves contain a membrane that regulates CSF flow. Slit valves are closed-end silicon tubes with slits allowing one-way CSF flow. When the pressure in the tube increases, the slits open to drain the CSF.

Figure 5. *Illustration of the basic mechanism of function of a differential pressure adjustable valve. The CSF inlet pressure opens the valve by displacing the ball in the cone permitting CSF outlet. The tension of the flat spring can be adjusted by an external device turning the stepper through magnetic force.*
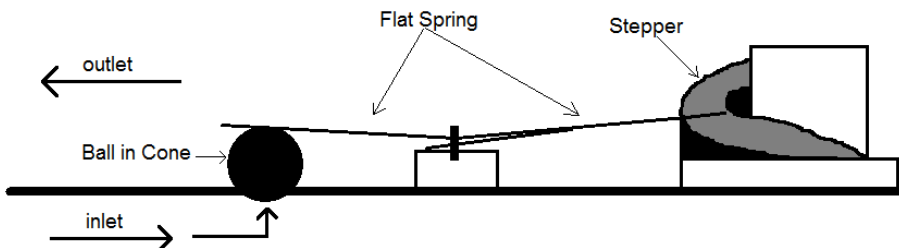
1.6.1 Fixed and Adjustable differential pressure valves

In fixed DP valves the tension of the spring is static while in adjustable valves the spring tension can be changed by means of an external device. Adjustable valves allow postoperative valve setting adjustments to prevent under or overdrainage and improve clinical outcome. The fixed pressure valve was first used clinically in the 1950s while the adjustable valve was introduced by Hakim in 1965 [91]. Commonly used fixed DP valves are the PS Medical Delta® and the Codman Hakim Precision Valve®, while adjustable DP valves include the Codman Hakim Programmable Valve®, the PS Medical Strata®, and the Sophysa Programmable Valve®. If an MRI is performed on patients implanted with any of these adjustable valves implanted, the valve setting must be subsequently checked because the magnetic field can lead to readjustment. Adjustable valves designed to resist resetting when undergoing MRI below three Tesla are under development or have recently been available for clinical use.

Portnoy described the pressure gradient (ΔP) driving CSF through the DP valve as the difference between the sum of ICP and hydrostatic pressure (ρgh) and the sum of valve setting (OP) and distal catheter pressure (DCP) [168]:

$$\Delta P = ICP + \rho gh - OP - DCP$$

where DCP is detemined by the location of the tip of the distal catheter (the intraabdominal pressure for VP shunts and the pressure in the right atrium of the heart for VA shunts).

1.6.2 Flow control valves

Flow-control valves were designed to regulate the CSF flow by means of a three stage mechanism. When the DP is low, as in the supine body position, the valve should act as a low resistance valve. This means that the valve should operate in the same way as a conventional DP valve with a preset opening pressure and remain in this configuration for as long as the CSF flow through the shunt is at the average level (20 ml/h). In stage 2 the valve should act as a flow regulator by increased valve resistance, causing the CSF flow to remain between 20 and 25 ml/h. The valve should function when the DP increases, as in the upright body position. In stage 3 the valve should act as a safety device permitting CSF flow when the DP exceeds 30 mmHg [191].

There are no randomized clinical trials indicating the benefit of DP valves compared to flow-control valves [92,225,231,233].

1.6.3 Siphoning regulatory devices

Different anti-siphoning mechanisms can be used for shunt treatment of hydrocephalus [120]. In the membrane-based siphon regulatory device (included in the Strata® shunt valve) the shunt is closed and remains so at a siphoning distal pressure (e.g. when body position is upright) and opens when proximal pressure rises [81,120].

A different mechanism is used in the Siphonguard® where CSF flow occurs through one of two pathways (high and low resistance). When flow increases (e.g. with siphoning), the low-resistance pathway closes and the high resistance pathway opens, significantly lowering the flow rate [48,120].

In the Miethke ShuntAssistant® the OP of the valve changes depending on its orientation and increases steadily in line with a gradual change of valve alignment from horizontal to vertical orientation [111,120].

2 AIM

The aims of this thesis were:

    I.   To prospectively evaluate perioperative risk factors for revision after shunt implantation in adult hydrocephalus patients.

    II.   To evaluate ICP and ICP wave amplitude at different shunt valve settings and body positions in hydrocephalus patients

    III.   To investigate whether a gradual reduction of the shunt valve setting decreases the complication rate in iNPH patients treated with a VP shunt.

    IV.   To examine the effect of gradually reducing the shunt valve settings on symptoms and signs of iNPH in order to assess the optimal use of adjustable valves.

3 PATIENTS AND METHODS

3.1 Patients

3.1.1 Study design

All four studies in the present thesis were prospective. Study I was an observational single-center (Gothenburg) cohort study; study II was double-center (Gothenburg and Umeå) and single-blinded; studies III and IV were double-center (Gothenburg and Oslo) and double-blinded with randomization by blocks of four.

3.1.2 Study period

	Duration
Study I	1995 (January) – 2004 (December)
Study II	2010 (October) – 2012 (January)
Studies III and IV	2008 (July) – 2011 (July)

3.1.3 Patient inclusion and exclusion criteria

The patients in all four studies were adults (above 16 years) and all but one underwent *de novo* shunt surgery. In study II one patient had previously undergone an ETV for aqueductal stenosis and the postoperative MRI showed signs of an open aqueduct. We included both iNPH and secondary hydrocephalus patients in study I and II but only iNPH patients in study III and IV.

In study I a total of 586 patients undergoing 932 shunt procedures were enrolled consecutively, of whom 450 underwent primary shunt surgery during a ten-year period, were evaluated. In the event of death, the date and cause were obtained from the National Board of Health and Welfare (Socialstyrelsen).

In studies II-IV, all patients presented with symptoms and signs of hydrocephalus and MRI showed communicating ventriculomegaly (Evans index > 0.3).

In study II, twenty patients were enrolled. Exclusion criteria were acute hydrocephalus, trauma or abdominal surgery during the previuos 6 months, inability to walk, and short life expectancy due to serious illness. Five patients were unable to complete the study; two due to technical problems with the ICP catheter, one withdrew from the study, one had a fulminant shunt infection, and one accidentally pulled out the ICP catheter. Complete data were obtained for the remaining fifteen patients.

The total number of patients included in studies III and IV was 68; 46 from Sahlgrenska University Hospital, Gothenburg, Sweden, and 22 from Oslo University Hospital, Oslo, Norway. Inclusion criteria were probable iNPH based on characteristic symptoms and signs, and an open cerebral aqueduct verified by MRI, in accordance with Guideline criteria [141]. Patients included in Oslo also had to present with an abnormal ICP dynamics defined as mean ICP wave amplitude above 4 mmHg and > 5 mmHg for at least 10% of the recording time. Exclusion criteria were inability to walk and short life expectancy due to serious illness.

3.1.4 Ethical aspects

Study I
The data on mortality rate and cause of death were collected by permission of The National Board of Health and Welfare (Sweden).

Study II
The study was approved by the Regional Ethical Review Board in Gothenburg (2010:341-10) and all patients provided written informed consent.

Studies III and IV
The studies were approved by the Regional Ethical Review Board in Gothenburg (Ref 020-07) and the Regional Committee for Medical and Health Research Ethics (Ref S-08007a), and the hospital authority of Oslo University Hospital (Ref 08/1196). All patients provided written informed consent.

3.2 Methods

Study I

Two protocols were designed to record perioperative data during shunt insertion (insertion protocol) and shunt revision (revision protocol), respectively. The protocols were completed during surgery by the scrub nurse and, in the case of missing or unclear data, by the surgeon directly after surgery. All shunts were designated as meeting one of two end points: (1) shunt failure requiring revision within 6 months or (2) no shunt failure within 6 months. Shunt revision within 6 months postoperatively was considered to be related to the shunting procedure. Suspected shunt obstruction was verified by shuntography [227], which revealed obstruction of the injected radionuclide, or a lumbar infusion test indicating a higher R_{out} than expected from the valve [139]. A shunt infection was diagnosed based on the clinical picture, elevated CSF cell count and the presence of a positive CSF culture. The etiologies of the hydrocephalus among the studied patients were obtained from the hydrocephalus database at the Hydrocephalus Research Unit, Institute of Clinical Neuroscience, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden.

Study II

All patients received a Strata® ventriculoperitoneal (VP) shunt and a Raumedic® intraparenchymatous ICP sensor. The shunt was initially ligated distal to the valve with a dura clip. All dura openings were sealed with Tisseel® tissue glue to prevent CSF leakage. The morning after surgery ICP was recorded for 10 minute periods with the patient supine, sitting, and walking with the shunt still ligated. The shunt was thereafter opened by removing the dura clip ligation under local anesthesia. The valve was preset to Strata® valve setting 2.5 and adjusted at 4 hour intervals to 1.5 and 0.5. During the 4 hour intervals the patient moved freely in the ward. The settings are equivalent to an opening pressure of 13.1 mmHg (setting 2.5), 7.7 mmHg (setting 1.5), and 3.4 mmHg (setting 0.5), in accordance with bench testing [135].

After surgery the patients underwent a skull x-ray to correct the measured ICP values with reference to the location of the shunt valve according to the following equation:

$$ICP = ICP_{sensor} + \rho g h_{sensor\text{-}valve}$$

where ρ is the density (constant), and g the gravitational force (constant), and $h_{sensor\text{-}valve}$ is positive when the sensor is above the valve.

After the measurements the ICP sensor was withdrawn and immediately tested for zero-drift by placing it in a dark coated measuring cylinder filled with water at 37.0 °C according to the manufacturers specifications.

The recorded ICP (100 Hz) data were transferred to files, one for each segment, coded and blinded for the analyzes conducted at Umeå University.

Each ICP segment was analyzed for mean ICP and mean AMP. An algorithm was developed in MATLAB for automatic detection of cardiac related pulsations and discarding noise. The ICP curves were visually inspected to obtain an overview. Fast fourier transform analysis of the signal was applied to estimate the cardiac cycle duration of each consecutive 6-second window. If the estimated cardiac cycle duration corresponded to a heart rate above 150 bpm or below 30 bpm, or if the peak was too near the start or end of the pulsation (<0.05 s), the 6 seconds of data were discarded as probable noise. For the remaining pulsations, AMP was calculated as peak ICP minus ICP at the first of the two troughs (filtered ICP) and ICP as the mean of the unfiltered ICP signal. Finally, the mean of all AMP and ICP values in the segment was calculated.

Studies III and IV

All patients were clinically evaluated using four tests preoperatively as well as postoperatively at 1, 2, 3, 4 and 6 months. The valves were adjusted in both groups immediately after each evaluation as can be seen in Figure 6.

Figure 6. *Flow diagram of the randomization and clinical evaluations, overdrainage symptoms and complications during the study. Patients lost to follow-up are presented in the diagram. The stars (*) indicate an event of SDH and the hash marks (#) indicate an event of over drainage symptoms.*
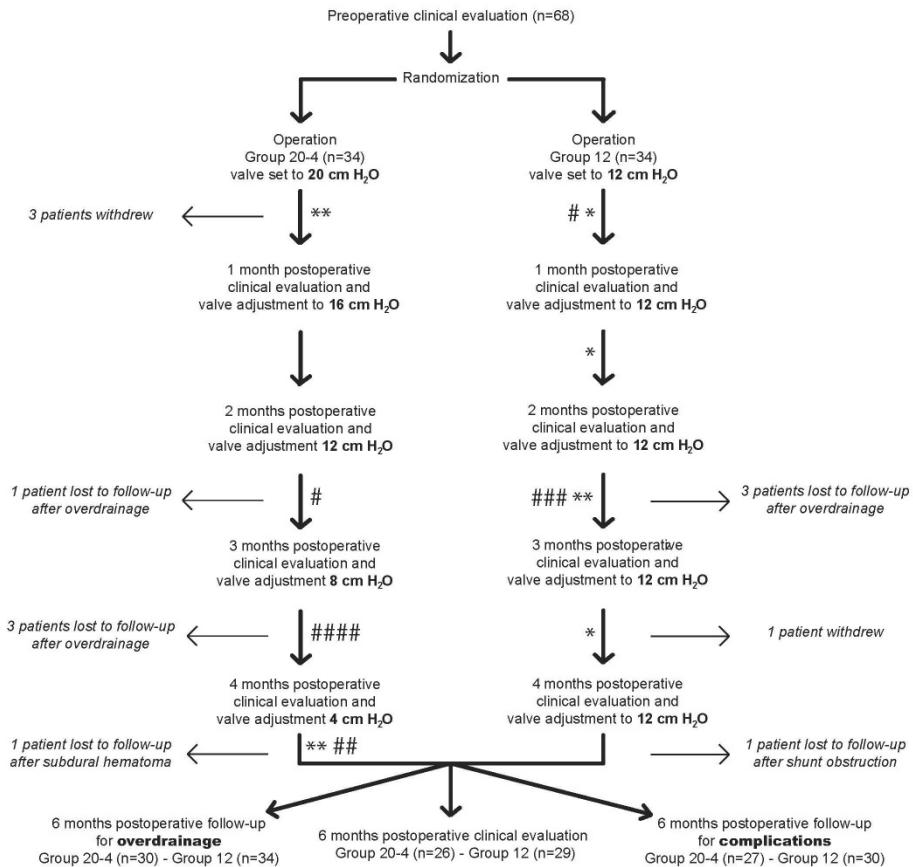
The four tests were: 1) the number of steps needed to walk 10 meters (Walk-steps), 2) the number of seconds it took to walk 10 meters (Walk-time), 3) the color-naming task of the Stroop test (Stroop) [21] and 4) the Grooved Pegboard test [21]. The time and number of steps needed to walk 10 meters were measured by instructing the patients to start at a designated line and walk as quickly as possible on an indoor floor without any slope to another line 10 meters further on, at the highest pace. The time (seconds) was measured using a stopwatch and the number of steps needed to reach a line 10 meters away registered. In the color-naming task of the Stroop test the patients were asked to name the colors of 100 rectangles presented in 10 rows on a paper sheet as quickly as possible [21]. In the Grooved Pegboard test the patients were instructed to place 25 pegs into holes with randomly positioned slots as quickly as possible using the dominant hand, while the time required to complete the task was measured [21].

In order to compare the scores of the four monthly tests, a standardized score (SDS) was generated based on the mean (Mean-preop) and standard deviation (SD-preop) of the preoperative test scores for all patients. The SDS of the individual test score was calculated according to the following equation:

SDS = (Mean-preop – individual test score) / SD-preop

The total SDS (tSDS) was calculated for each patient as the mean of the SDS for the four monthly tests.

During follow up the patients were asked about improvements, symptoms of complications, and under or overdrainage. If the patients had improved, adjustments were made according to the protocol. In cases of no clinical improvement, a CT was performed. If the ventricular size had decreased, the shunt was considered to be functioning, but if not, it was checked by means of shuntography [227] or ICP monitoring. When shunt function was established, the valve was adjusted in accordance with the protocol. Complications were classified as SDH, shunt infection, or shunt obstruction. Symptoms of under or overdrainage (headache, vertigo, nausea) were recorded.

Statistical analysis

In all four studies in the present thesis, continuous variables are described with means and standard deviations (SD) and cathegorical variables as n (number) and percent. Where applicable, 95% confidence intervals (CIs) were used. All tests were two-sided and conducted at a 0.05 significance level. For discrete data, the Fisher exact probability test was used to analyze dichotomous nominal variables and the regular chi-square test for analysis of non-dichotomous nominal variables. Mantel–Haenszel's chi-square test was used for ordinal variables. Continuous variables were analyzed using the Mann–Whitney U test. For survival analyzes, Kaplan–Meier estimates were calculated and formally tested with the log rank test. All tests were two tailed and conducted at a 5% significance level. The analyzes were performed in SAS® (Cary, NC).

In study II, the effect of body position and valve setting on ICP and AMP, respectively, was investigated by mixed model analysis with body position, valve setting and interaction set as fixed effects and patient as random effect to adjust for the within patient correlations. The normality of ICP and AMP was examined and found satisfactory. The relationships between ICP variables and height, weight and BMI (respectively) were investigated by Spearman correlation coefficients and tested between groups using the Mann-Whitney U-test.

In studies III and IV an adjustment of p-values for test between groups was performed using van Elteren's test with site as a blocking variable. Test of changes from baseline over time was done by using the Wilcoxon Signed rank test for all four tests separately as well as their mean value (tSDS). In order to compare the final tSDS between the two groups we also used analysis of covariance with the preoperative result as a covariate.

Table 3. *Summary of patient characteristics, outcome, and complications in the four studies included in the thesis. *An increase of > 5 points in the iNPH scale score and ≥ 1 in the NPH score was considered significant.*

	Study I (n=450)	Study II (n=20)	Study III (n=68)	Study IV (n=68)	All four studies (n=538)
Age, mean (SD)	57 (18)	71 (9)	71 (8)	71 (8)	57 (17)
Sex (F / M)	245 / 205	8 / 12	25 / 43	25 / 43	278 / 260
Hydrocephalus etiology (idiopathic / other)	125 / 325	11 / 9	68 / 0	68 / 0	204 / 334
Adjustable / fixed pressure shunt valves	235 / 214	20 / 0	34 / 34	34 / 34	289 / 248
iNPH / NPH scale score preop, mean (SD)	-	65 (20)	57 (19) / 10.1 (1.2)	57 (19) / 10.1 (1.2)	59 (19)
iNPH / NPH scale score postop, mean (SD)	-	72 (23)	71 (19) / 12.0 (1.6)	71 (19) / 12.0 (1.6)	71 (20)
Significant improvement*	-	10 of 15 (67 %)	40 of 55 (73 %)	40 of 55 (73 %)	50 of 70 (71 %)
Shunt revision within 6 months	85 of 450 (19 %)	2 of 20 (10 %)	13 of 57 (23 %)	13 of 57 (23 %)	100 of 527 (19 %)
Subdural hematoma	4 of 450 (5 %)	0 of 20 (0 %)	9 of 57 (16 %)	9 of 57 (16 %)	13 of 527 (3 %)
Overdrainage	2 of 450 (2 %)	0 of 20 (0 %)	11 of 64 (17 %)	11 of 64 (17 %)	13 of 534 (2 %)
Infection	24 of 450 (6 %)	1 of 20 (5 %)	1 of 57 (2 %)	1 of 57 (2 %)	26 of 527 (5 %)

4 RESULTS

In total, 538 patients were included in the present thesis (Table 3). The complication rate was 19 %. The rate of SDH (0-16 %) and overdrainage (0-17 %) varied between the four studies. The infection rate was 5 %. Fifty-four percent of the patients received shunts with adjustable valves. The postoperative improvement rate in studies II-IV was 71 % (50 out of 70 patients).

Study I

In total, 450 primary shunt insertions were performed, 9 % of which were ventriculoatrial (VA) shunts. Eighty-five patients (19 %) required shunt revision in the 6 month period after shunt insertion and the revision rates were similar for VA and VP shunts. The shunt revision rate decreased from 21 to 9 % during the 10 year study period (Figure 7). The hydrocephalus etiologies and shunt revision indications are presented in figures 8 and 9, respectively.

Figure 7. *Shunt revision rates between 1995 and 2004 (10 years). Linear correlation (r) and its probability (p) are presented.*
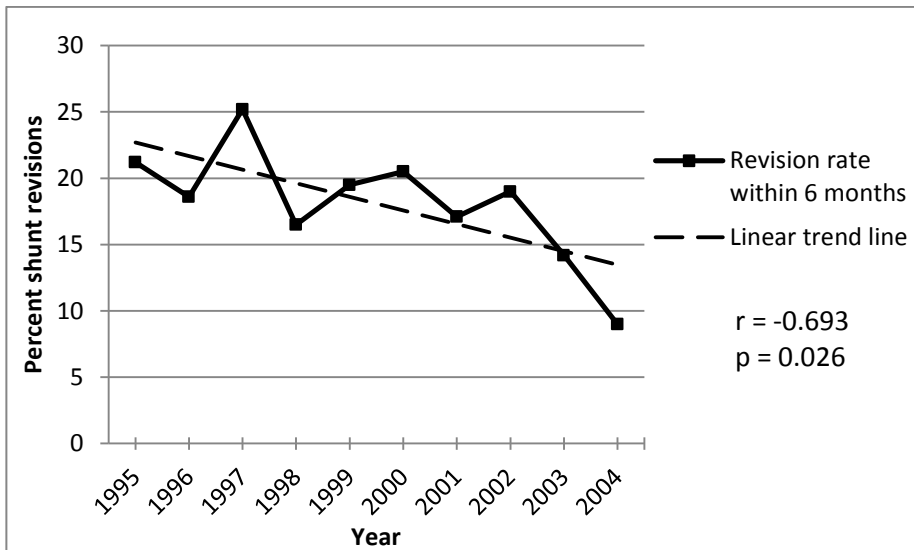
Figure 8. *Hydrocephalus etiologies of hydrocephalus among patients who underwent shunt insertion in the period 1995-2004 at the Department of Neurosurgery, Sahlgrenska University Hospital (n = 450).*

Figure 9. *Indications for shunt revision among patients who underwent shunt insertion in the period 1995-2004 at the Department of Neurosurgery, Sahlgrenska University Hospital (n = 450).*

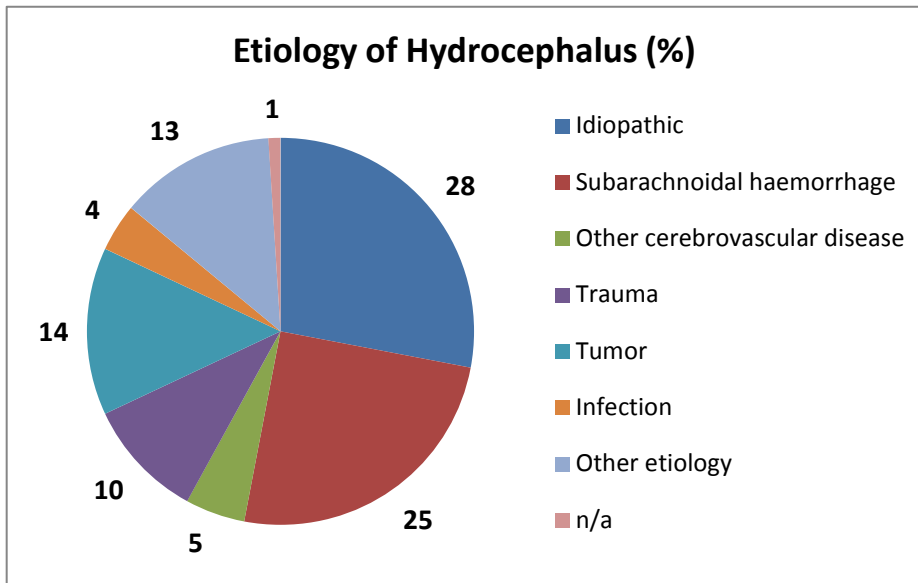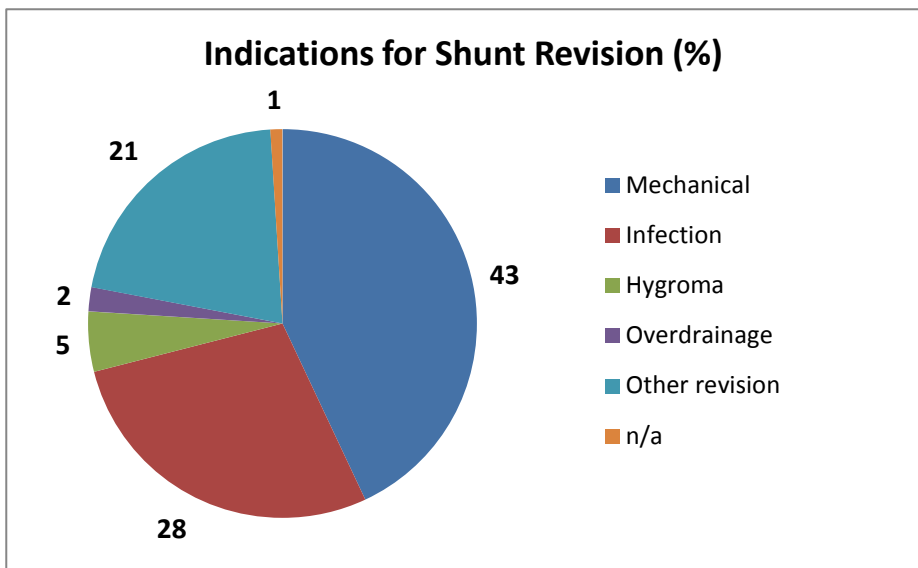Right frontal placement of the ventricular catheter ($p<0.001$), the shorter ventricular catheter length ($p=0.004$) and adjustable valve ($p=0.007$) was associated with a decreased risk of shunt revision within 6 months. A coincidence of the two variables occurred in 43 % of the cases. Other perioperative variables were not significantly associated with the risk of shunt revision (Figure 10).

Figure 10. *The perioperative insertion and revision protocols (revised). For each variable the p-value is indicated (n.s. = not significant).*

Insertion Protocol

Age (n.s.)	date of birth
Gender (n.s.)	female / male
Operator (n.s.)	attending / resident
Operating room used prior to the operation (n.s.)	yes / no
Total number of persons present in operating room (n.s.)	n
Procedure performed (n.s.)	ventriculo-peritoneal / ventriculo-atrial shunt
Ventricle catheter length ($p=0.004$)	cm
Catheter location ($p<0.001$)	frontal / occipital, right / left
Valve manufacturer (n.s.)	Delta / Strata / Sophy / Sigma / Codman
Opening pressure (n.s.)	cm H_2O
Peritoneal catheter length (n.s.)	cm
Superficial wounds (n.s.)	yes / no
Eczema or pimple (n.s.)	yes / no
Tracheostomy (n.s.)	yes / no
Preoperative ventricular drain (n.s.)	yes / no
Accessory incision(s) (n.s.)	n
Glove change (n.s.)	n
Length of operation (n.s.)	minutes

Revision Protocol

Priority	acute / elective
Indication for revision	mechanical (proximal to the valve) / mechanical (distal to the valve) / infection / overdrainage / subdural haematoma / other
Type of revision procedure	Total shunt system removal / total shunt system replacement / conversion from VP- to VA-shunt / conversion from VA- to VP-shunt / valve replacement / distal procedure / proximal procedure / other

Study II

ICP and AMP were significantly lower when the shunt was open at all three valve settings compared to the ligated shunt state in each body position. Overall, mean ICP and mean AMP in all positions decreased significantly with each lowering of the valve setting. In Table 4 mean ICP and mean AMP values in each body position at different opening pressures are presented. Figure 11 shows mean ICP and mean AMP in relation to shunt opening pressure in each body position.

In ICP, the mean difference between the 2.5 and 0.5 valve settings was 4.0 (1.9-6.1) mmHg in the supine position, 5.0 (2.9-7.1) mmHg when sitting, and 4.1 (2.0-6.2) mmHg when walking.

Table 4. *ICP and ICP wave amplitude (AMP) means and standard deviations (SD) at different opening pressurse and body positions. VS = valve setting.*

		Closed shunt	**VS 2.5**	**VS 1.5**	**VS 0.5**
Overall	ICP	5.81 (6.37)	2.52 (6.31)	0.33 (6.41)	-1.83 (7.15)
	AMP	*7.69 (2.63)*	*6.27 (2.16)*	*5.53 (2.32)*	*4.54 (2.26)*
Supine	ICP	12.85 (3.95)	9.74 (4.03)	7.78 (3.61)	5.78 (3.99)
	AMP	*6.22 (2.44)*	*4.99 (1.45)*	*4.33 (1.26)*	*3.35 (1.28)*
Sitting	ICP	2.28 (4.50)	-1.45 (4.25)	-4.41 (3.71)	-6.45 (5.57)
	AMP	*7.14 (2.16)*	*5.30 (1.19)*	*4.18 (0.82)*	*3.48 (1.15)*
Walking	ICP	2.30 (3.51)	-0.74 (2.55)	-2.39 (3.31)	-4.83 (4.36)
	AMP	*9.72 (2.02)*	*8.51 (1.72)*	*8.07 (2.05)*	*6.80 (2.21)*

Figure 11. *The relationship between a) mean ICP, b) mean ICP wave amplitudes (AMP) and shunt valve settings in different body positions.*

a)
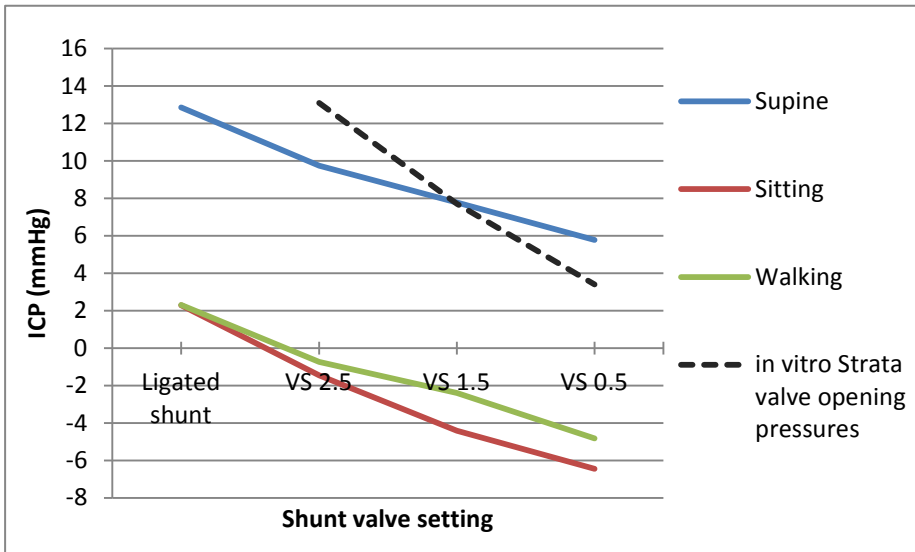
b)
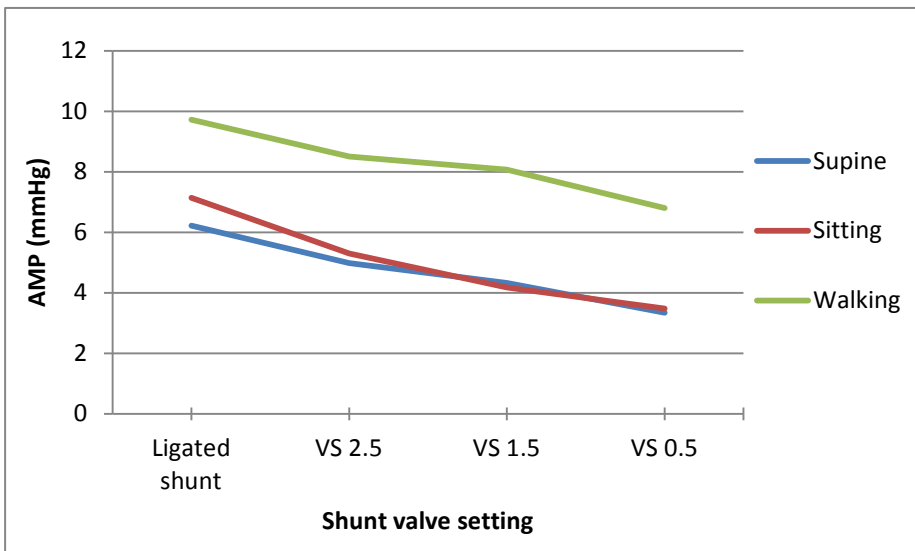
Studies III and IV

At the end of the study period, 18 of the 26 patients in the 20-4 group had a valve setting of 4 cm H_2O, seven a valve setting of 12 cm H_2O, and one a setting of 16 cm H_2O. In the 12 group, 25 patients had a valve setting of 12 cm H_2O, two a setting of 20 cm H_2O, and two a setting of 10 cm H_2O. Thus, the mean opening pressure at the end of the study was 7 cm H_2O in the 20-4 group and 13 cm H_2O in the 12 group.

There was no difference in the shunt complication rate between the 20-4 group (22 %) and the 12 group (23 %). The majority of complications (69 %) involved SDH. There was no difference in the occurrence of SDH between the 20-4 and the 12 group. Five patients who had SDH were successfully treated by increasing the valve setting, while in the remainder (n=4), the SDH was surgically evacuated.

Figure 12 presents the survival analysis for SDH and overdrainage symptoms. The rate of overdrainage symptoms did not differ significantly between the two groups over time, but more overdrainage symptoms occurred in the 20-4 group when the valve setting was ≤ 12 cm H_2O (n=7) compared to > 12 cm H_2O (n=0), which difference was significant (p<0.016).

Figure 12. *Kaplan-Meier analysis illustrating days until SDH occured in the two groups (20-4 and 12). The valve setting at each monthly clinical evaluation is presented above the x-axis.*
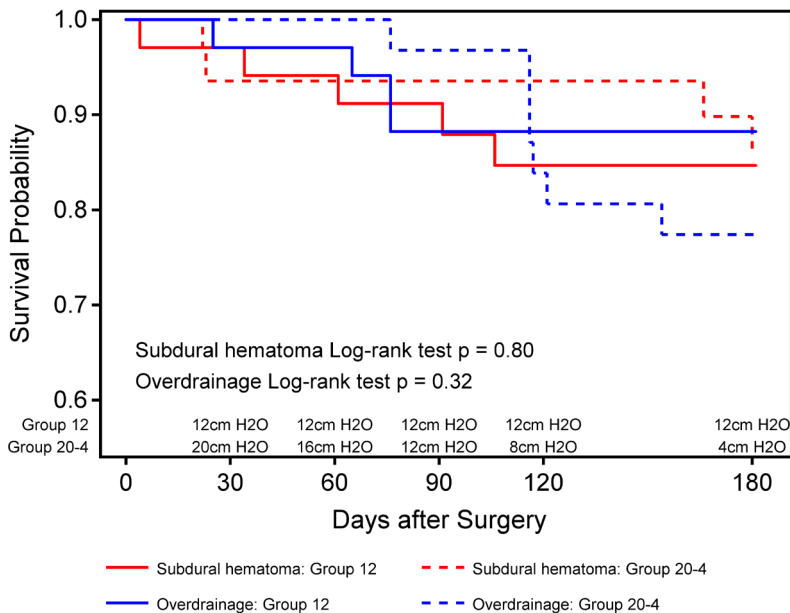
There were no significant differences between the two groups (20-4 and 12) preoperatively or at any time postoperatively. Both groups exhibited significantly improved tSDS after shunt insertion at all valve settings compared to the preoperative score, with the greatest improvement observed at the first postoperative evaluation. When comparing the number of significantly improved (> 5 points in the iNPH scale score or ≥ 1 in the NPH score) patients a statistically significant difference between the two groups (p=0.03) emerged. However, after adjustment to take account of the baseline differences between the groups and measurement of the improvement in tSDS, the difference in outcome did not reach statistical significance (p=0.10).

More patients had improved in tSDS at the 3 month postoperative evaluation than at 1 month (p<0.001), but no significant improvement occurred between the 3 and 6 month postoperative evaluation (p=0.60).

Both neuropsychological variables (Stroop and Grooved Pegboard tests) and the two gait variables (Walk-time and Walk-steps) improved significantly postoperatively. The gait variables improved more quickly than the neuropsychological ones (Figure 13).

Figure 13. *Mean values of the a) neuropsychological and b) gait tests over a 6 month period for the two groups (20-4 and 12).*

a)
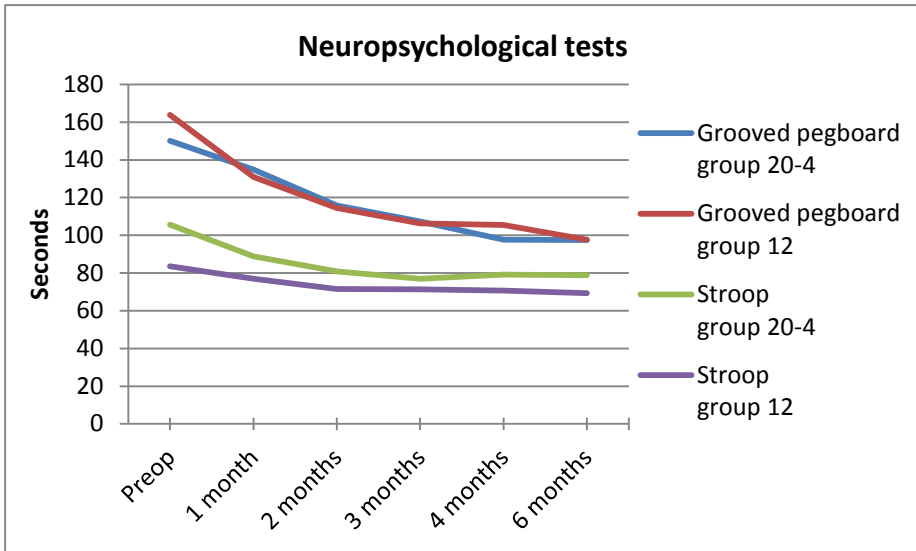
b)
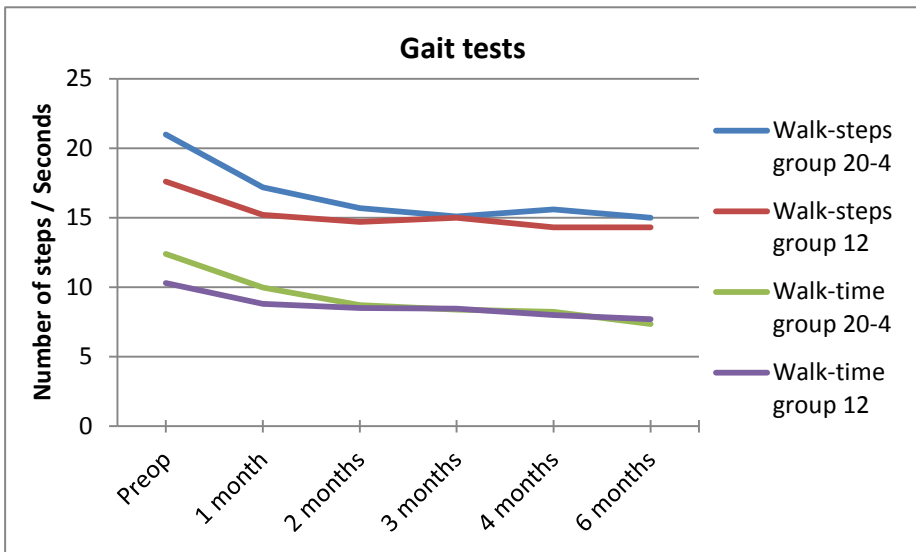
5 DISCUSSION

Adjustable shunt valves were introduced to ensure more optimal CSF drainage by enabling non-invasive adjustment of the valve setting (12). They are widely used despite a lack of randomized clinical trials and consensus about their benefit in shunt treatment of iNPH (1, 2, 28).

Complications

In study I, patients with adjustable valves had a lower risk (p=0.007) for postoperative shunt revision within the 6 months (16 %) compared to those with fixed valves (22 %). However, as we found a coincidence of adjustable valves and frontal placement of the shunt, it cannot be concluded that adjustable valves were independently associated with a lower shunt revision rate. Almost half (43.4 %) of the right frontal shunts were adjustable compared to a minority (14 %) of the right occipital shunts. External adjustment of the opening pressure in adjustable valves can be facilitated by support of the underlying tissue on which the shunt valve is placed. The awareness that frontal placement allows the valve to rest more firmly on the skull bone, compared to occipital placement that often results in the valve shifting over the muscular neck tissue, might have meant that the surgeon opted for frontal placement of the adjustable valve and may thus explain the coincidence of adjustable valves and right frontal placement of the shunt.

The reason for the lower revision rate of adjustable shunts could be that instead of revising the shunt immediately, the surgeon may try to adjust the valve setting, thereby delaying an inevitable shunt revision. However, if this was the case, a larger proportion of adjustable shunts should have required revision at 12 months compared with 6 months, yet the two revision rates were almost identical. Among shunts revised within a 12 month period, there was a lower proportion of adjustable valves (44 %) compared to fixed pressure valves (56 %).

The iNPH guidelines recommend starting with a high opening pressure and gradually lowering it in order to reduce the frequency of SDH [23]. Study III demonstrates that a gradual reduction of the valve setting from 20 to 4 cm H_2O did not increase the shunt complication rate in iNPH patients compared with a fixed pressure of 12 cm H_2O. The rate of overdrainage symptoms was also identical in both groups but such symptoms occurred significantly more frequently at a valve setting of $\leq$ 12 cm H_2O. The results of the RCT

conducted in the present thesis could not demonstrate a lower rate of SDH, but the two groups ended up with different opening pressures.

In a study by Boon et al., the group with a low opening pressure experienced more SDH than the group with a medium opening pressure. Similarly, Delwel et al. [56] observed a higher rate of SDH in the group that started at a low/medium valve setting (Strata® PL 1.0) in comparison with the group that started at a high valve setting (Strata® PL 2.5) that was gradually lowered. This is not supported by the RCT conducted in the present thesis, in which the patients in the 20-4 group who ended the trial at a low valve setting (4 cm H_2O) presented with the same rate of SDH as the group with a medium valve setting (12 cm H_2O). The discrepancy between the results could be interpreted to mean that gradual lowering of the opening pressure might have prevented the development of SDH, thus supporting the recommendation in the iNPH guidelines [23]. Delwel et al. found significantly more subdural effusions in the low/medium pressure group than in the high pressure group. For this reason, further improvement due to a lower valve setting could not be investigated. However, a confounding factor when comparing overdrainage symptoms and clinical outcome in different studies is the lack of common criteria for defining overdrainage and the use of different outcome scales.

Placement of the ventricular catheter

Left placement of the ventricular catheter, frontal as well as occipital, was associated with a greatly increased shunt revision rate and may be explained by the fact that shunt placement on the right side was always preferred if not contraindicated. Therefore, left sided placement of the ventricular catheter may have only occurred in complex cases that could increase the risk of shunt revision.

One explanation for the association of a lower shunt revision rate in right frontal placement of the ventricular catheter is that the ventricular catheters placed frontally are generally shorter (6-7 cm) than occipital catheters (9-12 cm). The lower complication rate associated with a shorter ventricular catheter may simply be explained by that frontal shunt placement requires a shorter ventricular catheter. When inserting the ventricular catheter during the shunt operation, the insertion angle is crucial for the location of the catheter tip. When comparing the insertion angle of long and short ventricular catheters, an equal change in insertion angle leads to a larger dislocation of the catheter tip with a longer (occipital) catheter compared to shorter (frontal) catheters.

Clinical outcome

The literature on the effect of low versus medium or high valve settings on outcome is conflicting and only a few prospective trials have been published. In Boon's study [32] the clinical effect of shunt treatment was better in the group treated with a low compared to a medium opening pressure, which contradicts the results of the study by Delwel et al. where the clinical effect was the same in both groups (low/medium valve setting group and high valve setting group). The purpose of the latter study was to lower the valve setting until the optimal level was identified. No patient in the high valve setting group was down-regulated to a low valve setting (Strata® performance level (PL) 0.5) and at the end of the study, only two patients in the low/medium group achieved a low valve setting. The mean valve setting (Strata® PL) at the end of the study was 1.1 in the low/medium and 1.9 in the high valve setting group. The study design may have restricted the inclination to further lower the valve setting when a patient obtained a satisfactory clinical effect at a certain level.

The manner of measurement differed between studies III and IV when measuring outcome. In study III, the number of significantly improved patients based on the iNPH / NPH scale was compared, while in study IV the tSDS was compared between the two groups. For practical and ethical reasons it was not possible to design the study as monthly assessments according to the iNPH / NPH scale. However, despite the divergent outcome measures employed in studies III and IV, the difference in probability was only 0.07, indicating that the clinical outcome assessed by tSDS was comparable with the number of significantly improved patients measured by the iNPH / NPH scale. Nevertheless, the main reason for the difference in improvement between the two groups is considered to be the fact that patients with more severe symptoms improve more than less impaired patients, which has been shown previously [96].

ICP when adjusting the opening pressure

The opening pressure was primarily defined as the amount of pressure measured in a manometer after insertion of a spinal needle into the subarachnoid space through a lumbar puncture. The opening pressure of a DP valve can be defined as the inlet pressure required to open the valve. The opening pressure of a DP valve can be determined by applying static fluid pressure *in vitro*. However, several additional variables are involved *in vivo* such as the fact that the shunt valve is exposed to dynamic inlet pressure, due to the waveform of the ICP curve caused by cardiac pulsations. The AMP in hydrocephalus patients is roughly around 5 mmHg and its duration is approximately 0.5-1 seconds. As the state of the valve during the ICP pulse

wave has not been determined, it is uncertain whether the valve remains open at peak pressure or whether it opens at the mean ICP level (Figure 14). In addition, the opening duration and the amount of CSF drainage during the ICP pulse wave have not been determined. Because of the differences between *in vitro* and *in vivo*, the opening (inlet) pressure and valve setting cannot be used synonymously.

Figure 14. *Mean intracranial pressure (ICP) level (red line) and ICP wave amplitudes. The mean ICP value of 8 mmHg reflects a dynamic ICP between 4 and 12 mm Hg (ICP wave amplitude). (y-axis = ICP (mmHg), x-axis = seconds).*
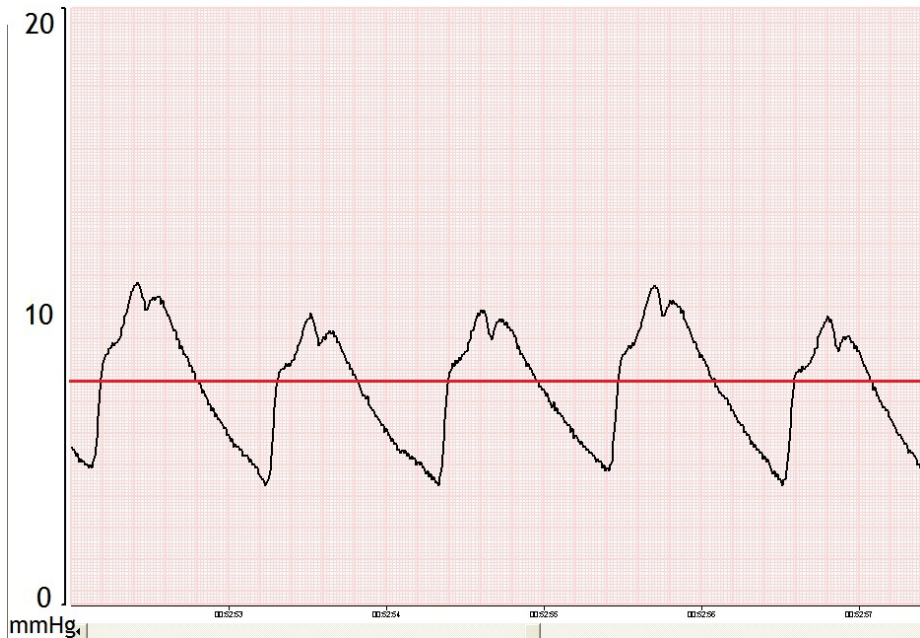
The opening pressure levels in adjustable valves have been determined based on *in vitro* measurements [135] but the ICP at different valve settings *in vivo* has been poorly studied. Bergsneider et al. explored the relationship between ICP, shunt valve opening pressure (using Codman Hakim programmable valve®) and body position in iNPH and found a linear correlation between valve setting and ICP that could not solely be predicted on the basis of Portnoy's equation [24].

The present thesis evaluated the effect of different valve settings in adjustable valves on ICP in mobile patients, showing that ICP dynamics differ

significantly in upright compared to supine position. Mean ICP was well below the opening pressures set by the valve, suggesting that the valve should not have opened in the upright position. The mean difference between the 2.5 and 0.5 valve settings was 4.4 mmHg compared to the 9.8 mmHg measured in a bench test study of the Strata valve by Lundkvist et al. [135]. One explanation may be that intermittent flows at the peak of the systolic pulses and B-waves, as well as other spontaneous ICP elevations, contributed to drainage of intermittent CSF boluses. Thus, it may be that the change in peak pressures, rather than the change in mean ICP should corresponds to the different shunt opening pressures.

The change in peak pressure caused by a lowering of the shunt setting is probably due to a reduction in mean ICP but also from decreased AMP variations, as the compliance increment from lowered ICP will cause the ICP variations to decrease.

Changes in ICP wave amplitude (AMP)

When investigating the ligated shunt it was found that despite the reduction in mean ICP, mean AMP only increased at trend level from the supine to the sitting position, suggesting that compliance was unchanged or only marginally decreased by posture. This was in accordance with previous studies which have indicated that AMP does not change with body position [69,175].

Figure 15 depicts the pulsatility curve (AMP versus ICP) as described by Qvarlander et al. [173,174]. It showed that at low ICP there is a phase where compliance and AMP are constant, while at higher ICP there is a phase during which the Marmarou model [142] is valid, with compliance that decreases and AMP that increases linearly with ICP [15,126]. The present data demonstrate that AMP is reduced when the ligated shunt is opened and decreases further when the valve setting is lowered, suggesting that ICP does not enter the phase with constant AMP (A), as described in the pulsatility curve.
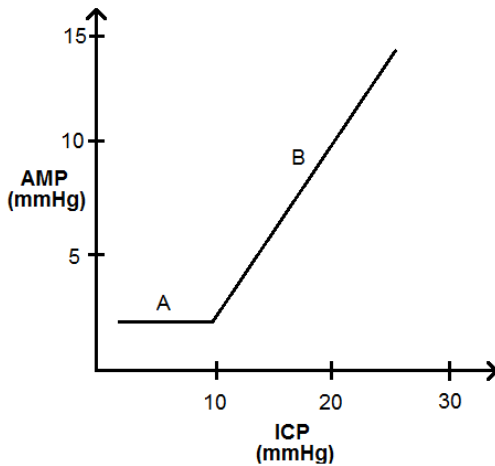
Figure 15. *The pulsatility curve [173] describes the relationship between AMP and ICP. The curve includes an ICP independent zone at low ICP (A), where AMP is constant, and an ICP dependent zone (B), where AMP increases linearly with ICP. ICP = intracranial pressure. AMP = ICP wave amplitude.*

Methodological aspects

In study I all patients were consecutively included over a ten year period while in the remaining three studies participation was voluntary. However the demographic characteristics in the three latter studies resembled previous studies with the exception of the unexpected male dominance. The patients came from two defined geographical areas in Western Sweden and Southern Norway (Studies III and IV). As we did not find any difference in CSF dynamics or clinical presentation between the sexes, we consider the participants representative of hydrocephalus patients.

Differences between the study sites could have influenced the result. In Oslo CSF dynamic testing was required for inclusion and as it was an established evaluation procedure we decided to retain it, as changing local policies often results in more problems than benefits. For the same reason we decided to keep the two different scoring scales used in Oslo and Gothenburg because of validation problems if we changed the scale at one center. Due to administrative policies at each hospital we also decided to retain the established routines for shunts with an ASD in Gothenburg and shunts without an ASD in Oslo. As the patients were randomized into two groups and there were no differences between them in terms of demographic data or between the three site-dependent differences described above, we believe that the two groups are comparable and the results valid.

Study I was an observatory study and the results were affected by changes over time in the surgical practice, for instance the choice of the shunt valve

type. The tested variables were not independent, which made interpretation of the results more difficult. Practically and ethically, it was not possible to evaluate several of the variables in an RCT. Nevertheless, it was a large population based study with many variables collected prospectively, providing an important evaluation of perioperative risk factors.

In study II the absolute levels of ICP were less reliable than the relative changes. Firstly, ICP recordings indicated the occurrence of a pronounced zero-drift in three patients. According to the manufacturer (Raumedic AG®), all ICP sensors were calibrated and tested at the laboratory prior to insertion. Previous studies indicate that ICP monitoring with solid ICP sensors is associated with zero-drift [66,150] possibly due to electrostatic discharges [66]. Nevertheless, this ICP monitoring technique is widely used in clinical practice due to the low long-term complication rate [47,199] and because of the accuracy of ICP wave amplitude measurements [66,68]. Even in the three sensors with zero-drift the relative pressure differences were accurate during calibration, indicating that the measurements of AMP were accurate.

For practical reasons, in studies III and IV, easily administered tests were considered important and the four tests were carefully selected to prevent learning effects leading to subsequently improved test results. A previous study on NPH patients did not show any learning effect on neuropsychological and motor tasks [203], and therefore we believe that the learning effect between the evaluations in this study was negligible. The validity of the test battery is illustrated by the relatively small difference of only 0.07 in the analyzed probability of improvement six months postoperatively between the iNPH / NPH scale and the tSDS.

The SDH rate in studies III and IV was appeared higher compared to studies I and II. In studies I and II patients were not prospectively evaluated for SDH, which may have caused an underestimation of the occurrence rate. The higher mean age of the patients in studies III and IV may have predisposed them to the risk of postoperative SDH because of age-associated cerebral atrophy. We believe that the postoperative SDH rate found in studies III and IV (17 %) is well representative of iNPH.

The sample size of 60 was considered appropriate based on the assumption of a complication rate of 30 % (SD 8 %) and a power of 90 %. The drop-out rate was fairly high due to complications, overdrainage problems, and unwillingness to travel to the hospital for the evaluations. Although a limited amount of type II error may have occurred, we believe the null hypothesis can probably be accepted.

Summary

The present thesis shows that adjusting the valve setting in adjustable valves has a smaller effect on complications and clinical symptoms than has previously been assumed [23,232]. The effect on ICP is also more modest than could be predicted from bench tests [135] and the difference between the opening pressures of the valve does not directly correspond to the magnitudes of difference in ICP.

Nevertheless, we could confirm some benefits with adjustable vales. Firstly, among the nine SDH patients observed in the study, five could be treated successfully only by up-regulation of the valve setting to 20 cm H_2O; the remaining four patients with SDH were operated with evacuation of the SDH. Secondly, the eleven patients with overdrainage symptoms could all be successively treated with up-regulation of the valve. Therefore, despite the lack of a proven beneficial effect of adjustable valves on improvement and subdural hematomas, some re-operations might be avoided by valve adjustments.

As mentioned previously, the intended effects of adjustable valves are lowering the shunt revision rate and improving outcome. The approval process for application of medical technology is somewhat different from that of pharmaceutical treatment. Before approval of a new pharmacological treatment, several stages must be passed. The United States FDA drug approval process comprises animal testing, safety, and effectiveness assessments including comparing the new drug with a placebo in an RCT. The same rationale is not applied in the development of medical technology [1], despite the fact that shunts are implantable devices. Although adjustable shunts have been routinely used for over 20 years in the treatment of hydrocephalus, no RCT has been required for approval. Regarding this lack of systematic data, it was an overall aim of this thesis to expand our current knowledge of adjustable valves in the treatment of adult hydrocephalus.

Finally, as health expenses are of growing importantce in public and privat health care, the price of each medical device and treatment has to be taken into account. Generally, the financial cost of adjustable valves is higher compared to fixed pressure valves. Table 5 lists the price of commonly used adjustable and fixed pressure valves. As the thesis could not conclude that that adjustable valves decrease shunt complications or improve clincial outcomes, their use must be questioned.

Table 5. *Prices of different hydrocephalus shunt valve types. The mean price of adjustable differential pressure (DP) valves is 38 % higher compared to fixed DP valves. All prices are retained from the resellers in Sweden (date: 17 April 2014) and include total shunt kits. ASD = antisiphon device.*

Shunt brand/manufacturer	Valve type	Cost (SEK)	Cost (EUR)	Cost (USD)
PS Medical Delta (1)	Fixed DP	10000	1097	1518
Codman Hakim Fixed with ASD (2)	Fixed DP	11534	1265	1751
Codman Hakim Fixed without ASD (3)	Fixed DP	9770	1072	1483
Sophysa Monopressure (4)	Fixed DP	5960	654	905
Sophysa Programmable (5)	Adjustable DP	14660	1609	2226
Sophysa Polaris (6)	Adjustable DP	18760	2059	2849
PS Medical Strata (7)	Adjustable DP	15820	1735	2402
Codman Hakim Programmable with antisiphon device (8)	Adjustable DP	15600	1711	2369
Miethke proGAV without shunt assistant (9)	Adjustable DP	18000	1974	2733
Orbis-Sigma (10)	Flow-control	10000	1097	1518
Mean price	**Fixed DP valves (1-4)**	**9316**	1022	1414
Mean price	**Adjustable DP valves (5-9)**	**16568**	1818	2516

6 CONCLUSIONS

Adjustable valves and frontal placement of the shunt catheter were both, although not independently, associated with a lower short-term shunt revision rate and thus it cannot be concluded if it was the adjustable valves or the placement of the ventricular catheter that contributed to a lower revision rate.

The pressure window in an adjustable valve was narrower *in vivo* than *in vitro*. Changing from a supine to an upright position significantly reduced ICP while AMP was not similarly affected.

Gradual reduction of the valve setting from 20 to 4 cm H_2O neither improved the clinical outcome nor the complication rate, compared to a fixed valve setting at 12 cm H_2O. Clinical improvement was evident within three months postoperatively and the effect was preserved.

7 FUTURE PERSPECTIVES

This thesis could not prove a beneficial effect of adjustable valves compared to fixed pressure valves. Adjustable valves do not prevent SDH but may be valuable in the treatment of SDH in hydrocephalus patients. However, further studies evaluating this issue prospectively are required.

As shunt treatment is currently the best treatment modality, studies to improve patient selection for shunt surgery and assessment of variables predicting shunt outcome would be of great importance.

Shunt treatment is obviously beneficial for patients with hydrocephalus. Over the past 50 years, treatment of hydrocephalus has consisted of shunting, which has been and still is, associated with a relatively high complication rate. The research on physical and mechanical aspects of hydrocephalus has been extensive, probably because shunting has been the main treatment. As the pathophysiology of hydrocephalus remains unclear, it has been difficult to target the research for other treatment modalities. A simple search on PUBMED (date: 19 April 2014) on "hydrocephalus pressure" resulted in more hits (5894) compared to a search on "hydrocephalus pathophysiology" (3795). This can be partly explained by the fact that shunt treatment is deemed to alter intracranial pressure dynamics but it also reveals one source of our limited knowledge of the pathophysiology. The trend during the recent decades has been towards the development of shunt devices to optimize outcome, but studies have recurrently failed to show significant improvements with new shunt devices. Further advances in the treatment of hydrocephalus may not only consist of the development of new shunt devices, as it is equally important to improve understanding of the pathophysiology of hydrocephalus in order to target novel treatment modalities.

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