Cerebrospinal fluid infusion methods
Development and validation on patients with idiopathic normal pressure hydrocephalus

Nina Andersson

Department of Radiation Sciences,
Department of Pharmacology and Clinical Neuroscience and Centre of Biomedical Engineering and Physics, Umeå University, Sweden.
Department of Biomedical Engineering and Informatics,
Umeå University Hospital.

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“The problem isn’t with what we don’t know, the problem is with what we do know that isn’t so.”

Will Rogers
Abstract

Cerebrospinal fluid (CSF) infusion tests can be used to estimate the dynamic properties of the CSF system. Idiopathic normal pressure hydrocephalus (INPH) is a syndrome signified by a disturbance to the CSF system, where the cause is unknown and the diagnosis is difficult to determine. As an aid in identifying patients with INPH who will improve after shunt surgery, infusion tests are commonly used to determine the outflow conductance ($C_{out}$), or outflow resistance ($R_{out} = 1/C_{out}$), of the CSF system. The tests are also used to determine shunt function in vivo. The general aim of this thesis was to develop and validate CSF infusion methods, to investigate the dynamics of the CSF system. The methods should be applicable to patients with INPH, to aid in the quest to further improve the diagnosis and management of this syndrome.

An existing mathematical model describing the dynamics of the CSF system was further developed. The characteristics of the model were verified and the effect of expanding intracranial air on the intracranial pressure (ICP) was simulated. The simulations supported the recommendation to maintain sea-level pressure during air ambulance transportation of patients with suspected intracranial air.

A recently developed infusion apparatus was evaluated, on an experimental model as well as on a patient material. The repetitiveness in estimating $C_{out}$ was found to be good. A statistically significant difference was found between the repeated $C_{out}$ estimations in the patient group, indicating that there might have been a small physiological change introduced during the infusion test. A parameter, $\Delta C_{out}$, was proposed and evaluated. It proved to reflect the reliability of individual $C_{out}$ investigations in a clinically useful way, as well as to provide easily interpreted information.

An adaptive algorithm for assessment of $C_{out}$ was developed and evaluated on a patient group. The new algorithm was shown to reduce the investigation time, from 60 minutes, by $14.3 \pm 5.9$ minutes (mean $\pm$ SD), $p<0.01$, without reducing the reliability of the estimated $C_{out}$ below clinically relevant levels.

The relationship between ICP and CSF outflow was studied in a group of
patients investigated for INPH. It was found that in the range of moderate increase from baseline pressure, the assumption of a pressure independent $R_{out}$ was confirmed ($p=0.5$). However, at larger pressure increments, the relationship had a non-linear tendency ($p<0.05$). This indicates that the traditional view of a pressure independent $R_{out}$ might have to be questioned in the region where ICP exceeds baseline pressure too much.

Infusion tests can be performed in different ways, where three main categories may be distinguished. The bolus infusion method was compared to the constant pressure and constant flow infusion methods, on an experimental model as well as on a patient material. When physiological pressure fluctuations were added to the model, significant differences were found in the determination of $C_{out}$ in the range of clinical importance, i.e. low $C_{out}$ ($p<0.05$). The finding was supported by the patient investigations, the difference was however not significant.

With the application of the new methods developed in this thesis, and the increased knowledge concerning relationships between CSF dynamic parameters, the CSF infusion test was further improved with the ability to increase measurement reliability in a reduced time. This constitutes a good basis to perform a large multi-centre study with the main goal to determine the predictive value of the parameter $C_{out}$. 
## Contents

1 **ORIGINAL PAPERS** 9  
2 **LIST OF ABBREVIATIONS** 10  
3 **INTRODUCTION** 11  
4 **BACKGROUND** 13  
   4.1 **HISTORY** 13  
   4.2 **CSF CIRCULATION** 14  
   4.3 **IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS** 17  
   4.4 **PATIENTS WITH INTRACRANIAL AIR** 18  
5 **MODEL OF THE CEREBROSPINAL FLUID SYSTEM** 21  
   5.1 **ELECTRICAL CIRCUIT EQUIVALENT** 21  
   5.2 **COMPLIANCE** 22  
   5.3 **MATHEMATICAL MODEL** 23  
6 **CSF INFUSION METHODS** 25  
   6.1 **CONSTANT PRESSURE INFUSION** 25  
   6.2 **CONSTANT FLOW INFUSION** 25  
   6.3 **BOLUS INFUSION** 26  
7 **AIMS OF THE STUDY** 27  
8 **SUMMARY OF PAPERS** 29  
   8.1 **PAPER I** 29  
   8.2 **PAPER II** 29  
   8.3 **PAPER III** 30  
   8.4 **PAPER IV** 30  
   8.5 **PAPER V** 31  
9 **MATERIAL AND METHODS** 33  
   9.1 **PATIENT POPULATION** 33  
   9.2 **ETHICAL CONSIDERATIONS** 34  
   9.3 **THE INFUSION APPARATUS** 34  
   9.4 **THE EXPERIMENTAL MODEL** 35  
   9.5 **THE INFUSION TEST** 37  
   9.6 **ADAPTIVE SIGNAL ANALYSIS ALGORITHM** 43  
   9.7 **STANDARDIZATIONS** 44
10 **RESULTS AND DISCUSSION** 45

10.1 **OUTFLOW CONDUCTANCE VERSUS OUTFLOW RESISTANCE** 45
10.2 **PATHOLOGICAL OUTFLOW CONDUCTANCE** 45
10.3 **APPLICATION OF CSF MODEL TO AIR AMBULANCE TRANSPORTATION** 46
10.4 **VALIDATION OF INFUSION APPARATUS AND ΔC_{OUT}** 49
10.5 **REDUCTION OF INVESTIGATION TIME** 53
10.6 **ICP DEPENDENCY OF R_{OUT}** 55
10.7 **COMPARISON OF INFUSION METHODS** 59

11 **CONCLUSIONS** 67

**ACKNOWLEDGEMENTS** 69

**LIST OF REFERENCES** 71
1 Original papers

This thesis is based on the following papers*, which are referred to by their Roman numerals in the text.


V. Andersson N, Andersson K, Marmarou A, Malm J and Eklund A. Does the cerebrospinal fluid outflow conductance determined by steady state infusion methods differ from that of the bolus infusion method? In manuscript.

* Papers I-III are reprinted with permission from the publisher.
2 List of abbreviations

C Compliance of the CSF system
CNS Central nervous system
C\textsubscript{out} Outflow conductance of the CSF system
CSF Cerebrospinal fluid
CT Computed tomography
IAHS Idiopathic adult hydrocephalus syndrome
ICP Intracranial pressure
INPH Idiopathic normal pressure hydrocephalus
MR Magnetic resonance
NPH Normal pressure hydrocephalus
PVI Pressure volume index
R\textsubscript{out} Outflow resistance
SAS Subarachnoid space
SD Standard deviation
SEM Standard error of mean
SNPH Secondary normal pressure hydrocephalus
3 Introduction

The main treatment of patients diagnosed with hydrocephalus is the performance of shunt surgery. A cerebrospinal fluid (CSF) shunt system is a purely mechanical implant which affects the dynamics of the CSF system, thus it is important to know the state of the CSF dynamical parameters of the patient before surgery is considered.

The CSF infusion test was clinically introduced in 1970 by Katzman and Hussey,\textsuperscript{32} and has since then been developed and extensively used as an auxiliary test for diagnosing potential hydrocephalus patients, for testing patency of CSF shunts \textit{in vivo} and for research. When performing an infusion test, artificial CSF is introduced into the CSF system and the response of the system to that perturbation is studied. The main parameter estimated is the outflow conductance, $C_{\text{out}}$ (or outflow resistance, $R_{\text{out}} = \frac{1}{C_{\text{out}}}$) of the CSF system. The principle idea is that since the CSF shunt implant dramatically increases $C_{\text{out}}$ of the patient, preoperative deficits in the outflow pathways, manifested by a pathologically low $C_{\text{out}}$, would imply that improvement could be expected by shunt surgery. In contrast, a high preoperative $C_{\text{out}}$ would indicate well functioning outflow pathways, and thus it is unlikely that the patient should improve by shunt surgery.

The predictive power of $C_{\text{out}}$ has been debated for decades, some claiming that the parameter has a high predictive value,\textsuperscript{6,7,55,59,11} while others finding it less useful.\textsuperscript{34,28,22} In the recently published guidelines on idiopathic normal pressure hydrocephalus (INPH), it was stated that the value of supplementary tests to predict which patients would benefit from placement of a shunt has not been established. It was also stated that measures of $R_{\text{out}}$ can increase the sensitivity for identifying patients who will benefit from shunting above that obtained with clinical assessment, and that the determination of $R_{\text{out}}$ via an infusion test carries a sensitivity of 57-100% and a positive predictive value of 75-92%.\textsuperscript{39} In a review over diagnosis and management of NPH it was said that it is regrettable that the tests with the highest predictive accuracy are technically complex and seem reliable only in the hands of hydrodynamic virtuosos.\textsuperscript{64}

At the Umeå University Hospital the history of performing CSF infusion tests is long. Professor Jan Ekstedt introduced the method of constant pressure infusion in the 1970 decade,\textsuperscript{25,26} and it has since then been in clinical use investigating the CSF dynamics of more than 4000 patients.
Continuous development of the infusion technique and equipment has been made, and in 2004 the latest version of the infusion apparatus, including e.g. automated and standardized infusion protocols for simplified management and reduced subjectivity, was clinically introduced.\textsuperscript{2}

To finally determine the predictive power of $C_{\text{out}}$, there is a need for standardized and objective investigations performed on a large patient material. Regardless of the infusion method used, it is important that the estimated parameters are readily comparable, and that additional uncertainties introduced by each investigator are avoided. There is also a need to distinguish those individual investigations that are reliable enough to expect predictability out of, and to disregard the rest.

In this thesis, the CSF infusion test was further developed concerning reliability, adaptive time consumption and comparison of methods. Fundamental assumptions of the most commonly used CSF dynamical model were also investigated.
4 Background

4.1 History
The earliest scientific description of hydrocephalus has been ascribed to Hippocrates (466-377 BC), who pointed out symptoms such as headache, vomiting and visual disturbance. The symptoms were explained by a liquefaction of the brain due to epileptic seizures. Claudius Galen of Pergamon (130-200 AD) and medieval Arabian physicians also described cases of hydrocephalus, believed to be due to an extracerebral accumulation of water.4

The first historically documented ventricular puncture was performed in 1744 by Le Cat, but it was not until the late nineteenth century, when sufficient pathophysiological knowledge and aseptic conditions were gained, that surgical procedures were truly introduced into the hydrocephalus area. As a result, ventricular punctures, external CSF drainage, serial lumbar punctures and placement of the first permanent ventriculo-subarachnoid-subgaleal shunt were performed. In the following decades different kinds of shunts were developed, but the mortality rate was high, mostly due to insufficient implant materials. Around 1960 the new and indispensable silicone material, as well as the invention of artificial valves, led to a therapeutic breakthrough. By the development of the implantable shunt system, hydrocephalus went from being a fatal disease to becoming curable.4

In 1965 Hakim and Adams described a new category of patients, being symptomatic with a normal cerebrospinal fluid pressure, that also improved from shunt surgery.30 The syndrome was named normal pressure hydrocephalus (NPH), and since then extensive work has been put into finding and developing new methods to identify those patients with NPH that will improve from shunt surgery.

Today ventricular shunting is one of the most commonly performed neurosurgical procedures, including communicating and non-communicating hydrocephalus as well as shunt malfunction.44
4.2 CSF circulation

In Figure 1 the outlining of the human CSF system is shown. CSF is a clear, colourless liquid contained within the cerebral ventricles and the subarachnoid spaces. The approximate CSF volume in man is 1500 mL. Its main functions are to support the brain physically, take part in intracerebral transport and control the chemical environment of the central nervous system (CNS).²⁷

Figure 1: Anatomical picture of the CSF system. (Modified from www.resed.ac.uk/eselect/cc1.htm).
4.2.1 CSF production

The choroid plexus, placed in the walls of all four ventricles inside the brain, is considered to be the main, and perhaps only, production site of CSF today. The choroid plexus can be described as a capillary complex with an outer layer of epithelial cells, and CSF is created through a secretion process where a filtrate is generated from the plasma in the capillaries, and then transported through the epithelial cells to the ventricles. CSF circulates from the ventricles through the median (foramen of Magendie) and lateral (foramen of Luschka) apertures in the fourth ventricle to the cerebral and spinal subarachnoid space (SAS).

Many different methods have been used to estimate the rate of CSF secretion in both animal and man,\textsuperscript{18,42,43,65} and an approximate value in man is 7 µL/s (25 mL/h).\textsuperscript{26} The secretion rate of CSF has been accepted as independent of intraventricular pressure. This is in concordance with processes of secretion in general, which can work against high hydrostatic pressures. Thus it is not likely that a moderate increase in ventricular pressure should affect the CSF secretion rate, at least not with ICP being less than 2.7-4 kPa.\textsuperscript{21} The pathology of hydrocephalus also indicates that when the CSF drainage is impaired, the secretion still continues although ICP might increase considerably. A reduction in CSF production at high intraventricular pressures is not unreasonable though, since this might reduce the rate of filtration from blood plasma in the choroid plexus.\textsuperscript{21} Other factors seen to affect the CSF production rate are e.g. medical inhibitors such as acetazolamide (Diamox), hypothermia and hypoglycaemia.\textsuperscript{10,20,54}

4.2.2 CSF absorption

The main absorption site of CSF from the SAS back to venous blood is considered to be the arachnoid villi (arachnoid granulations), though other absorption sites, such as the lymphatic system, has also been suggested.\textsuperscript{9,12,31} The arachnoid villi are protrusions of the arachnoid membrane into the subdural space and the dural sinuses (Figure 2). The connection between the arachnoid villi and the venous blood has not been fully elucidated, some claiming that each villi is covered by a membrane completely separating the CSF from the blood,\textsuperscript{67} others having found tubings within the villi extending from the CSF side to venous blood,\textsuperscript{70} and yet others suggesting that the transport mechanism could be based on
vacuoles.$^{15,61}$ It is clear though, that the flow is unidirectional and that the absorption ceases when the pressure in the SAS is lower than that of venous blood. Arachnoid villi are mainly found in the cerebral SAS, but also in the spinal SAS. $^{71,72}$ In a recent study it was shown that $38\%$ of the CSF absorption could be attributed to the spinal area in healthy individuals.$^{23}$

In an early model by Weed, the CSF absorptive process was described as dependent on the hydrostatic pressure difference between the SAS and the dural sinus, as well as on the colloid osmotic pressure given by the difference in protein concentrations in CSF and plasma.$^{66,68,69}$ This concept was questioned, however, and a new model where the absorption depended only on the hydrostatic pressure difference was proposed.$^{16,17,19}$ Today the latter model is widely accepted, and the CSF outflow according to this model is described by the Davson equation:

$$\text{CSF outflow} = \frac{\text{ICP} - P_d}{R_{out}} = C_{out} \left(\text{ICP} - P_d\right),$$  \hspace{1cm} (1)

where $P_d$ is the dural sinus pressure and $R_{out}$ and $C_{out}$, being each others inverse, are the outflow resistance and outflow conductance of the CSF system respectively.
4.3 Idiopathic normal pressure hydrocephalus

Normal pressure hydrocephalus (NPH) follows from a disorder in the CSF system, and the main clinical features are balance and gait disturbance with or without cognitive decline and urinary incontinence. The syndrome was first described in 1964 by Hakim and in 1965 by Hakim and Adams, who defined a condition with the above mentioned symptom triad in combination with enlarged ventricles (Figure 3a) and an essentially normal ICP. An MR or CT scan also reveals a communication between the ventricles and the SAS. For about 40% of the patients diagnosed with NPH, the diagnosis is secondary to some insult to the central nervous system, such as subarachnoidal hemorrhage or head trauma (SNPH). In these cases the diagnosis is often relatively easy to make. In the remaining 60% there is no known cause of the syndrome, and thus it is named idiopathic NPH (INPH). The diagnosis is more difficult in these cases, and in addition to the clinical and radiological findings, the results of auxiliary tests are often needed.

Figure 3: CT images of the ventricles of the brain. a) Image taken prior to shunt surgery. b) Image taken after shunt surgery. The white dot in the left ventricle is the tip of the proximal shunt catheter.
The nomenclature ‘normal’ pressure hydrocephalus is somewhat misleading, in the sense that the average ICP in a group of NPH patients generally is higher than in a group of healthy individuals. In 1989 Ekstedt put forward the nomenclature Adult Hydrocephalus Syndrome, to revert from any statement regarding the pressure, and to emphasise that it is a condition mainly found in elderly (mean age 67 years in a recent study of the Swedish population). In studies II and III of this thesis the name IAHS has been used, while in studies IV and V INPH was used, since this is still the most common nomenclature world wide.

The treatment of NPH consists of surgically placing a shunt system which passes CSF in a silicone tube from the ventricles of the brain (Figure 3b) to another cavity of the body (mainly the abdomen). With careful selection about 70% of the patients improve postoperatively. In a study conducted in Sweden in 2005, the incidence of shunt operations in adults varied between 2.3-6.3 operations/100 000 inhabitants/year (mean 3.4) at six neurosurgical centers. About 30% of these operations were performed under the diagnosis of INPH and 20% under secondary NPH, which together gives about the same incidence as multiple sclerosis in northern Sweden.

4.4 Patients with intracranial air
After intracranial surgery some quantity of air is often left inside the skull. Depending on the procedure, air may be present almost anywhere including epidural, subdural, subarachnoidal, and intraventricular locations. The volume of air is usually small, causes no symptoms and is spontaneously absorbed. Intracranial air may be present up to 3 weeks after surgery. Thus, in most cases intracranial air following surgery is not a problem. The situation is different though, when transportation by air ambulance is necessary. During air transportation, the increase in aircraft altitude causes a decrease in cabin pressure. Gas contained within distensible body cavities increases in volume as the cabin pressure decreases. However, air trapped within the rigid skull cannot readily expand, and may instead raise ICP.
Due to limitations in our knowledge of the effects of intracranial air on ICP, it is currently standard procedure to maintain sea-level pressure during air transport whenever there is any suspicion that intracranial air might be present. Keeping the cabin pressure at sea-level has its disadvantages, since the limits of the aircraft pressurization system leads to a reduction of the operational ceiling to 14000 ft (4200 m) rather than the usual 31000 ft (9300 m). At this lower altitude, the air is more turbulent and has a higher resistance, resulting in a more difficult flight for the patient, a more difficult job for the pilot, and greater fuel consumption. In addition, turbulence raises the risk of a mishap which leads to an increased risk for everyone on board.
5 Model of the cerebrospinal fluid system

5.1 Electrical circuit equivalent
In 1978 Marmarou et. al. suggested a mathematical model of the CSF system with an electrical circuit equivalent (Figure 4). This model, with various modifications, has since then extensively been used in studies when trying to determine and understand the physiology of the CSF system.

![Figure 4: Model describing the dynamics of the CSF system, incorporating intracranial pressure (P), CSF production (I_f), external infusion (I_ext), compliance (C), outflow resistance (R_{out} = 1/C_{out}) and dural sinus pressure (P_d). I_{tot} is the total flow through the system, I_a is the part absorbed into venous blood, and I_r is that which remains in the CSF system.

The system being considered consists of CSF, blood and brain/spinal tissue. A schematic picture of the dynamic components of the system is shown in Figure 4. I_{tot} is the total inflow of liquid in the system. It is given by I_{tot} = I_f + I_{ext}, where I_f is the formation rate of CSF and I_{ext} is the rate of external infusion of artificial CSF. A certain amount of fluid is continuously absorbed from the system, this part is denoted by I_a, while the part which remains in the system is denoted by I_r. Thus, I_{tot} = I_a + I_r. In Figure 4, R_{out} = 1/C_{out} is the outflow resistance of the absorption pathways, and P_d is the dural sinus pressure. These parameters will influence the size of I_a, since the driving force of the absorption is considered to be the...
hydrostatic pressure difference between the intracranial pressure \( P \) and \( P_d \) multiplied by \( C_{\text{out}} \) or divided by \( R_{\text{out}} \), is

\[
I_a = C_{\text{out}} (P - P_d) = \frac{P - P_d}{R_{\text{out}}}. \tag{2}
\]

### 5.2 Compliance

The variation in brain and spinal blood volume, and the compression of tissue in the craniospinal compartment, are the sources of compliance \( C \) in the CSF system. By definition it is given by the quotient of the change in volume and the change in pressure, \( \frac{dV}{dP} \), of the CSF system.\(^{41}\) The pressure of the CSF system is an exponential function of the volume, \( \Delta V \), according to equation (3) (Figure 5)

\[
P = P_r e^{K\Delta V}, \tag{3}
\]

where \( P_r \) is the pressure of the system at equilibrium (resting pressure) and \( K \) is a mathematical constant describing the slope of the curve.\(^{41}\)

---

**Figure 5:** An example of a pressure volume curve illustrating the compliance function of the CSF system.
Thus

\[
C = \frac{\text{d}V}{\text{d}P} = \frac{1}{K \cdot P}.
\] (4)

In Figure 5 it can be seen that the pressure increase associated with a specific volume increase ($\Delta V_0$) is larger when the total volume $\Delta V$ is larger ($\Delta P_2 > \Delta P_1$), this is due to a decreased compliance of the system.

By plotting the pressure response of a certain volume change on a logarithmic scale, the curve will become linear. The linearized volume/pressure slope has been defined as the pressure volume index (PVI), interpreted as the amount of fluid (in mL) necessary to raise ICP ten times, and it is given by

\[
\text{PVI} = \frac{\Delta V}{\log_{10} \left( \frac{P_p}{P_{\text{start}}} \right)}.
\] (5)

5.3 Mathematical model

To find a mathematical expression for the intracranial pressure as a function of time, the components of equation (6) below needs to be defined

\[
\frac{\text{d}P(V(t))}{\text{d}t} = \frac{\text{d}P}{\text{d}V} \cdot \frac{\text{d}V}{\text{d}t}.
\] (6)

By using equation (4), equation (6) can be expressed as

\[
\frac{\text{d}P}{\text{d}t} = K \cdot P \frac{\text{d}V}{\text{d}t},
\] (7)

and since $\text{d}V/\text{d}t$ is actually the same as $I_r$, (7) can be rewritten as

\[
\frac{\text{d}P}{\text{d}t} = K \cdot P(I_{\text{tot}} - I_a)
\] (8)
Finally, using equation (2) in equation (8), the following differential equation will result

\[
\frac{dP}{dt} + \frac{KP^2}{R_{out}} - \frac{K \cdot P}{R_{out}} \left( R_{out} I_{tot} + P_d \right) = 0.
\]  

(9)

From equation (2) it can be seen that at equilibrium the relationship \( P_r = P_d + I_t R_{out} \) is valid, where \( P_r \) is the resting pressure of the patient. Using this expression the dural sinus pressure and formation rate of CSF can be removed from equation (9) through

\[
R_{out} I_{tot} + P_d = R_{out} I_{ext} + P_r,
\]

(10)

and thus equation (9) can be rewritten as

\[
\frac{dP}{dt} + \frac{KP^2}{R_{out}} - \frac{K \cdot P}{R_{out}} \left( R_{out} I_{ext} + P_r \right) = 0.
\]

(11)

To solve equation (11) a substitution which makes the equation linear can be applied, followed by an integration where the integrating factor is used (see appendix of study I). The following expression for the intracranial pressure as a function of time will then result

\[
P(t) = e^{-\frac{K}{R_{out}} \int_0^t R_{out} I_{ext}(t) + P_r dt} \left( e^{\frac{K}{R_{out}} \int_0^t R_{out} I_{ext}(t) + P_r dt} P(t) - \frac{1}{P(0)} \int_0^t e^{\frac{K}{R_{out}} \int_0^\tau R_{out} I_{ext}(t) + P_r dt} d\tau \right).
\]

(12)

This general solution may be simplified for different kinds of external infusions (\( I_{ext} \)), which will be seen in section 6.
6 CSF infusion methods

To determine the dynamic parameters of the CSF system, infusion tests of different outlining may be used. The most commonly used methods today are constant pressure infusion, constant flow infusion and bolus infusion.

6.1 Constant pressure infusion
The method of constant pressure infusion was clinically introduced by Ekstedt in 1977.25,26 When using the constant pressure infusion method, ICP is regulated to specific pressure levels, and the inflow of artificial CSF needed to maintain that pressure is measured. This can be achieved e.g. with a peristaltic pump and a regulating system. Several predetermined pressure levels are employed, and on each pressure level mean ICP and net flow is determined. From equation (2) it is seen that the flow should be linearly dependent on ICP (given that the dural sinus pressure and the formation rate of CSF are constant), and thus $C_{\text{out}}$ is assessed as the slope of the linear regression between flow and corresponding mean pressures.

6.2 Constant flow infusion
The method of constant flow infusion was first introduced as a clinical tool in 1970 by Katzman and Hussey.32 The method was later modified by others.13,14,33 Artificial CSF is infused, usually through a lumbar or intraventricular needle, into the CSF space at a constant rate, and the corresponding rise in ICP is registered and analysed. From equation (2) it can be seen that when ICP reaches a steady state level (plateau), where the external input of artificial CSF added to the formation rate is equal to the absorption rate, the outflow conductance is given by

$$C_{\text{out}} = \frac{I_{\text{ext}}}{P_{\text{plateau}} - P_r}, \quad (13)$$

where $I_{\text{ext}}$ is the rate of external infusion, $P_{\text{plateau}}$ is the mean ICP on the new steady state plateau, and $P_r$ is the resting pressure prior to infusion. This method is referred to as ‘static’, since it is only the mean pressures during the phases where ICP is on static levels that are considered in the analysis.
Another way of deducing $C_{out}$ from a constant flow infusion is by using equation (12). When inserting $I_{ext} = \text{constant}$ and $P(t=0) = P_{start}$, the following solution for the pressure as a function of time is found:

$$P_{\text{const inf}} = \frac{P_r + \frac{I_{ext}}{C_{out}}}{1 + \left( \frac{P_r + \frac{I_{ext}}{C_{out}}}{P_{start}} - 1 \right) e^{-K(I_{ext}+C_{out}P_r)t}},$$

(14)

where $P_{start}$ is the starting pressure immediately prior to the infusion. $C_{out}$, $K$ and $P_r$ can thus be estimated by fitting a curve according to (14) to the measured ICP data. This method is referred to as ‘dynamic’ since the entire pressure curve during infusion is considered in the analysis.

6.3 Bolus infusion

The bolus infusion test is based on a fast injection of a small volume, $\Delta V$, of artificial CSF (usually around 4 mL), and the study of the ICP response to that injection. From the immediate pressure rise following the injection, PV$V_I$ can be deduced according to equation (5).

$C_{out}$ is determined from the declining slope following the end of the bolus infusion ($I_{ext} = 0$). By simplifying equation (12) and solving for $C_{out}$, the following expression is found

$$C_{out} = \frac{P_{VI} \cdot \log_{10} \left( \frac{P_t}{P_p} \frac{P_t - P_r}{P_p - P_r} \right)}{t \cdot P_r},$$

(15)

where $t$ is any time instant after the bolus infusion has stopped, $P_t$ is the pressure at time $t$, $P_p$ is the peak pressure after the bolus infusion and $P_r$ is the resting pressure of the patient.
7 Aims of the study

The general aim of this thesis was to develop and validate cerebrospinal fluid (CSF) infusion methods to investigate the dynamics of the CSF system. The methods should be applicable to patients with idiopathic normal pressure hydrocephalus (INPH), to aid in the quest to further improve the diagnosis and management of this syndrome.

The specific aims were:

- To develop and evaluate a theoretical model describing the dynamics of the CSF system, in order to simulate the influence of intracranial air on ICP during decreasing ambient pressure.
- To propose and evaluate a method for real time estimation of the reliability of individual infusion tests. To evaluate the repetitiveness of infusion tests performed with a new infusion apparatus.
- To develop and evaluate an adaptive analysis algorithm for assessment of $C_{out}$. The algorithm should minimise the investigation time, without reducing the reliability of the estimated $C_{out}$ below clinically relevant levels.
- To study the ICP dependency of $R_{out}$ in patients investigated for INPH, as to test the generally accepted assumption of a linear relationship between CSF outflow and ICP.
- To compare the bolus infusion method to the constant flow infusion method and the constant pressure infusion method. The main question to be addressed was: Does $C_{out}$ determined by steady state infusion methods differ from those of the bolus infusion method?
8 Summary of papers

8.1 Paper I: Air transport of patients with intracranial air: computer model of pressure effects

In this paper a theoretical model of the CSF system was extended to include the existence and influence of intracranial air during decrease of the ambient pressure. It was shown that the model behaved as expected under the prevailing conditions, and a solution to the differential equation (12) describing ICP as a function of time was found when a volume increase of the intracranial air according to Boyle-Mariotte’s law was applied. The main clinical conclusion from this study was that a continued preservation of sea-level pressure should be endorsed when transporting patients with suspected intracranial air by air ambulance, since an impaired clinical state following an ICP increment could not be excluded.

8.2 Paper II: Assessment of cerebrospinal fluid outflow conductance using constant-pressure infusion - a method with real time estimation of reliability

A new apparatus for performing infusion tests in a standardized and automated way was developed. The apparatus was evaluated on an experimental model as well as on a patient material. The repetitiveness in the estimation of $C_{out}$ was found to satisfy the criteria essential for a clinically useful infusion test, although there was a significant difference between repeated investigations performed in the patient group (n=14, p<0.05). A method for real time estimation of the reliability of individual investigations was proposed, and the parameter $\Delta C_{out}$ was found to reflect the reliability in a useful manner. To perform the evaluations, an experimental model mimicking the dynamics of the CSF system was built, where the parameters of the model were reference values from the literature.
8.3 Paper III: Adaptive method for assessment of cerebrospinal fluid outflow conductance

An adaptive signal analysis method was developed, which reduced the time consumption when performing a constant pressure infusion test, without substantially reducing the reliability of the results. The method took the individual ICP variations of each patient into consideration. It was evaluated against the standard, clinically used, method, where the time for each investigation is fixed to 60 minutes. When applying the new adaptive method to a patient group (n=28), a reduction of the investigation time by 14.3 ± 5.9 minutes (mean ± SD), p<0.01, was achieved. The reduction of reliability in the $C_{out}$ estimation was found to be clinically negligible. This adaptive analysis enables the possibility of customizing the infusion test to each individual patient, and reducing the investigation time needed without compromising anything else.

8.4 Paper IV: Intracranial pressure dependency of the outflow resistance

The relationship between ICP and CSF outflow was investigated in 30 patients with suspected INPH. For each patient ICP and corresponding infusion flow were measured on six pressure levels during a lumbar infusion test performed with constant pressure levels.

$R_{out}$ was found to be independent of ICP in the region of baseline (resting) pressure and moderately increased pressure (p=0.5). However, a slightly decreased $R_{out}$ was detected when the increment from baseline pressure was larger, and this resulted in a statistically significant non-linear tendency of the relationship between ICP and CSF outflow (p<0.05). The conclusion from this study was that the pressure independent $R_{out}$ proposed by Davson et. al.\textsuperscript{16,17} is valid in the normal physiological pressure range. Precaution should be taken though, when extrapolating the model into a region of increased intracranial pressure.
8.5 Paper V: Does the cerebrospinal fluid outflow conductance determined by steady state infusion methods differ from that of the bolus infusion method?

C_{out} was estimated by three different CSF infusion methods, constant pressure infusion, bolus infusion and constant flow infusion (static and dynamic analyses). The investigations were performed on an experimental model with and without pressure fluctuations, as well as on 22 patients with suspected or treated INPH. In each case all infusion methods were applied during the same session.

A systematically and significantly higher C_{out} was found with the bolus method as compared with the other methods on the experimental model in the region of low, and thus clinically relevant, C_{out} when physiological pressure fluctuations were present (p<0.05). The finding was supported by the preoperative patient investigations, the difference was however not significant (p=0.2). The difference was thought to be due to difficulties in correctly estimating the pressure parameters of the bolus method. For the shunted patients C_{out} as estimated by the constant pressure infusion method tended to be higher, and closer to the in vitro C_{out} of the shunt, than C_{out} as estimated by the other methods.


9 Material and methods

9.1 Patient population
In study II, 14 patients were included. Nine patients were investigated due to suspected INPH, and five were investigated postoperatively to determine shunt function. The mean age of the patient population was 69 ± 6 years (± SD); four of the patients were women and ten were men.

Twenty-eight patients with suspected INPH were included in study III. The mean age of the patient population was 71 ± 10 years; seven of the patients were women and 21 were men. Thirteen of the 28 patients underwent shunt surgery following the preoperative investigation. Eight patients were improved, two were not improved, one shunt failed to work and the outcome of two patients had not yet been followed up.

The patients included in study IV were the same as in study III, with the addition of two men. The mean age of the group was the same as in study III. Twenty-one patients fulfilled the INPH diagnosis according to the international INPH guidelines. The remaining nine patients had enlarged ventricles and suspicion of INPH, but did not fulfil the criteria for INPH. Sixteen of the 21 INPH patients were operated on. Postoperatively, eleven of the 16 operated patients were improved, three were not improved and the outcome of two patients had not yet been followed up.

In study V all patients included had communicating hydrocephalus on MRI scan and probable or possible diagnosis of INPH according to the INPH guidelines. Infusion tests were performed either as part of a preoperative investigation to determine whether or not to perform shunt surgery, or as a postoperative investigation to confirm CSF shunt patency in shunted INPH patients. The study included 22 patients (preoperative n=15; postoperative n=7). Five patients were excluded prior to analysis due to investigational problems; in one case the data recording did not function correctly, and the other four investigations were terminated after the application of only one out of three infusion methods. The reasons were headache and nausea in one case, and blockage of the orifice of the infusion needle during withdrawal of CSF in the other three cases.
Thus, the population in study V consisted of 17 patients (preoperative n=11; postoperative n=6). The age of the patient population (n=17) was 71.7 ± 9.5 years (mean ± standard deviation (SD)); five of the patients were women and 12 were men.

9.2 Ethical considerations
Studies II and V were prospectively performed. All patients included gave their informed consent after receiving written as well as oral information about the study. All aspects of these studies were approved by the local ethics committee according to the Helsinki declaration.

Studies III and IV were retrospectively performed. The patient data included were de-identified to ensure that the ethical considerations of the studies were fulfilled.

9.3 The infusion apparatus
The infusion apparatus used to perform the investigations in studies II, III, IV and V was developed in house prior to initiating the studies. Special features of the apparatus were the inclusion of standardized and automated protocols, and real time analysis. The apparatus was PC-based with a user interface consisting of a computer screen and a track ball (Figure 6). It also included an electronic control unit, two pressure transducers, a peristaltic pump, a bottle holder for artificial CSF (or in a later version a 1000 mL bag of Ringer solution), an emergency stop and a set of tubing.

Data collection and communication between software and hardware were performed using two data acquisition cards. The electronic control unit included pressure amplifiers, analogue safety checks which stop the pump at dangerously high or low ICP, and a signal to ensure communication with the PC. A built-in horizontal laser line was used for zero level alignment of the equipment in relation to the patient. The components were mounted on an electrically manoeuvred pillar to ensure good ergonomic conditions for the operator, and the pillar was mounted on wheels to make the system mobile. The software was developed in LabVIEW®. A thorough hazard analysis was performed.52
9.4 The experimental model

In studies II, IV and V an experimental model of the CSF system was used to test the hypotheses of each study. One main advantage of using an experimental model, as compared to solely measuring on human subjects, is that the parameters of the model are well defined by construction and does not change by the intervention of measurement. The experimental model (Figure 7) consisted of a cavity formed in Polymethylmetakrylat. The shape of the cavity corresponded to the compliance of the CSF system and was deduced from the pressure-volume relationship first presented by Marmarou et. al. The PVI was chosen to be 25.9 mL. Resting pressure was set to 1.56 kPa through the use of a container with continuous overflow (Figure 7). A changeable T304 stainless steel tubing, denoted 'pipe' henceforth, connected the cavity and the overflow container. The conductance of the pipe simulated $C_{out}$ of the CSF system. A peristaltic pump was used to produce physiological pressure fluctuations in the model,
related to the volume variation due to cerebrovascular variation in a human subject. The infusion apparatus was connected to the model using a double lumen arrangement. The liquid used in the model was de-aerated water, as to avoid errors due to bubbles of air in the system. To achieve adequate physiological pressure fluctuations to apply to the experimental model, a lumbar resting pressure measurement from a patient with suspected INPH was extracted. The ICP data were filtered using a band pass filter with limiting wavelengths of 5 and 120 seconds. Using the compliance of the experimental model at resting pressure, the corresponding flow pattern was calculated and applied to control the pump in order to reproduce the physiological pressure fluctuations. During measurement this pattern was continuously repeated, and the starting index was randomized for each investigation.

**Figure 7:** An illustration of the experimental model used in studies II, IV and V. The shape of the cavity corresponded to the compliance of the CSF system, and pipes of different length and diameter simulated $C_{\text{out}}$. The pump on the left in the figure was used to produce physiological pressure fluctuations in the model.
9.5 The infusion test

In general, in those studies where investigations were performed both on the experimental model and on a group of patients (studies II, IV and V), the same protocol was applied in both cases. However, in study IV the data from the first repetition of the constant pressure infusion on the experimental model of study II were used. Also, in study V the resting pressure measurement was 10 minutes shorter on the experimental model since the resting pressure was stable by construction. In study II the measurement time on each pressure level was longer, and in study V the relaxation times after each infusion were increased and the stabilization periods before the next protocol was applied were increased on the experimental model as compared with the patient investigations, since on the model a long investigation time was not a limiting factor.

All infusion tests performed on patients were started at about 8.30 am after 12 hours of bed rest. Two needles (outer diameter 1.2 mm) were inserted in the L3-4 interspace (Figure 8) while the patient was in the sitting position. To diminish the disturbance of the CSF system prior to measuring the resting pressure of the patient, the physician was told to minimize the leakage when inserting the needles.

The patient was then placed in the supine position, on a specially designed bed with a hole in the back, and the zero-pressure reference level of the infusion apparatus was placed at the centre of the auditory meatus using the horizontal laser line. \( C_{out} \) was determined as described below.

Figure 8: The position of the two needles when performing a lumbar infusion test. (Modified from www.about.adam.com/encyclopedia).
9.5.1 Constant pressure infusion

For the constant pressure infusion method, $C_{\text{out}}$ was determined by regulating ICP to six consecutive, predetermined pressure levels in steps of 0.4 kPa (Figure 9a). The first pressure level was dependent on the individual mean ICP measured during five minutes immediately prior to the start of infusion, and it was set to be the nearest pressure level at least 0.4 kPa larger than the initial mean ICP. On the experimental model the first level was always 2.3 kPa, since mean ICP prior to infusion was approximately 1.6 kPa by construction.

On each pressure level mean ICP was measured, and the flow needed to maintain that pressure level was determined as the slope of the linear regression of the accumulated volumes of infused artificial CSF versus time (Figure 9b). To ensure that only states of equilibrium were included in the analysis, the analysis on each level did not start until 20 seconds after a new pressure level had been reached (ICP within 50 Pa of the desired pressure). If an error occurred which caused the pump to stop, the data registered were not included in the analysis until the pump was restarted, ICP was back at the desired pressure level and another 20 seconds had passed. ICP was automatically increased to the next level when the time set for that level was exceeded. $C_{\text{out}}$ was assessed as the slope of the linear regression between flow and corresponding mean pressure (Figure 9c). The 95% CI of $C_{\text{out}}$, denoted $\Delta C_{\text{out}}$, was estimated using conventional statistical methods for linear regression.48
Figure 9: a) Patient registration during an infusion test with constant pressure levels. The solid line represents ICP, and the dashed line represents net infused artificial CSF. b) Net volume on the first and third pressure levels during constant pressure infusion. The slope of the linear regression corresponds to the net flow on the first pressure level. c) Net flow on each pressure level as a function of mean pressure. The slope of the regression line constitutes $C_{out}$ of the patient.
9.5.2 Constant flow infusion

For the constant flow infusion method, artificial CSF was infused at a flow rate of approximately 1.5 ml/min. The infusion was continued for 20 minutes (Figure 10). Analyses were made using both a ‘static’ (\(C_{\text{out stat}}\)) and a ‘dynamic’ (\(C_{\text{out dyn}}\)) method. For the static method the plateau pressure, estimated as the mean pressure over the last five minutes of infusion, and the resting pressure of the patient was utilized in equation (13) to estimate \(C_{\text{out stat}}\). For the dynamic method, the Levenberg-Marquardt least squares fitting method was used to fit equation (14) to the pressure curve, \(P_{\text{const inf}}\), measured during infusion. \(P_r\) was measured at the beginning of the investigation and \(P_{\text{start}}\) was the average over the last five seconds prior to the constant flow infusion. \(C_{\text{out dyn}}\) and K were estimated from the fitting.

**Figure 10:** Patient registration during an infusion test with constant flow. The black line represents ICP of the patient, and the grey line shows the net infused volume of artificial CSF.
9.5.3 Bolus infusion

For the bolus infusion method approximately 4 ml of artificial CSF was infused at maximum pump speed (≈15 ml/min). Three consecutive bolus infusions were performed, and between each bolus the relaxation time was five minutes for the patients and 15 minutes on the experimental model (Figure 11). Visual fittings to the exponentially decreasing pressure curves were performed (Figure 12), where \( t \) was defined as any time instant along the fitted curve after the bolus infusion had stopped. \( P_p \) was the pressure where the visually fitted curve crossed the point of ended infusion and \( P_t \) was the pressure at time \( t \). PVI was estimated according to equation (5) and the outflow conductance as estimated by this method, \( C_{\text{out bol}} \), was given by equation (15).

![Figure 11](image_url)

**Figure 11:** Patient registration during a bolus infusion test with three repetitions. The black line represents ICP of the patient, and the grey line shows the three bolus infusions.
Figure 12: Schematic picture of ICP before, during and after a bolus infusion, accompanied by a visually fitted, exponentially decreasing curve. The different pressures used in the analysis, $P_p$, $P_t$ and $P_{\text{start}}$ are indicated in the figure. The grey line at the bottom of the figure shows the duration of the bolus infusion.

PVI was calculated once for every bolus infusion, and $C_{\text{out bol}}$ was calculated at $t = 30$, $60$, $90$ and $120$ s for each bolus. The final $C_{\text{out bol}}$ that resulted from each investigation was the mean value of all $12$ estimates from the three bolus infusions. If the pressure increase $(P_p - P_{\text{start}})$ for one bolus was less than $0.53$ kPa (4 mm Hg), that bolus was excluded from the analysis.
9.6 Adaptive signal analysis algorithm

In study III, an adaptive signal analysis algorithm was developed to be implemented during constant pressure infusion investigations. The data were treated as a time series, and main focus was to find the point in time on each pressure level when the reliability of the investigation did not further substantially improve. The investigation should then continue to the next pressure level.

Through an iterative process an estimation of the flow, \( \hat{F} \), and the 95 % CI of the flow, \( \Delta\hat{F} \) (see Figure 13), were calculated on each pressure level. The difference (over 10 seconds) of \( \Delta\hat{F} \) was also calculated as the parameter \( \text{diff}\Delta\hat{F} \). A limit, \( \text{diff}\Delta\hat{F}_{\text{thres}} \), was placed on that difference, such that the infusion continued to the next pressure level when ten consecutive values of \( \text{diff}\Delta\hat{F} \) was smaller than \( \text{diff}\Delta\hat{F}_{\text{thres}} \).

The method was evaluated by comparing \( C_{\text{out thres}} \), \( \Delta C_{\text{out thres}} \) and time consumption at several different threshold levels, with the reference values \( C_{\text{out tot}} \) and \( \Delta C_{\text{out tot}} \) obtained from the ordinary, fixed time, infusion investigation.

![Figure 13: The 95 % CI of the estimated flow (\( \Delta\hat{F} \)) as a function of time. In the figure data from the first and last pressure levels of one patient can be seen.](image-url)
9.7 Standardizations

In study IV, the relationship between ICP and CSF outflow was studied. Infusion tests with constant pressure levels were performed, but since the pressure levels used depended on each patient’s individual baseline (resting) pressure, they were not the same for all patients. Thus the pressure levels had to be standardized for comparison. The corresponding flow on each level also had to be standardized, to eliminate the impact of $R_{\text{out}}$ of each patient but still preserving all information regarding the curve form between pressure and flow. Standardizations were made according to

\begin{align*}
Z_{\text{ICP}} &= \frac{\text{ICP}_{\text{lev}} - \bar{\text{ICP}}}{\text{ICP}_{\text{SD}}} \quad (16) \\
Z_{\text{Flow}} &= \frac{\text{Flow}_{\text{lev}} - \bar{\text{Flow}}}{\text{Flow}_{\text{SD}}} \quad (17)
\end{align*}

$\text{ICP}_{\text{lev}}$ and $\text{Flow}_{\text{lev}}$ are mean pressure and corresponding flow on each pressure level for each patient, $\bar{\text{ICP}}$ and $\bar{\text{Flow}}$ are mean pressure and flow for each patient from the six pressure levels, and $\text{ICP}_{\text{SD}}$ and $\text{Flow}_{\text{SD}}$ are the standard deviations for each patient from the six pressure levels.
10 Results and discussion

10.1 Outflow conductance versus outflow resistance

The outflow pathways of the CSF system are characterised by a resistance ($R_{\text{out}}$), or a conductance ($C_{\text{out}}$), to flow. Here $R_{\text{out}}$ describes the resistance met by CSF when passing through the arachnoid villi or any other outflow pathway from the SAS, and $C_{\text{out}}$ describes the ‘ease’ with which CSF can pass through the same cannels. $R_{\text{out}}$ is the most common CSF outflow parameter presented in international literature. The parameters are interchangeable by inversion, but when studying the dynamic behaviour of the CSF system using the method of constant pressure infusion, representation by $R_{\text{out}}$ has some serious drawbacks when it comes to looking at the reliability of measurements. ICP is regulated to predefined levels, and thus the physiological disturbances will mainly affect the estimation of the net infusion flow, while the error in the ICP measurement is negligible. According to equation (1) $R_{\text{out}}$ is inversely proportional to the CSF outflow, and thus the estimated error, $\Delta R_{\text{out}}$, will be dependent on the actual size of $R_{\text{out}}$. Using $C_{\text{out}}$ on the other hand, the error will be independent of the size of $C_{\text{out}}$.

The advantage of using $C_{\text{out}}$ is thus that the interpretation of the error estimation will be greatly simplified, if the size of the error has the same meaning regardless of the size of the estimated parameter.

In studies I and IV the condition of the CSF outflow pathways was used merely as a numerical value and part of a model respectively, and so the parameter itself was never estimated. Thus, $R_{\text{out}}$ was used to ease the interpretation of the papers to the reader. In papers II, III and V the reliability of the estimated parameter was specifically addressed, and thus $C_{\text{out}}$ was used.

10.2 Pathological outflow conductance

$C_{\text{out}}$ in healthy individuals is higher than in patients with NPH, this makes the parameter a possible diagnostic tool and predictor of outcome after shunt surgery. Previous studies have found that a $C_{\text{out}}$ smaller than approximately 7 µl/(s kPa), as determined by a lumbar constant rate
infusion or a lumboventricular perfusion, is indicative of a disturbed CSF system,\textsuperscript{5,7} and in a study performed with constant pressure infusion on a group of healthy individuals, a mean $C_{\text{out}} = 18 \, \mu l/(s \, kPa)$ was found.\textsuperscript{26} Thus, in the area close to the interval 7 - 18 $\mu l/(s \, kPa)$ it is especially important to have reliable estimations. If the reliability is not good enough to clearly state whether an individual investigation is pathological or normal, an erroneous conclusion might easily be drawn from the data. This in turn would significantly reduce the sensitivity and specificity of the test.

When determining shunt function the precision of the measurement is not as crucial as in the preoperative case. $C_{\text{out}}$ of most shunts is much larger than the physiological $C_{\text{out}}$ of the CSF system (range 25-60 $\mu L/(s \, kPa)$),\textsuperscript{3,36} and the main objective when looking at postoperative CSF dynamics is usually only to determine whether the shunt is functioning or not. Thus, an investigation resulting in $C_{\text{out}} = 45 \pm 10 \, \mu L/(s \, kPa)$ will lead to the same conclusion as will $C_{\text{out}} = 45 \pm 2 \, \mu L/(s \, kPa)$. Of course, a higher precision is always preferable and may also tell something about a partially occluded shunt.

### 10.3 Application of CSF model to air ambulance transportation

A model correctly describing a system under investigation is undoubtedly of great value when trying to determine the parameters of the system. In study I a proposed model of the CSF system was extended to incorporate intracranial air. It was proposed that expanding air affected ICP in a similar manner as the infusion of artificial CSF does, and thus equation (12) could be solved for the special case of air expansion during air ambulance transport.

The idea to investigate the effect of intracranial air on ICP during reduced ambient pressure was initiated by the neurosurgeons at the Umeå University Hospital. When air transport of a patient with suspected intracranial air was in question, an ordination was always made saying that the transport should be undertaken during preserved sea-level pressure for the safety of the patient. The question raised was whether or not this was actually necessary, and there was no support to be found in the literature to aid in the matter.
Simulations where different initial intracranial air volumes, cabin altitude rate of changes and resting pressures of the patient were considered showed that the model behaved in agreement with physical expectations. Figure 14 shows the expansion of the intracranial air volume during ascent. At normal maximum cabin altitude (8000 ft = 2438 m) the initial volume has increased by approximately 30%.

![Figure 14](Image)

**Figure 14:** The change of intracranial air volume during ascent, simulated for three different initial volumes. The vertical dotted line marks the maximum cabin altitude (8000 ft) for B King Air 2000.

In Figure 15 simulations showing ICP as a function of cabin altitude are shown. For an intracranial air volume of 30 ml the estimated worst-case increments of ICP from sea level to maximum altitude would be from 10 mm Hg to 21.0 mm Hg, or from 20 mm Hg to 31.8 mm Hg. In the same figure an example of the simulated effect of a lack of CSF system compliance on ICP is also shown. By comparison to the simulations...
Figure 15: The change in ICP, simulated for three different initial volumes and a resting pressure of 10 mm Hg, when the cabin altitude rate of change is 500 ft/min. Dash-dotted line indicates simulated ICP when no compliance of the system is considered.

incorporating compliance, it can be seen that the effect of compliance predominates during small pressure changes, while outflow resistance takes over for ascent to higher altitudes. Note that the steady, unceasing ICP increments in Figure 15 are due to the continuously increased $I_{IA}$. For a constant $I_{IA}$ the pressure would at some point reach equilibrium.

It was concluded that the proposed and extended model of the CSF system could be used to simulate the behaviour of ICP during air transport of patients with intracranial air. Simulations showed that the increase in ICP was strongly dependent on the aircraft altitude rate of change, and on the initial intracranial air volume. Since for large initial intracranial air volumes and high resting pressures, ICP may reach considerably high levels, this study supported a preserved sea-level pressure during air ambulance transportation. The validity of the model has to be further examined, and the current results should be verified in a study on animals.
10.4 Validation of infusion apparatus and $\Delta C_{\text{out}}$

10.4.1 Infusion test on experimental model

The physiology of the CSF system and patophysiology behind NPH are not fully understood, and means for discovering more details to correctly draw the larger picture are always sought for. One such mean is the infusion test. Manipulation of the CSF system by adding or withdrawing fluid gives us the possibility to estimate some of the dynamic parameters which determine the system, and to possibly find out in what way these parameters correlate with the symptoms seen in NPH patients.

A new apparatus designed to perform standardized and automated infusion tests was constructed. In study II it was shown on an experimental model that the repetitiveness of the $C_{\text{out}}$ estimation was good, with a 95% CI of less than $\pm 2$ µL/(s kPa) for the five steel pipes when physiological pressure fluctuations were present (n=6) (Figure 16).

![Figure 16](image_url)

**Figure 16**: Repeated $C_{\text{out}}$ investigations on the experimental model using five different pipes with the addition of physiological pressure fluctuations (n = 6). Error bars show $\Delta C_{\text{out}}$. The squared marker corresponding to each pipe shows mean $C_{\text{out}}$ from the six repeated infusion tests, and here the error bars display the 95% CI based on the distribution of $C_{\text{out}}$. 
A parameter representing the reliability of each individual investigation, $\Delta C_{out}$, was suggested and evaluated. In a statistical sense, $\Delta C_{out}$ cannot strictly be interpreted as the 95% CI of $C_{out}$, since the pairs of measurements are acquired from the same biological system, and it cannot be assumed that the statistical requirement of independent sets of data is fulfilled. However, each pair of data points represents the mean value from at least five minutes of recording, which should reduce most of the time dependent fluctuations. $\Delta C_{out}$ was shown to reflect the reliability of each investigation in a valuable way. The true $C_{out}$ of each pipe was unknown, but on the experimental model all individual $C_{out} \pm \Delta C_{out}$ included mean $C_{out}$ of their corresponding pipe (Figure 16), which was the best approximation available. This indicated that $\Delta C_{out}$ was not too small. In addition, there was no significant difference between $\Delta C_{out}$ and the distribution of $C_{out}$ ($p=0.135$). This indicated that $\Delta C_{out}$ could be viewed as a not too large predictor of the interval in which the true $C_{out}$ was. Thus it can be used to reflect the reliability of individual infusion tests, giving easily interpreted information.

The reason why we felt that $\Delta C_{out}$ was a truly important parameter to estimate, was that $C_{out}$ is used daily at many neurosurgical centres for prediction of shunt responsiveness.35,63 These $C_{out}$ determinations are, however, performed without any numerical feedback to the user concerning the reliability of the results. It might well be that some disturbing factors, such as extreme pressure fluctuations, coughing or body movement, or even naturally large vasogenic variations, severely affected the outcome of an investigation without the awareness of the investigator. The results are thus used for predictive purpose although they are affected by unphysiological data or determined in an unsatisfying manner.

To avoid this situation we strongly believe that in every situation where a conclusion is about to be drawn from measured data, it is important to know the reliability of the measurement. Looking at $\Delta C_{out}$ gives the physician an estimate of the reliability of $C_{out}$ from a specific investigation. If $\Delta C_{out}$ is small the probability of a correctly estimated parameter is large, but if $\Delta C_{out}$ is large we might have to consider performing another test, or even excluding $C_{out}$ as a predictive factor for that patient. Not taking the reliability of $C_{out}$ into account can lead to erroneous selection of patients for
surgery, and may explain the variation in previous studies regarding the predictive power of $C_{\text{out}}$.6,7,11,22,28,34,55,59

10.4.2 Infusion test on patients

In study II repeated constant pressure infusion tests were also performed on 14 patients with suspected or treated INPH. In Figure 17 the second infusion test is plotted as a function of the first. The correlation coefficient was $R=0.99$ (p<0.05). The mean difference between the first and second infusion test was $-2.46 \mu L/(s \text{ kPa})$ (p<0.05).

![Figure 17](image_url)

**Figure 17:** The second infusion test plotted as a function of the first for the 14 patients included in study II. Also shown is the regression line between the repeated measurements.
In Figure 18 all individual patient investigations including $\Delta C_{\text{out}}$ are shown. Despite the high correlation between the repeated measurements, there was a significant systematic difference between the first and second infusion test (paired t-test). This suggested that there might have been a physiological change introduced to the CSF system during the infusion test. Despite the systematic difference the $\Delta C_{\text{out}}$'s overlapped in all but one case in Figure 18, indicating that $\Delta C_{\text{out}}$ is a valuable indicator of reliability also in the clinical setting.

**Figure 18:** Repeated measurements on a group of 14 patients (n=2). The error bars indicate $\Delta C_{\text{out}}$. 
10.5 **Reduction of investigation time**

A concern often expressed within care giving organizations is the time consumption of different tests and procedures, and the cost that comes along with it. When performing a CSF infusion test a kind of ‘time consumption versus accuracy’ paradox is encountered, where there is a trade off between the parameters. In study III, an adaptive algorithm for the assessment of $C_{out}$ was developed. It was evaluated against the standard constant pressure infusion method with fixed times on each pressure level. The main purpose was to adjust the investigation to each individual patient, and to reduce investigation time without reducing the reliability of the estimated parameter below clinically relevant levels.

As the infusion method to be improved was based on the regulation of ICP to specific levels, we found that most of the remaining variations were in the measurement of the net infusion flow. Hence an iterative signal analysis algorithm for determining the 95 % CI of the net flow, $\Delta F$, on each pressure level in real time was constructed. Since it was likely that $\Delta F$ at total investigation time could vary between pressure levels, for each patient as well as between patients, and the goal was to find out when the precision of the flow measurement did not further sufficiently improve, we chose to study the time difference of $\Delta F$, $\Delta F_{\text{diff}}$. The model behaved as expected, with a general decrease in $\Delta F$ as a function of time.

Based on clinical experience, the study was designed with the criteria that $C_{out \text{ thres}}$ and $\Delta C_{out \text{ thres}}$ at the most could differ 2 µL/(s kPa) from the reference values $C_{out \text{ tot}}$ and $\Delta C_{out \text{ tot}}$. In Figure 19 the differences $C_{out \text{ thres}} - C_{out \text{ tot}}$ for all patients at 11 different levels of the threshold $\Delta F_{\text{thres}}$ are shown. Table 1 shows the 95 % CI of the differences in $C_{out}$ and $\Delta C_{out}$ at five different threshold levels as compared with at total time.
Figure 19: The difference in $C_{out}$ at 11 different threshold levels, and at the total investigation time. Dotted lines indicate limits within which 95% of the patients are expected to be found to fulfil the clinical criteria of the study.

In Table 1 it can be seen that out of the threshold levels that fulfilled the clinical criteria, 0.04 µL/s was the level that reduced the investigation time the most. At this threshold the difference $C_{out\,thres} - C_{out\,tot}$ was -0.3 µL/(s kPa), and $\Delta C_{out\,thres} - \Delta C_{out\,tot}$ was 0.4 µL/(s kPa). Both differences were significant ($p<0.05$), but found clinically negligible. In Figure 20 the time reduction for different thresholds can be seen. Using the threshold level 0.04 µL/s, the reduction was $14.3 \pm 5.9$ min (mean ± SD, $n = 27$), $p<0.01$.

Table 1: Differences in $C_{out}$ and $\Delta C_{out}$.

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<thead>
<tr>
<th>Threshold [µl/s]</th>
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<td>$C_{out,thres} - C_{out,tot}$</td>
<td>$\Delta C_{out,thres} - \Delta C_{out,tot}$</td>
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<td>[µl/(s kPa)]</td>
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<td>0.02</td>
<td>-1.0 – 0.6</td>
<td>-0.7 – 0.5</td>
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<tr>
<td>0.03</td>
<td>-1.4 – 0.9</td>
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<td>-1.0 – 1.7</td>
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<td>0.05</td>
<td>-2.1 – 1.3</td>
<td>-1.3 – 1.8</td>
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<tr>
<td>0.06</td>
<td>-2.3 – 1.7</td>
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This study showed that it was possible to develop an adaptive method of analysis that reduced the investigation time of an infusion test performed with constant pressure levels, without any clinically relevant reduction of the accuracy of the measurement. By using the adaptive signal analysis algorithm, the investigation time could be significantly reduced by approximately 25%. The only downside being a slight, and clinically irrelevant, reduction of $C_{out}$.

10.6 ICP dependency of $R_{out}$

The outflow resistance of the cerebrospinal fluid (CSF) system has generally been accepted as independent of intracranial pressure (ICP), but there are also those claiming that it is not. The general belief is that this question has been investigated numerous times in the past, but few studies have actually been specifically aimed at looking at this relationship, and no study has been able to provide scientific evidence to fully elucidate this fundamental and important issue. In the most commonly accepted mathematical model describing the CSF system, $R_{out}$ (or $C_{out}$) as given by the Davson equation \cite{16,17}, is independent of ICP.\cite{41} In study IV the relationship between ICP and CSF outflow was investigated.

Figure 20: Time reduction for all patients as a function of threshold level.
Figure 21 shows the measured, unstandardized pressure/flow relationships from constant pressure infusion tests on two patients. In Figure 21b the corresponding data have been transformed according to equations (16) and (17).

**Figure 21:** a) Unstandardized infusion flow as a function of ICP for two patients. b) Corresponding standardized parameters for the same patients. Notice how the shapes of the flow/pressure patterns are conserved through the standardizing transformations.
It can be seen that the transformations have standardized the data so that they are statistically comparable, but the shapes of the pressure/flow curves are left unaffected.

In Figure 22 the relationship between standardised outflow and standardised ICP according to equations (16) and (17) are individually shown for the 30 patients incorporated in the study. Figure 23 shows the mean values of the same data for all patients at each standardized pressure level.

Figure 22: Standardized ICP and net flow for all patients (n=30). The regression line is based on the three lowest pressure levels (squares).
Figure 23: Mean values of the standardised ICP and outflow for all patients (n=30). The regression line is based on the three lowest pressure levels (squares). The error bars indicate SEM of the measurements.

The relationship between ICP and CSF outflow was close to linear when using all elevated pressure levels (Table 2 and Figure 22), the quadratic term contributed significantly though (p<0.05, n=30x6). Analyzing only the three lowest pressure levels, the contribution of the quadratic term was not significant (p=0.5).

<table>
<thead>
<tr>
<th>Mean ICP on each pressure level</th>
<th>Mean ICP increase from baseline pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>[mm Hg]</td>
<td>[kPa]</td>
</tr>
<tr>
<td>Level 1</td>
<td>16.6</td>
</tr>
<tr>
<td>Level 2</td>
<td>20.2</td>
</tr>
<tr>
<td>Level 3</td>
<td>23.6</td>
</tr>
<tr>
<td>Level 4</td>
<td>27.0</td>
</tr>
<tr>
<td>Level 5</td>
<td>30.2</td>
</tr>
<tr>
<td>Level 6</td>
<td>33.5</td>
</tr>
</tbody>
</table>
On the experimental model the relationship between standardized flow and pressure was linear in the entire pressure range ($R^2 = 1$, $n=5\times6\times6$). Apart from possible leakage at the incision point of the needles, this was a verification that the deviation from linearity seen at the higher pressure levels in the patient investigations was likely to be physiological, and not due to an error in the measurement system.

Thus, this study implied that the relationship between ICP and CSF outflow was linear in the region of normal and slightly increased ICP, that is, $R_{\text{out}}$ was independent of ICP in this region. This was in accordance with Ekstedt who concluded a linear relationship between ICP and CFS outflow from visual inspection,25,26 and Børgesen et al and Sklar et. al. who concluded a linear relationship from a high correlation between the parameters.8,53

When the pressure increment from resting pressure was larger, the relationship had a non-linear tendency. This indicates that the CSF outflow from the subarachnoid space was facilitated, i.e. a lower $R_{\text{out}}$ at higher levels of ICP. A decrease in $R_{\text{out}}$ was also seen by Davson et. al. for ICP larger than approximately 22 mm Hg when performing an infusion study on rabbit.17

Thus, the model of the CSF system incorporating a pressure independent $R_{\text{out}}$ was supported in the physiological ICP range where the CSF system is commonly operating. However, in the region where ICP exceeds resting pressure too much, the classical textbook theory of a pressure independent outflow resistance might have to be questioned.

10.7 Comparison of infusion methods

Several different methods can be used to estimate $C_{\text{out}}$ of the CSF system. The methods may be divided into three main categories; constant pressure infusion,1,25 constant flow infusion13,32,33 and bolus infusion40,41. When discussing and interpreting results, the outcome from the different methods are often mixed, even though the cut off levels for the methods are not
Figure 24: $C_{out}$ for each pipe as measured by the four different methods a) when no physiological pressure fluctuations were present and b) when physiological pressure fluctuations were present. The error bars show SEM (n=6). For the first three pipes, ICP did not reach a pressure plateau during constant flow infusion.
necessarily the same and proper control studies for each method are not available. Thus, it is important to compare these methods in both experimental and clinical settings.

In Figure 24a and b $C_{\text{out}}$ from the four methods evaluated in study V are shown (constant pressure infusion ($C_{\text{out \ cp}}$), constant flow infusion with dynamical analysis ($C_{\text{out \ dyn}}$), constant flow infusion with static analysis ($C_{\text{out \ stat}}$) and bolus infusion ($C_{\text{out bol}}$)). The results are separated for each pipe, without and with the addition of physiological pressure fluctuations respectively.

The general agreement between the methods was good. However, with fluctuations (Figure 24b) $C_{\text{out bol}}$ was significantly different from all other $C_{\text{out}}$ for pipes 1 and 2, and for pipe 3 $C_{\text{out bol}}$ was significantly different from $C_{\text{out cp}}$ and $C_{\text{out dyn}}$.

In Table 3 mean $C_{\text{out}}$ as estimated by each method for all patients investigated preoperatively in study V, where successfully performed investigations and analyses were achieved from all four methods ($n=7$), are shown. There was an indication that $C_{\text{out bol}}$ was larger than $C_{\text{out}}$ as obtained by the other three methods, confirming the results from the experimental model and in concordance with previous studies, no significant differences were found though ($p=0.2$).

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{out \ cp}}$</th>
<th>$C_{\text{out \ dyn}}$</th>
<th>$C_{\text{out \ stat}}$</th>
<th>$C_{\text{out bol}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>($\mu$L/(s kPa))</td>
<td>($\mu$L/(s kPa))</td>
<td>($\mu$L/(s kPa))</td>
<td>($\mu$L/(s kPa))</td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>7.6 ± 1.6</td>
<td>8.5 ± 2.0</td>
<td>9.2 ± 1.4</td>
<td>12.3 ± 2.3</td>
</tr>
</tbody>
</table>

Figure 25 shows the individual $C_{\text{out}}$ for each of the 17 patients investigated in study V. In general, and specifically for the constant pressure infusion method, $C_{\text{out}}$ was higher for the shunted than for the non-shunted patients.
The finding that all methods had a high degree of agreement on the experimental model when no pressure fluctuations were added, and that $C_{\text{out bol}}$ was significantly higher for the pipes with the lowest $C_{\text{out}}$ when fluctuations were added, indicates that it was problems in the analyses, caused by the disturbances, which created the differences between the methods.

One difference between the bolus method and the other methods was the magnitude of the created pressure increase. For constant pressure and constant flow infusion there was always an increase of approximately 2-3 kPa for a typical patient. Both these methods also used steady state recordings of their pressure levels, and by estimating mean values the precision could be improved. For the bolus method there was a wide range of increase in pressure, from 0.5 to 4.0 kPa. However, for the bolus

![Figure 25: $C_{\text{out}}$ for each of the 17 patients in study V. For patients No. one, eight and nine ICP did not reach a pressure plateau during constant flow infusion.](image-url)
method, the crucial pressure changes were the momentarily measured pressure drops on the relaxation curve, which always were much smaller, and especially when $C_{out}$ was low. From equations (5) and (15) it can be seen how the pressure drop from $P_p$ to $P_t$ (Figure 12) was essential for determining $C_{out}$. As an example, Figure 26 shows that on the experimental model, the maximum undisturbed pressure drop (at 120 s) was as low as 0.08 kPa (0.57 mm Hg) for the first bolus on the pipe with the lowest $C_{out}$. Bearing in mind that the simulated vasogenic pressure disturbances in the experimental model create a variation of approximately $\pm 0.11$ kPa ($\pm 0.84$ mm Hg) ($\pm 2$ SD at ICP $\approx 2.1$ kPa), the signal to be estimated was small as compared with the size of the disturbances. Due to this sensitivity to the accuracy of the measured pressure for the bolus method, a too low resolution or a small systematic error might significantly affect the estimated $C_{out}$.

Figure 26: Pressure drops ($P_p - P_t$) for the seven pipes, after the first bolus infusion, without physiological pressure fluctuations. In the shaded area the size of the physiological pressure fluctuations are larger than the pressure drops.
One could also argue that the impulse response of the bolus method could be an advantage, since it is likely to induce a minimal perturbation to the CSF system. Therefore it might potentially be measuring a more physiological $C_{\text{out}}$, which could be lower than the steady state estimates.

### 10.7.1 Low resolution

Many research centres use standard monitoring equipment for ICP measurement, with a typical resolution of 1 mm Hg (0.13 kPa). Using the data from the experimental model and equations (5) and (15), we see that the minimum measurable $C_{\text{out bol}}$ with a resolution of 1 mm Hg is approximately $9.7 \, \mu L/(s \, \text{kPa})$ ($R_{\text{out}} = 12.9 \, \text{mm Hg/mL/min}$). A 2 mm Hg pressure drop would correspond to $C_{\text{out bol}} = 23.1 \, \mu L/(s \, \text{kPa})$ ($R_{\text{out}} = 5.4 \, \text{mm Hg/mL/min}$). This means that when using a monitor with a resolution of 1 mm Hg, the $R_{\text{out}}$ threshold of 18 mm Hg/mL/min suggested for the constant flow infusion test by the Dutch study is not possible to reach, since such small pressure drops are not measurable. With pressure drops larger than 2 mm Hg, $R_{\text{out}}$ will be lower than 4 mm Hg/mL/min, which is the threshold suggested for the bolus method.

A lower compliance and multiple bolus infusions would have resulted in a larger pressure increase ($P_{p-P_{\text{start}}}$) and larger pressure drops ($P_{p-P_t}$), since the relaxation generally does not reach $P_{\text{start}}$ of the previous bolus infusion in five minutes. Averaging over multiple bolus infusions would also reduce the error, but this analysis is illustrative and emphasizes the importance of a high resolution of the recording system. It also indicates that a higher bolus volume, like the 10 mL suggested by Takeuchi et. al. could improve the accuracy of the determined $C_{\text{out bol}}$.

### 10.7.2 Systematic errors

An explanation to the systematically and significantly higher $C_{\text{out}}$ found with the bolus method on the experimental model when pressure fluctuations were present, could lie in a systematic error in the visual fitting. It is likely that the operator intuitively expected a pressure drop following a typical exponential curve. This was satisfied in the region of high $C_{\text{out}}$ where there were marked pressure drops. Therefore, the differences were limited to the low $C_{\text{out}}$ region, where the pressure drops
were small as compared with the pressure fluctuations, and a tendency to create a more pronounced exponential shape than what was actually present must be suspected.

10.7.3 High $C_{out}$

When investigating shunt function by a CSF infusion test, typically a large flow in the shunt is expected if the shunt is working properly ($C_{out}$ for Strata and Codman shunts approximately 58 and 23 µL/(s kPa) respectively$^{3,36}$).

$C_{out}$ was generally higher in the shunted than in the non-shunted patients, and specifically $C_{out\,cp}$ approached the expected in vitro $C_{out}$ of the shunts. The constant pressure infusion method is designed to measure outflow on pressure levels above resting pressure, and to most patients this will also mean that outflow is measured through an open shunt. Thus, it was always the joined $C_{out}$ of the shunt and the patient that was determined by this method. The constant flow infusion method initially measures CSF outflow in the ICP region where even a properly working shunt could be closed, and in those cases $C_{out}$ would be underestimated. In most cases this will not propose a problem for determining shunt function, but it makes it more difficult to determine partial occlusion of the shunt. This exemplifies an advantage of the constant pressure infusion method, which generates a pressure/flow curve that in greater detail describes the characteristics of the system.$^{24}$

It was concluded that in the area of clinical importance (i.e. low $C_{out}$), $C_{out}$ as determined by the bolus infusion method does differ from $C_{out}$ as determined by the steady state methods. The difference was thought to be due to difficulties in correctly estimating the pressure parameters of the bolus method, since the measured signal was small compared to the pressure fluctuations.
11 Conclusions

In this thesis, methods for performing CSF infusion tests were developed and evaluated. A widely adopted mathematical model of the CSF dynamical system was also questioned, further expanded to include intracranial air and used for simulations. The primary aim was to improve diagnosis and management of patients with idiopathic normal pressure hydrocephalus.

This work has lead to improvements of the constant pressure infusion method regarding real time estimation of the reliability of individual investigations, validation of a recently clinically introduced infusion apparatus, and an adaptive assessment of $C_{out}$ with a general reduction in investigation time without a clinically relevant reduction in reliability.

The relationship between CSF outflow and ICP was investigated, and it was concluded that the classical textbook theory of a linear relationship between the parameters was supported in the normal ICP range where the CSF system is commonly operating. A significant non-linear contribution was found in the region where ICP exceeds resting pressure too much, indicating a slightly facilitated outflow in this pressure region.

This thesis has also resulted in a comparison between the three most commonly used infusion methods. A possible explanation to the enigma concerning the discrepancies generally found between the bolus infusion method and the steady state infusion methods was presented.
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