Fluid dynamic principles for analysis of intracranial pressure control

Application towards space medicine and hydrocephalus

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Umeå, Sweden, 2019
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Dissertation for PhD
ISBN: 978-91-7855-029-6
ISSN: 0346-6612
New series No. 2018
Cover art by Åsa Holmner
Printed by: UmU Print Service, Umeå University
Umeå, Sweden 2019
Inspiration is the main regulator of human CSF flow

/Steffi Dreha-Kulaczewski
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Abstract

Intracranial pressure (ICP) is an important component of the fluid dynamic environment of the brain and plays a central role with regards to the maintenance of normal cerebral blood flow and neuronal function. However, many regulatory mechanisms controlling the ICP are still poorly understood. One major gap in knowledge in this regard is the mechanism behind the postural/gravitational control of ICP. This is partly due to the fact that most ICP investigations are performed with the patients in a supine or recumbent position. Since most people spend 16 hours a day in an upright position, understanding these mechanics is highly motivated. Also spurring research on this topic is the increasing number of reports of the spaceflight-associated neuro-ocular syndrome (SANS) found in astronauts after prolonged exposure to weightlessness (i.e. microgravity), where evidence suggests that a disrupted balance between ICP and intraocular pressure (IOP) may be an underlying cause. Understanding how ICP is regulated with respect to posture could therefore provide important insight into the alterations introduced by microgravity, where postural effects are removed, and how to improve the safety of astronauts who are susceptible to this syndrome. Here on earth, disturbances in the ICP or cerebrospinal fluid (CSF) dynamics are associated with the development of chronic neurological diseases. One particular disease of interest is communicating hydrocephalus, where the cerebral ventricles are enlarged despite the absence of macroscopic CSF flow obstructions. A common finding in these patients is that of altered pulsatile flow in the CSF. The overall aim of this thesis was to utilize fluid dynamic principles to describe and validate potential regulatory mechanisms behind postural changes in ICP and causes of ventriculomegaly. The thesis is based on four scientific papers (paper I—IV).

A postural dependency of the IOP-ICP pressure difference was verified by simultaneous measurements of ICP (assessed through lumbar puncture) and IOP (measured with an Applanation Resonance Tonometer) (paper I). Based on these measurements, a 24-hour average of the IOP-ICP pressure difference at the level of the eye was estimated for the state of microgravity, predicting a reduced pressure difference in space compared with that on earth.

A hypothesis where postural changes in ICP are described by hydrostatic effects in the venous system, and where these effects are altered by the collapse of the internal jugular veins (IJVs) in more upright positions, was evaluated (paper II and III). Using ultrasound data, it was shown that the venous hydrostatic pressure gradient was balanced by viscous pressure losses in the collapsed IJVs to uphold a near atmospheric pressure at the level of the neck in the upright posture (paper II). A full evaluation of the hypothesis was then performed,
based on simultaneous assessment of ICP, central venous pressure (through a PICC-line) and venous collapse in 7 postures of upper-body tilt in healthy volunteers (paper III). The proposed description could accurately predict the general changes seen in the measured ICP for all investigated postures (mean difference: -0.03±2.7 mmHg or -4.0±360 Pa).

Pulsatile CSF flow-induced pressure differences between the ventricles and subarachnoid space were evaluated as a source for ventriculomegaly in communicating hydrocephalus (paper IV). The pressure distributions resulting from the pulsatile CSF flow were calculated using computational fluid dynamics based on MRI data. The estimated pressures revealed a net pressure difference (mean: 0.001±0.003 mmHg or 0.2±0.4 Pa, p=0.03) between the ventricles and the subarachnoid space, over the cardiac cycle, with higher pressure in the third and lateral ventricles.

In conclusion, the results of this thesis support venous hydrostatics and jugular venous collapse as key governing factors in the postural/gravitational control of ICP. Furthermore, a postural dependency of the IOP-ICP pressure difference was demonstrated, providing a potential explanation for how an imbalance between the pressure of the eye and brain can be introduced in microgravity. Computational fluid dynamic analysis revealed that the altered pulsations in communicating hydrocephalus generate a pressure gradient within the CSF system. However, the gradient was small and additional effects are probably needed to explain the ventriculomegaly in these patients.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>$\Delta P_{\text{hydro}}$</td>
<td>pressure difference due to hydrostatic effects</td>
</tr>
<tr>
<td>$\Delta P_{\text{visc}}$</td>
<td>viscous pressure losses in the internal jugular veins</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>upper body tilt-angle</td>
</tr>
<tr>
<td>$\rho$</td>
<td>fluid density</td>
</tr>
<tr>
<td>$\mu$</td>
<td>fluid viscosity</td>
</tr>
<tr>
<td>$\Delta P_{\text{net}}$</td>
<td>time-average pressure difference across the cerebral aqueduct</td>
</tr>
<tr>
<td>$A_{\text{meas}}$</td>
<td>measured cross-sectional area in the collapsed section of the jugular veins</td>
</tr>
<tr>
<td>$A_c$</td>
<td>predicted cross-sectional area of the internal jugular veins based on hydrostatic and viscous pressure balance</td>
</tr>
<tr>
<td>CA</td>
<td>cerebral aqueduct</td>
</tr>
<tr>
<td>CFD</td>
<td>computational fluid dynamics</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CVP</td>
<td>central venous pressure</td>
</tr>
<tr>
<td>FEM</td>
<td>finite element method</td>
</tr>
<tr>
<td>FIESTA-C</td>
<td>Fast imaging employing steady state acquisition cycled phases</td>
</tr>
<tr>
<td>$g$</td>
<td>gravitational acceleration</td>
</tr>
<tr>
<td>GLM</td>
<td>Generalized linear model</td>
</tr>
<tr>
<td>HDT</td>
<td>head-down tilt</td>
</tr>
<tr>
<td>HIP</td>
<td>hydrostatic indifference point</td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td>$I_{\text{form}}$</td>
<td>formation rate of cerebrospinal fluid</td>
</tr>
<tr>
<td>IIH</td>
<td>idiopathic intracranial hypertension</td>
</tr>
<tr>
<td>IJV</td>
<td>internal jugular vein</td>
</tr>
<tr>
<td>INPH</td>
<td>idiopathic normal pressure hydrocephalus</td>
</tr>
<tr>
<td>IOP</td>
<td>intraocular pressure</td>
</tr>
<tr>
<td>$k$</td>
<td>ellipse factor for the internal jugular veins</td>
</tr>
<tr>
<td>$k_{\text{dis}}$</td>
<td>discharge coefficient for pressure losses at sudden contractions/enlargements</td>
</tr>
<tr>
<td>LC</td>
<td>lamina cribrosa</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>$L_{\text{collapse}}$</td>
<td>vertical distance from the top of the internal jugular vein collapse to the auditory canal</td>
</tr>
<tr>
<td>MMSE</td>
<td>mini-mental state examination</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NTG</td>
<td>normal tension glaucoma</td>
</tr>
<tr>
<td>ONSAS</td>
<td>optic nerve subarachnoid space</td>
</tr>
<tr>
<td>PCMRI</td>
<td>phase contrast magnetic resonance imaging</td>
</tr>
<tr>
<td>PDE</td>
<td>partial differential equation</td>
</tr>
<tr>
<td>$P_{\text{dural}}$</td>
<td>dural venous sinus pressure</td>
</tr>
<tr>
<td>PICC</td>
<td>peripherally inserted central catheter</td>
</tr>
<tr>
<td>$Q$</td>
<td>flow rate</td>
</tr>
<tr>
<td>ROI</td>
<td>region of interest</td>
</tr>
<tr>
<td>$R_{\text{out}}$</td>
<td>cerebrospinal fluid outflow resistance</td>
</tr>
<tr>
<td>SANS</td>
<td>space flight-associated neuro-ocular syndrome</td>
</tr>
<tr>
<td>SV</td>
<td>stroke volume</td>
</tr>
<tr>
<td>TBI</td>
<td>traumatic brain injury</td>
</tr>
<tr>
<td>TLCPD</td>
<td>trans-lamina cribrosa pressure difference</td>
</tr>
<tr>
<td>TOST</td>
<td>two one-sided t-test</td>
</tr>
<tr>
<td>$u$</td>
<td>vector of velocity</td>
</tr>
<tr>
<td>$U_{\text{max}}$</td>
<td>maximum velocity measured by ultrasound</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
<tr>
<td>VIIP</td>
<td>visual impairment intracranial pressure</td>
</tr>
<tr>
<td>VP</td>
<td>venous pressure</td>
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Original papers

This thesis is based on the following original papers, referenced by their roman numerals when appearing in the text:


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Populärvetenskaplig sammanfattning


I denna avhandling undersöktes hur hjärntrycket regleras med avseende på kroppsposition. Detta gjordes genom att studera hjärntryck, ventryck och kollapsbara halsvener under förflyttning från en liggande till en upprätt kroppsposition. Vidare undersöktes balansen mellan ögon- och hjärntryck genom att studera dessa tryck i en liggande, sittande och nedåtlutande kroppsposition.

Slutligen tillämpades numeriska beräkningsmetoder för att studera hjärntryckets lokala variationer mer i detalj, med målet att försöka förklara sjukdomen kommunicerande hydrocefalus, där hjärnans vätsksfyllda hålrum expanderar trots avsaknaden av någon detekterbar flödesobstruktion. Resultaten av den numeriska analysen i hydrocefalus visade på tryckeffekter som är i linje med en förstoring av hålrummen i hjärnan, men dessa effekter var alldeles för små för att ensamma kunna förklara de expansiva förändringarna i dessa patienter.

Vidare visade resultaten i avhandlingen att hjärntrycket i olika kroppspositioner kan beskrivas med hjälp av fluidynamiska principer för vensystemet, inklusive halsvenernas kollaps i upprätta kroppspositioner. Detta antyder att hjärntrycket under största delen av vår vakna tid regleras av venkollaps i halsen. Denna koppling mellan venkollaps och hjärntryck öppnar upp möjligheter till nya hypoteser kring flera neurologiska sjukdomar, där avvikelser i halsvenernas
dynamik kan spela en potentiell roll i sjukdomsutvecklingen i de drabbade patienterna.

Slutligen bekräftades att balansen mellan ögontryck och hjärntryck på jorden är positionsberoende. Detta ger en potentiell förklaring till hur avsaknaden av gravitation för astronauter kan resultera i en störda tryckbalans mellan öga och hjärna. Resultaten motiverar mätningar av dessa tryck i rymden för jämförelse med det jordbundna tillståndet.
Introduction

The space within the intracranial cavity is shared by blood, cerebrospinal fluid and the brain parenchyma (i.e. brain tissue). Intracranial pressure (ICP) is the pressure within the cerebrospinal fluid and the brain tissue. ICP plays a major role with respect to cerebral blood flow by acting as a counter pressure to arterial blood pressure [1]. Disturbances in the ICP are associated with many neurological diseases, such as traumatic brain injury (TBI) [2], idiopathic intracranial hypertension [3] and hydrocephalus [4], making assessment of ICP regulation important for understanding and/or treating these disorders. However, despite its importance, many regulatory mechanisms controlling ICP are still poorly understood. One major area in this regard is the postural/gravitational control of ICP where the underlying mechanisms have not been determined. Observations have shown that ICP is not the same in the supine position as in more upright positions [5]–[7], yet ICP is still almost exclusively investigated in the supine position. This is despite the fact that most people spend a majority of their time in an erect position. Thus, understanding the (fluid dynamic) mechanisms behind the postural/gravitational ICP regulation could both fill a gap in our knowledge of basic physiology and improve our ability to diagnose and treat patients with suspected ICP disturbances.

ICP is linked to venous pressure in the dural veins of the cranium [8]–[10] and it is known that venous pressure in the upper body is affected by body posture [11]. However, postural ICP control has instead been suggested to relate to changes in the CSF, more specifically to a hydrostatic indifference point within the CSF system, located somewhere between the C6 and T5 vertebrae [12]. Thus, there is a missing link between venous dynamics and the postural control of ICP that remains to be determined. A model describing this relationship has recently been proposed [7], providing a possible way forward for explaining the postural regulation of ICP.

In recent years, the interest in the link between gravity and ICP has been spurred on by the spaceflight-associated neuro-ocular syndrome (SANS), a disease that affects the visual acuity of astronauts on extended missions in weightlessness (i.e. microgravity) [13], [14]. The symptoms and signs of SANS partly overlap with that of patients with an increased ICP on earth, suggesting that a disrupted balance between the ICP and the intraocular pressure (IOP) may be a potential cause [15]. Understanding how the balance between ICP and IOP changes with posture might provide important insight into the effects of space travel on these astronauts, as postural/gravitational effects are removed in microgravity.
On earth, disturbances in the ICP or cerebrospinal fluid (CSF) dynamics can result in the development of chronic neurological diseases. One particular disease of interest is a subclass of hydrocephalus known as communicating hydrocephalus, in which the cerebral ventricles are enlarged despite the absence of macroscopic CSF flow obstructions [4]. While the ventricular enlargement suggests a pressure gradient within the CSF system, so far, in vivo measurements have been unable to detect any abnormal pressure gradients [16], [17]. One hypothesis is that the altered pulsatility in the CSF may provide an explanation for the ventricular enlargement; experimental studies have hinted at a causal relationship between the two [18], [19]. This motivates further studies of the local fluid dynamic pressure variations related to CSF pulsatility within the CSF system.

In this thesis, fluid dynamic principles and in vivo measurements of ICP, venous pressure and venous collapse were combined to explain the regulatory mechanisms behind postural ICP control. The postural dependency of the pressure difference between eye and brain was also tested, and the results were related to the SANS. Lastly, using computational fluid dynamics, local CSF dynamics associated with altered CSF pulsatility were investigated in communicating hydrocephalus in order to increase our understanding of the development of ventriculomegaly in these patients.
Background

This chapter provides background information relevant for the work of this thesis, starting with general information on the main physiological systems involved. This is followed by background information more directly related to the specific knowledge gaps where the thesis aims to contribute. The chapter ends with descriptions of specific methods that were utilized during this work and a short chapter summary.

THE CEREBROSPINAL FLUID SYSTEM

The cerebrospinal fluid system consists of the cerebral ventricles and the subarachnoid space covering the brain and the spinal cord. The CSF itself is a water-like incompressible fluid whose purpose is to provide support for the brain as well as participating in the transport and clearance of chemical components and waste products [20]. The intracranial volume of CSF in healthy elderly has been estimated to be somewhere in the range 70-260 ml [21] with roughly 15-77 ml occupying the cerebral ventricles [22].

**CSF production**

The main production site of CSF is thought to be the choroid plexus of the cerebral ventricles, where the CSF is secreted from capillary blood [23]–[25]. The production of CSF through the choroid plexus is commonly accepted to be independent of changes in ICP during normal physiological conditions [26] but may decrease with large increases in ICP. The production rate is roughly 600 ml/day [27]. While CSF flow is mainly pulsatile, there is a small bulk flow from its production sites in the ventricles to the spinal and cranial subarachnoid spaces (Figure 1). In addition to the choroid plexus, evidence has suggested that other sources for CSF production may exist, such as a fluid exchange between the CSF and the interstitial fluid of the parenchyma [24], [28], [29].

**CSF absorption**

The CSF is generally considered to be absorbed through the arachnoid villi (arachnoid granulations) of the cranial subarachnoid space. The arachnoid villi are protrusions of the subarachnoid space that penetrate the dura mater, allowing for CSF to be reabsorbed to the venous blood of the dural venous sinuses [9], [30]. In contrast to the production of CSF, the absorption through the arachnoid villi is thought to be pressure driven, working as a one-way valve where the pressure difference between the CSF (i.e. ICP) and the dural veins drives the absorption [31], [32]. If the venous pressure increases beyond the ICP, absorption through the arachnoid villi is expected to cease. While
seemingly not as numerous, arachnoid villi also exist in the spinal subarachnoid space [33], and a recent study has suggested that up to 38% of the CSF in humans may be absorbed spina1ly [34]. Evidence has also suggested that CSF absorption may occur through drainage into the lymphatic system [24], e.g. through paraneural routes, and through fluid exchange between CSF and brain interstitial fluid [35], [36]. Furthermore, recent experimental observations suggest that paravascular pathways, together with CSF and interstitial fluid exchange, may allow for a bulk flow of fluid through the brain parenchyma, effectively flushing waste products from the brain akin to the lymphatic system for the rest of the body [37]. The final destination of this potential bulk flow has not been fully described but suggests an alternate pathway for CSF outflow.

![Image of CSF circulation](image)

**Figure 1.** The CSF circulation. Black arrows indicate bulk flow directions. The CSF circulates from the lateral (LV) and third ventricles (3rd), through the cerebral aqueduct (CA) to the fourth ventricle (4th), and from there it passes the lateral (foramina of Luschka) and median (foramen of Magendie, MA) apertures out to the subarachnoid space covering the brain and the spine. Choroid plexuses are located in all ventricles. FM: foramen of Monro.

**CSF pulsatility**

The Monro-Kellie doctrine postulates that the volume within the cranium is fixed, meaning that the constituents within (i.e. CSF, brain tissue and blood) must change in tandem to maintain intracranial volume and pressure within normal limits [38]. This means that as the arterial blood volume is cyclically changing over the cardiac cycle, the CSF and venous blood have to accommodate those changes. During systole, where arterial blood is actively pumped to the brain by the heart, CSF is pushed out of the ventricles towards the subarachnoid space, with the process being reversed during diastole. This generates a pulsatile flow in the CSF in and out of the cranium, and in and out of the ventricles [39], [40]. As a result of the intracranial volumetric changes, pulsations are also induced in the ICP. While arterial and venous pressures are
their own entities, the pressure within the CSF and brain tissue has been shown to be the same [41]. Thus, in this thesis, both CSF and brain tissue pressure will be referred to as ICP.

**Intracranial pressure**
The average level of the ICP can be expressed by the well-established Davson’s equation [8]–[10], which describes the CSF absorption to the dural venous sinuses:

\[
\text{ICP} = R_{\text{out}} \cdot I_{\text{form}} + P_{\text{dural}}
\]

In Eq. 1, \( R_{\text{out}} \) is the CSF outflow resistance, \( I_{\text{form}} \) is the formation/production rate of CSF and \( P_{\text{dural}} \) is the pressure in the dural veins. Eq. 1 describes the equilibrium ICP, as the absorption rate of CSF is then assumed to be the same as the rate of formation/production. Davson’s equation highlights the link between venous pressure and ICP, and postulates that a change in venous pressure should lead to a corresponding change in ICP under normal physiological conditions, assuming a constant outflow resistance and formation of CSF. This equation has been verified in the supine position [42] but has not been validated in upright body postures. Although ICP is affected by changes in posture [5]–[7], ICP has almost exclusively been investigated in the supine or recumbent position, where the pressure is roughly 10 mmHg [43], [44].

**THE CRANIAL VENOUS DRAINAGE**
The cerebral veins of the brain drain into the dural venous sinuses that transport the blood out of the cranium [45]. The dural venous sinuses are venous channels that are enclosed and supported by the dura mater [45], and are therefore thought to be fairly rigid structures. The dural sinuses drain into the veins of the neck, among them the internal jugular veins (IJVs) (Figure 2). These extra-cranial veins commonly receive most of the blood from the brain in horizontal positions [46], [47], although individual variations can occur [48]. As these veins leave the cranium, they are no longer attached to the dura mater, and may collapse if the internal pressure decreases towards the surrounding atmospheric pressure [47], [49]. When the IJVs collapse, their venous blood is partly redistributed to other, parallel pathways, such as the vertebral venous plexus and the epidural veins [46]–[49]. The IJVs drain into the brachiocephalic veins, which empty into the superior vena cava, which returns the blood to the right atrium of the heart. The reference for pressure within the venous system is the central venous pressure (CVP) of the right atrium.
COLLAPSIBLE VESSELS

There is a substantial body of work done on collapsible vessels and tubes, and their behaviour in different situations. In a collapsible tube, the shape and the resistance to flow are adjusted based on the balance between the internal and surrounding (external) pressure, i.e. the transmural pressure. The behaviour of a collapsible tube can be described by the relationship between the transmural pressure and the tube cross-sectional area \([50]\). This behaviour can be modelled by 1-D models often referenced as “tube laws” \([51]\), \([52]\). The tube law depends on parameters such as the wall thickness of the tube and the resting cross-sectional area.

A typical transmural pressure-cross-sectional area curve describes the different phases of a thin-walled collapsible tube (Figure 3). For high transmural pressures the tube is in an elastic phase, where the tube is cylindrical and the walls are stretched by the positive transmural pressure. The cross-sectional area increases slowly for increasing transmural pressures in this phase. For low transmural pressures, the tube buckles and may demonstrate highly complex non-linear behaviour \([50]\), \([53]\), \([54]\). Eventually the shape of the tube changes to a state where it is partly compressed, for strongly negative pressure differences. The phase in between provides a region of high distensibility. This is a highly compliant phase (also complex in its behaviour) where the cross-sectional area is easily adjustable so that only small changes in transmural
pressure are required for large changes in area (or volume) [50], [55]. Based on the pressure-area curve, a collapsed vessel is not necessarily a fully occluded vessel, but one that is no longer inflated by a positive transmural pressure.

**Figure 3.** A schematic sketch of the transmural pressure-area curve of a thin-walled collapsible tube. \( P_{\text{int}} \) is the internal pressure of the tube and \( P_{\text{ext}} \) is the external, surrounding pressure.

**POSTURAL INTRACRANIAL PRESSURE CONTROL**

The ICP in an adult is roughly 10 mmHg in the supine position [43], [44] and drops to around zero when moving to an upright position [5]–[7]. This decrease follows a two-phase behaviour, where ICP drops much faster for small angles of upper-body tilt and is followed by a more gradual reduction for higher tilt-angles [6], [7], [56]. Reversely, the ICP increases with increasing head-down tilt (HDT) in a similar way as the fast decline for small positive tilt-angles [6]. However, even though it has been observed how ICP changes with posture, the underlying mechanisms controlling these changes have not been determined.

A commonly accepted/suggested description of the postural regulation of ICP is the one presented by Magnaes, which is based on a hydrostatic indifference point (HIP) within the CSF system, located somewhere between the C6 and T5 vertebrae [12]. A HIP is a point within a system where pressure does not change regardless of the orientation of the system [57]. The location of the HIP for the CSF should theoretically be determined by the compliance of the CSF system. However, due to the two-phase nature of the postural changes in ICP, it may not be possible to fully describe the postural ICP behaviour by a single indifference
point [7]. Therefore, an alternative hypothesis was recently presented where the postural changes in ICP are explained by the interaction between ICP and venous dynamics through Davson’s equation (Eq. 1) [7]. Assuming that Davson’s equation is valid regardless of body position, Eq. 1 suggests that the mechanisms regulating the dural venous pressure $P_{\text{dural}}$ to a large extent should also control the changes in ICP.

**Venous dynamics**

While direct measurements of dural venous pressure in adults are limited [58], venous pressure is known to decrease in the upper body when we stand up [11], with observations suggesting a venous hydrostatic indifference point located slightly below the heart (at the bottom of the sternum) [59]. This decrease is due to hydrostatic effects generated by gravity as it acts on the column of the venous blood in upright positions. For horizontal positions and positions of low upper-body tilt, the central venous pressure (CVP) is the pressure reference for the venous system and the cranial venous pressure [60]. However, as pressure in the head and neck decreases, the pressure within the collapsible veins of the neck, i.e. the IJVs, will decrease toward surrounding atmospheric pressure, leading to collapse of these veins [47], [61]. The collapse of the IJVs alters the pressure in the neck, maintaining it at near-atmospheric levels in the upright posture [60], [62], effectively interrupting the hydrostatic pressure continuity along the venous column. This should mean that the collapsed IJVs provide a new reference point for the cranial venous pressure, resulting in a $P_{\text{dural}}$ in upright that is not as negative as a hydrostatic column to the heart would predict (Figure 4).

![Figure 4](image-url)

**Figure 4.** A suggested description of the dural venous pressure alterations with posture. In supine the CVP is the pressure reference for $P_{\text{dural}}$ while the near-zero IJV pressure in the collapsed IJVs becomes the new pressure reference in the upright posture. $\rho g h_{\text{collapse}}$ is the pressure difference due to the hydrostatic column from the top of the collapsed IJVs. $\rho$ is the fluid density, $g$ is the gravitational acceleration, and $h_{\text{collapse}}$ is the height. IJVP: IJV pressure.
Postural model for ICP
By combining Davson’s equation with the hydrostatic effects in the venous system and the collapse of the IJVs in upright postures, an expression for ICP in different postures can be derived [7]. The idea behind this model is that hydrostatics of the venous system can explain the faster decline in ICP at low upper-body tilt, while the altered venous pressure due to IJV collapse can explain the phase of more gradually declining ICP. The feasibility of this suggested model has been tested [7] but the model remains to be validated by simultaneous direct measurements of the principle components: ICP, venous pressure and IJV collapse.

Upholding the new pressure reference
As mentioned, the pressure in the collapsed IJVs in the upright human is near atmospheric at neck level [60], [62]. However, the fluid dynamic justification for the upholding of this pressure has not been fully described. More recent studies of the IJVs have shown that these vessels do not appear to occlude entirely in the upright posture [46], [63], meaning that fluid communication is preserved. Thus, the pressure has to be upheld despite the IJVs being partly open.

Bench-model experiments have shown that a vertically placed collapsible tube self-adjusts its cross-sectional area based on the flow through it, so that the transmural pressure along the collapsible segment of the tube is near-zero [64]–[66], i.e. close to the vertical zero line in Figure 3. With a constant surrounding pressure outside the tube, this requires that the internal pressure is constant along the tube despite the hydrostatic gradient. This means that the hydrostatic gradient must be balanced by the other internal pressure components. Such a pressure balance could thus provide a possible explanation for the near-zero pressure in the human IJVs, and by extension the ICP, in the upright posture, and motivates investigations of the mechanism in humans.

SPACEFLIGHT-ASSOCIATED NEURO-OCULAR SYNDROME

The disorder
The spaceflight-associated neuro-ocular syndrome (SANS) is a syndrome affecting astronauts on long-duration space missions in microgravity [13], [14]. The main symptom for the astronauts susceptible to the syndrome is a loss of visual acuity, and retrospective analyses of questionnaires suggest that up to 60% of astronauts on long-duration spaceflights may be affected [67]. Signs of SANS discovered upon return to earth include choroidal folds, globe flattening and papilledema [15], and recently also slightly enlarged cerebral ventricles.
Given that the symptoms occur within 6 months of spaceflight, and that the symptoms seem to persist after return to earth [14], SANS is considered one of the major obstacles to deep space missions, including travels to Mars, which will take years to complete including the trip back to earth. If astronauts have their vision impaired, they may not be able to perform their tasks or guarantee their own safety.

The syndrome was previously referred to as the visual impairment intracranial pressure syndrome (VIIP) [13] due to the fact that the symptoms and signs partially overlap with those of idiopathic intracranial hypertension (IIH) [15], [69], an earth-bound disease where ICP is abnormally increased [3]. Specifically, the symptoms of globe flattening and papilledema may suggest an increased pressure at the posterior part of the eye without a compensatory increase in the IOP [70]. The expected ICP increase in microgravity has been suggested to be caused by the fluid shift towards the head that follows with the removal of gravity [71], [72]. As of yet, no direct ICP measurements have been performed while in orbit, making the balance between ICP and IOP in microgravity unknown, although post-flight measurements (through lumbar puncture) may hint at a slightly elevated ICP [15]. Furthermore, to understand how the removal of gravity alters the pressure balance between IOP and ICP, the effects that gravity imposes on this pressure difference on earth must first be determined.

**Intraocular pressure**

The intraocular pressure (IOP) is the pressure within the eye. It is maintained by the formation and reabsorption of aqueous humour, a water-like fluid, which fills the anterior and posterior chambers of the eye. It is the dynamics of the aqueous humour that determines the pressure and volume of the intraocular fluid [73]. The aqueous humour is formed from arterial blood in the ciliary processes. After passing through the canal of Schlemm in the sclera (the white outer protective layer of the eye), the aqueous humour is reabsorbed into the episcleral veins. The IOP helps support the spherical shape of the eye.

The IOP can be measured using applanation tonometry techniques. The applanation methods are based on the Imbert-Fick law [74], which states that the pressure within a spherical object will exert a force that is in equilibrium with the force applied upon it. To measure IOP, a flat surface (e.g. a small rod) is lightly pressed against the spherical surface of the cornea of the eye and the IOP is calculated based on the force applied and the surface area of contact. The IOP is normally around 15 mmHg [75]. As is the case for the ICP, the IOP is affected by changes in posture, but the changes in between the supine and upright
postures are generally only a few mmHg [76]. The IOP is most commonly measured in the sitting posture.

**The pressure difference between eye and brain**
The subarachnoid space of the CSF extends to the posterior part of the eye via the optic nerves [77] (Figure 5). This optic nerve subarachnoid space (ONSAS) fills the space in between the optic nerve and the optic nerve sheath and terminates as the optic nerve head reaches the eye [78]. The dividing line between the intraocular space of the eye and the ONSAS is the lamina cribrosa (LC) (Figure 5), a membrane that is a continuation of the inner layer of the sclera, through which the optic nerve fibres can exit the eye [79]. The LC thus provides a point of fluid dynamic contact between the CSF and the eye. The pressure difference across the LC, or the trans-lamina cribrosa pressure difference (TLCPD), is believed to be the difference between the IOP and the pressure of the ONSAS.

![Figure 5. A simplified schematic sketch of the lamina cribrosa separating the eye from the CSF-filled optic nerve subarachnoid space (ONSAS).](image-url)
The TLCPD is very interesting from a biomechanical perspective. Disturbances in this pressure difference have been hypothesized to relate to several diseases that affect the eye, e.g. glaucoma, IIH and the aforementioned SANS [70]. However, a neglected aspect of TLCPD research is the postural/gravitational component, something that has not been previously explored and may be crucial for understanding these diseases. The TLCPD has previously been estimated, but often the IOP and ICP have been assessed in different body postures [80]–[82]. The studies that have investigated both pressures in the same body posture have not investigated the effect of changing body posture on the TLCPD [83], [84]. By simultaneous assessment of IOP and ICP in different body postures, the postural/gravitational dependency of the TLCPD can be investigated.

**COMMUNICATING HYdroCEPHALUS**

**The disorder**

Hydrocephalus in adults is a disorder in which the cerebral ventricles are enlarged [4]. Hydrocephalus can be either communicating or non-communicating. The non-communicating hydrocephalus involves an obstruction of the CSF outflow from the ventricles, explaining the ventriculomegaly. The most common location of such CSF obstructions is in the cerebral aqueduct (CA) [85], the thin canal that connects the cerebral ventricles to the subarachnoid space [86] (Figure 1). In communicating hydrocephalus however, the ventricles are enlarged despite the lack of CSF outflow obstructions between the ventricles and the subarachnoid space. Studies have suggested that in up to 84% of adults treated for hydrocephalus, no apparent flow obstruction is visible on radiology [87].

The largest subgroup of communicating hydrocephalus is idiopathic normal pressure hydrocephalus (INPH) [87], in which the ICP is normal. It was first described in the 1960’s by Hakim and Adams [88], [89]. The patients present with gait and balance disturbances together with mild dementia and/or urinary incontinence [90]. The prevalence is roughly 1.3% amongst elderly (>65) [91]. The condition is treated by neuro-surgically implanting a cerebrospinal fluid shunt that drains excess CSF from the ventricles to another body cavity [92], [93], making INPH one of very few conditions with a reversible dementia. However, predicting the response to treatment is not straightforward [94], and a large percentage of INPH research focuses on predictive tests to identify shunt responders. The diagnostics are also complicated due to comorbidities of INPH [95], such as Parkinson’s disease, and the fact that many symptoms are shared among different types of dementias. The enigma of INPH has long eluded scientists and remains unresolved today.
The ventriculomegaly in hydrocephalus is thought to be due to an active distension of the ventricles [4] as opposed to atrophy, which occurs in other dementias such as Alzheimer’s disease [96]. Such distension would require a pressure gradient between the ventricles and the subarachnoid space surrounding the brain (i.e. a transmantle pressure gradient). So far, in vivo pressure measurements have been unable to detect any static pressure gradient in communicating hydrocephalus [16], [17]. As opposed to a static pressure gradient, it has been suggested that altered pulsations within the cranium could potentially play a role in the cause of the ventriculomegaly [18], [97], [98], something that has been supported by experimental animal studies, which hint at a causal link between the pulsations and ventricular enlargement [18], [25]. So far, these hypotheses have not been fully verified.

**Pressure differences across the cerebral aqueduct**

Altered CSF pulsations in communicating hydrocephalus are often detected through flow measurements in the CA. The CA is the smallest canal of the CSF system and is the location of the largest pressure gradients and the highest flow velocities [99], [100]. This makes the CA a region of high interest even in the case of communicating hydrocephalus. If pulsation-related detrimental pressure gradients between the ventricles and the subarachnoid space do occur in communicating hydrocephalus, the CA is a likely location where such gradients could be detected.

There is an abrupt change in geometry going into the CA from the third and fourth ventricles (see Figure 1) where flow velocity changes rapidly. Fluid flow through sudden contractions and/or enlargements introduces discharge effects that lead to non-reversible losses of pressure. Such effects can be described by the Borda-Carnot relation [101], [102]:

\[
\Delta P = k_{dis} \left( \frac{\rho U^2}{2} \right) = k_{dis} \left( \frac{8 \rho Q^2}{\pi^2 D^2} \right)
\]

where \( k_{dis} \) is a discharge coefficient dependent on the flow geometry, \( \rho \) the fluid density, \( D \) is the diameter of the constriction, \( U \) is the mean velocity, and \( Q \) is the flow rate. Eq. 2 reveals that this type of pressure loss is non-linearly dependent on the flow rate. Thus, even if the net flow is zero, an asymmetric pulsatile flow (with higher maximum flow in one direction compared with the other) could yield non-zero net pressure differences across a rapidly changing geometry. This is unlike regular Poiseuille losses, which are linearly dependent on flow rate and do not contribute any net pressure effects if net flow is zero. As the flow in the CA is asymmetric [40], with higher maximum outflow from the ventricles during systole compared with the slower more gradual inflow (Figure
6), particular combinations of pulsatile flows and CA geometries could potentially introduce pressure gradients within the ventricular system that generate a net pressure difference over time. This may provide a fluid dynamic explanation for how the altered pulsations in communicating hydrocephalus could lead to ventriculomegaly.

![Figure 6. CA flow curve in INPH patients. Data from Qvarlander et al. [40]. The curve represents an average of 16 INPH patients. Note the higher (positive) outflow from the ventricles.](image)

The fact that in vivo measurements have not been able to detect any pressure gradients between the ventricles and the subarachnoid space suggest that if any gradient does exist it is likely small in magnitude. Furthermore, due to the sensitive location and small size of the CA (only 1-2 mm in diameter in healthy adults [86]), local pressure distributions may not be feasible to assess by in vivo measurements. An alternative for studying pressure variations within the CSF system on a small scale is computational fluid dynamics (CFD). Such computations require high-resolution imaging modalities for correctly representing the CSF system before calculations of the pressure distributions can be performed.
IMAGING TECHNIQUES

**Magnetic resonance imaging**

Magnetic resonance imaging (MRI) is an imaging modality useful for imaging structures within the human body. It is based on the interaction between magnetic fields and nuclear spin \([103]\), the latter being a quantum property of all elementary particles. Due to the spin property, nuclei placed in a stationary magnetic field start to precess (or move) around the direction of the magnetic field. By utilizing radiofrequency pulses that match the precession frequency, the nuclei can be excited and upon relaxation they emit their own energy pulses that can be detected and presented in the form of an image. By contrasting the relaxation of nuclei in different tissues, MRI can generate structural images of the human body, in which different tissues can be delineated, such as white and grey matter and the CSF spaces \([104]\). Different settings and scanning protocols are suitable for highlighting different types of tissues.

Velocity measurements can also be performed using MRI by detecting moving nuclei (and thus tissues). One specific method developed for this purpose is phase contrast MRI (PCMRI) \([105]\). PCMRI utilizes the fact that within a spatially varying magnetic field, moving nuclei (or tissues) experience a different magnetic field than stationary nuclei (or tissues). This difference in magnetic fields leads to a difference in the precession frequency of the nuclei, and over time a difference in phase. This difference in phase can be used to separate moving tissues from stationary tissues. PCMRI is most often performed in a 2D slice through a region of interest (2D-PCMRI), which provides velocity information of tissues moving in the direction through the plane. 2D-PCMRI is commonly used for measurements of cerebral blood flow in arteries and veins or CSF flow through the CA. To correctly represent the phase differences, and to avoid aliasing of the signal, a maximum detectable velocity must be chosen for PCMRI measurements. This is called the velocity encoding (or VENC).

**Ultrasound**

Ultrasound makes use of high frequency sound waves (roughly 2-15 MHz) to image interior organs and tissues. The ultrasound signal is sent into the human body and echoes return from reflections at interfaces between tissues of different acoustic impedance \([106]\), for example between blood and vessel walls. The reflected echoes can be detected, and depending on the time between the emitted and reflected pulse the distance to the objects and organs within the body can be determined. Ultrasound can be used to detect structures such as blood vessels. Ultrasound is most commonly performed using Brightness mode.
(B-mode) imaging, where a cross-section through the body is observed over time.

Ultrasound can also be used for visualizing and measuring blood flow velocities [107]. Ultrasound velocity measurements make use of the Doppler effect. For blood flow velocity measurements, the ultrasound pulses are echoed from red blood cells travelling in the flowing blood, and the resulting Doppler frequency shifts between the emitted and received pulses relate to the direction and velocity of the blood flow [107]. For determining the location of the velocities detected, pulsed wave ultrasound is utilized, in which several pulses are sent out in succession, and the time of flight can determine the distance to the point of reflection.

**COMPUTATIONAL FLUID DYNAMICS**

Computational fluid dynamics (CFD) describes computational methods that are used for numerically solving fluid dynamic problems [108]. CFD handles fluid flow problems by solving the governing equations of fluid motion, which are the mass, momentum and energy conservation laws, known collectively as the Navier Stokes system of equations. CFD is commonly applied to systems or setups where the behaviours of unknown variables are too difficult to assess through measurement and/or too chaotic to solve analytically. There are many different ways that CFD simulations can be performed, and the one used in this thesis is the finite element method (FEM). The finite element method is a numerical method used for approximating solutions to partial differential equations (PDEs). This method is advantageous to use for problems of complicated geometries and can be used to solve a variety of physics problems including those of fluid flow [108]. There are several steps involved in solving physics problems using the FEM.

Firstly, the problem needs to be well defined. The unknown variables of interest, the type of physics involved (i.e. the PDEs), and whether the simulations are to model transient (i.e. time-resolved) or stationary behaviour all need to be determined before simulations can ensue. In the case of the CSF, the transient Navier Stokes equations are to be solved for the CSF velocity and pressure distributions. Since the CSF is an incompressible Newtonian fluid, the Navier Stokes equations for the CSF system take on the form:

\[
\rho \frac{\partial \mathbf{u}}{\partial t} + \rho (\mathbf{u} \cdot \nabla) \mathbf{u} - \nabla \cdot [\rho I + \mu (\nabla \mathbf{u} + (\nabla \mathbf{u})^T)] = 0
\]

\[
\nabla \cdot \mathbf{u} = 0
\]

(3)
where $\mathbf{u}$ and $P$ represent the CSF velocity and pressure to be solved for. $\rho$ is the fluid density and $\mu$ is the viscosity of the fluid. These two equations describe the conservation laws for momentum and mass, respectively.

Secondly, the problem needs to be modelled, which includes recreating the geometry, applying the PDEs to the geometry, choosing the right materials and material properties (such as density and viscosity in the case of a fluid) and applying appropriate boundary conditions to the model. Boundary conditions normally come in the form of Dirichlet, Neumann or the more general Robin conditions [108]. Dirichlet conditions set a variable to a specific value at a boundary, while Neumann conditions set values for variable derivatives, and Robin conditions are a combination of the two.

Thirdly, the FEM needs to discretize the problem domain into small, simple elements called finite elements (hence the name), resulting in what is called a computational mesh (Figure 7), where the solution to the problem is approximated at each node of the mesh. The PDE problem then defines equations for each node in the mesh that can be solved and put together to approximate the real solution over the entire domain [109].

After these three steps, the computations can be performed, and the results can be post-processed. The distributions of the variables of interest, e.g. the CSF velocity and pressure, as well as geometric and mesh related parameters, can be displayed at each point within the problem geometry (Figure 8). Since errors are always present to some degree, it is important to validate the simulation results against measurement data when possible. In addition, optimizing the model complexity, the input data and the computational mesh (i.e. increasing the number of elements) are other ways of minimizing errors, although it comes at the expense of an increased computational cost.

![Figure 7](image-url) A computational mesh for performing CFD using the finite element method.
Figure 8. An example of visualization of the velocity distribution (colour streamlines) through a model of pipe flow through a constriction.
SUMMARY

Research of SANS/VIIP has highlighted clear knowledge gaps in basic physiology relating to postural/gravitational control of systems within the human body. Motivated by this area of research, this thesis tries to fill the gap in knowledge regarding the postural/gravitational control of intracranial pressure on earth as well as the relationship between posture and the pressure balance between the eye and brain. This thesis also aims to further our understanding of the local CSF pressure distributions in communicating hydrocephalus with the hope of moving closer to the answer to the unexplained ventriculomegaly in these patients.
Aims

The overall aim of this thesis was to apply fluid dynamic principles to describe and evaluate regulatory mechanisms behind postural/gravitational ICP control in healthy volunteers, as well as the unexplained ventriculomegaly in communicating hydrocephalus. The specific aims for each original paper were:

I. To simultaneously assess the changes in IOP and ICP when going from the supine to upright and head-down positions in order to detect any postural/gravitational dependency of the pressure difference between the eye and brain.

II. To assess if the near atmospheric internal pressure in the collapsed human internal jugular veins can be explained by a balance of viscous and hydrostatic pressure gradients in the upright posture.

III. To simultaneously measure ICP, venous pressure and IJV collapse to validate the fluid dynamic model where postural changes in ICP are predicted by venous hydrostatics and jugular collapse.

IV. To assess whether the pulsatile CSF flow across the cerebral aqueduct can generate a pressure difference between the cerebral ventricles and the subarachnoid space, in order to explain the development of ventriculomegaly in communicating hydrocephalus.
Materials and Methods

SUBJECTS
The study participants consisted of healthy volunteers (I-III) and patients investigated for communicating hydrocephalus (IV).

The healthy volunteers (I-III) were recruited through an advertisement in a local newspaper. For inclusion, the criteria were: 30-60 years of age, normal blood pressure (<140/90 mmHg) and no past or present neurological, cardiovascular or psychiatric diseases. Volunteers were excluded if they were on any medication affecting the cardiovascular system or the central nervous system. The selection process for papers I-III is described in Figure 9.

The study of paper IV included thirty-two patients referred to the Department of Neurology at Umeå University for investigation of communicating hydrocephalus during the time period from October 2016 to May 2017. For the patients to be investigated, they had to have enlarged cerebral ventricles (Evan’s ratio ≥ 0.3) and symptoms of normal pressure hydrocephalus (i.e. gait and balance disturbances, cognitive decline and/or urinary incontinence [90]). Two patients were excluded from the analysis: one with a CA obstruction, and one where the ICP was highly elevated (29 mmHg). Therefore, the total number of subjects included in the analysis was 30, where 15 out of these 30 were ultimately diagnosed as INPH, 9 got a different hydrocephalus diagnosis (e.g. secondary causes), and 6 were diagnosed with diseases other than hydrocephalus (mainly dementias, but still with enlarged ventricles and a communicating CA). Table 1 shows the specifics for the patients who were analysed.

Table 1. Characteristics of the patients investigated for communicating hydrocephalus of paper IV.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>30 (Total)</td>
<td>-</td>
</tr>
<tr>
<td>• INPH</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>• Communicating hydrocephalus</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>• Other</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Sex [Female/Male]</td>
<td>14/16</td>
<td>-</td>
</tr>
<tr>
<td>Age [years]</td>
<td>75±6</td>
<td>60-86</td>
</tr>
<tr>
<td>MMSE</td>
<td>24±5</td>
<td>15-30</td>
</tr>
<tr>
<td>Evans’ Index</td>
<td>0.37±0.04</td>
<td>0.31-0.47</td>
</tr>
<tr>
<td>Heart rate [bpm]</td>
<td>72±13</td>
<td>47-98</td>
</tr>
</tbody>
</table>

MMSE: mini-mental state examination.
Figure 9. Selection process for the healthy volunteers. ICP and IOP were needed for the analysis of study I. ICP, VP and US (during the pressure investigation) were needed for the analysis in study III. For study II, a separate US investigation (without pressure measurements) was performed for all N=17. US: ultrasound. VP: venous pressure.

ETHICS

The Regional Ethical Review Board in Umeå approved the studies. Approval numbers: 2014/223-31 (I-III) and 2012-396-32M (IV). All participants gave their informed, written consent and the studies adhered to the declaration of Helsinki.
MODELLING

The trans-lamina cribrosa pressure difference
The TLCPD is defined as the difference between the pressure of the eye just anterior of the LC and the pressure of the ONSAS just posterior of the LC, i.e. IOP\textsubscript{LC} - ICP\textsubscript{LC}. Therefore, in paper I, the measurements of ICP and IOP were hydrostatically corrected to the LC for accurately assessing the TLCPD. The TLCPD in microgravity was simulated by using the uncorrected pressures in the supine position, i.e. IOP-ICP, since hydrostatic effects are removed in the state of microgravity. The simulated TLCPD was compared with an estimated 24-hour average TLCPD on earth, based on 8 hours in the supine position (sleep) and 16 hours in an upright posture (awake).

Pressure balance in the collapsed IJVs
In paper II we investigated if the finding of an approximately atmospheric pressure in the collapsed IJVs in the upright posture can be explained by a balance of the internal pressure gradients within these veins. For collapsible vessels inclined to some angle, the internal pressure gradients are that of hydrostatic effects and viscous pressure losses, the latter occurring through flow resistance. If internal pressure is to remain close to atmospheric pressure along the collapsed but non-occluded IJVs, these two components must be balanced (Figure 10).

The hydrostatic pressure difference between two points within a fluid column is

$$\Delta P_{\text{hydro}} = \rho gh = \rho g L \sin \alpha$$  \hspace{1cm} (4)

where \(h\) is the height of the fluid column between the points of interest, \(\alpha\) the tilt-angle of the column, \(g\) is the gravitational acceleration, \(L\) is the total distance between the points of interest, and \(\rho\) is the fluid density. The viscous losses within a tube-like vessel can be described by the Poiseuille equation

$$\Delta P_{\text{visc}} = R Q = k \frac{8 \pi \mu L}{A^2} Q$$  \hspace{1cm} (5)

where \(R\) is the resistance of the vessel, \(Q\) is the flow rate through it, \(A\) is the vessel cross-sectional area and \(\mu\) is the viscosity of the fluid. In Eq. 5, the Poiseuille equation was slightly modified by adding the parameter \(k = (a^2 + b^2)/2ab\) (here referred to as the ellipse factor) that describes the shape of the vessel as a function of the semi-minor \((a)\) and semi-major \((b)\) axes of the vein [64]. This was done to account for the more elliptical shape of the collapsed IJVs in the upright posture (Figure 3).
Figure 10. A near zero transmural pressure along the collapsed IJVs requires the gradients of pressure to balance. The viscous and hydrostatic pressure gradients are opposite in direction.

Setting Eq. 4 = Eq. 5 and solving for $A$, the expression for the area predicted by viscous and hydrostatic pressure balance ($A_c$) becomes:

$$A_c = \frac{4\pi \mu k U_{\text{max}}}{\rho g \sin \alpha}$$  \hspace{1cm} (6)

where we have assumed a parabolic flow profile (i.e. $Q=AU_{\text{max}}/2$). To calculate $A_c$, the tilt-angle $\alpha$, the ellipse factor $k$ and the velocity $U_{\text{max}}$ have to be measured. By calculating $A_c$ and comparing it to measurements of the cross-sectional area in the collapsed IJVs ($A_{\text{meas}}$) the hypothesis for pressure balance in the IJVs was tested (paper II).

**Model for postural ICP control**

In paper III, Davson's equation (Eq. 1) and the postural effects on venous pressure were used to derive a set of equations describing the postural changes in ICP (slightly modified from Qvarlander et. al [7]). By definition, the hydrostatic reference level for $P_{\text{dural}}$ is the same as that of ICP in Eq. 1. In paper III, this reference point was the auditory canal. Assuming that $R_{\text{out}}I_{\text{form}}$ is constant [26], [42], [110] and that the venous pressure in the dural veins of the cranium in the supine position is the same as the CVP (Figure 4), $R_{\text{out}}I_{\text{form}}$ of Eq. 1 can simply be expressed as $\text{ICP}_{\text{supine}} - \text{CVP}_{\text{supine}}$. $P_{\text{dural}}$ can, in turn, be described by the CVP minus a hydrostatic distance corresponding to the height between the reference points for CVP and $P_{\text{dural}}$. ICP for a communicating non-collapsed venous system then reads as:
ICP = ICP_{supine} - \rho \cdot g \cdot (h_{ICP} - h_{CVP}) + CVP-CVP_{supine} \quad \alpha < \alpha_{collapse} (7)

where \( \rho \) is the density of blood (1060 kg/m^3), and \( \alpha_{collapse} \) is the tilt-angle at which venous collapse occurs (i.e. when venous pressure at the level of the IJVs has reached zero), since the IJVs are then no longer inflated by a positive internal pressure. The \( h_{ICP} - h_{CVP} \) is the vertical distance between the reference points of CVP and ICP. The CVP is included in Eq. 7 to account for changes in this variable during the measurement procedure.

Due to the expected decoupling of the hydrostatic column that occurs when venous pressure in the neck reaches ambient pressure and the IJVs go from inflated to collapsed [60], [62], the \( P_{dural} \) should no longer be described by changes in CVP but should instead be controlled by the effective hydrostatic column from the top of the collapse to the reference point for ICP (assuming a zero ambient pressure around the neck). ICP for a venous system with collapsed IJVs can then be described as:

\[
ICP = ICP_{supine} - CVP_{supine} - \rho \cdot g \cdot L_{collapse} \cdot \sin \alpha \\
\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ quad
Figure 11. Tilting protocols for the different studies. A: For the studies including pressure measurements (I & III), the tilting procedure consisted of a 15-min baseline measurement in the supine position followed by the tilting procedure where the subjects were tilted from supine to a sitting position in 5 steps (8°, 16°, 24°, 32° and 40°) spending 5 min at each tilt level, then the subjects were positioned in the sitting position (69°), a second supine position, and finally a position of 9° head-down tilt (for approx. 7 min each). B: For the measurements of study II, the patients were investigated in the supine position, a half-sitting position (16°) and the sitting position (71°). The coloured lines indicate in which body positions the different measurements were performed. ICP and IOP were needed for the analysis of study I. ICP, VP and US were needed for the analysis in study III. For study II, a separate US investigation was required (and did not include pressure measurements). The ultrasound investigations of study II included blood flow velocity measurements as opposed to the investigations of study III. US: ultrasound. VP: venous pressure.

Pressure measurements
ICP was assessed through lumbar puncture in papers I and III. A needle was inserted into the lumbar space (at L3-L4) through a hole in the backrest of the investigation bed, and the needle was connected to a CELDA® infusion measurement apparatus (Likvor AB, Umeå, Sweden) for the pressure recording using standard tubing and pressure sensor equipment. No infusion measurements were performed, only pressure measurements. The auditory canal was used as the reference level for ICP, and the sensor’s zero-level was placed at the level of the auditory canal in the supine position. The ICP was monitored continuously throughout the entire tilting process. Lumbar puncture is a less invasive alternative to direct intracranial pressure measurements, and the approach has been shown to agree with that of intra-parenchymal pressure measurements [41]. Furthermore, the pressure change going from supine to upright has been shown to be very similar regardless if assessed by lumbar puncture [7] or by intracranial sensors [5], [6], [111].
In paper I, the IOP was assessed using an Applanation Resonance Tonometer (ART; BioResonator Good Eye, Umeå, Sweden) utilizing the applanation principle. This sensor is specifically constructed to be independent of gravity and could thus be used in any body posture [112], [113]. Eye drops in the form of lidocaine hydrochloride 4% and fluorescein sodium 0.25% (Chauvin Pharmaceuticals, Kingston-Upon-Thames, UK) were applied before each measurement as aesthetic. This was the reason for the inclusion of a second supine position as repeated anaesthetics and applanation of the eye has been shown to reduce IOP [114] and a second reference measurement before HDT was thus motivated. An average of 6 measurements (3 per eye) per body position was used as the measure of the IOP.

In paper III, the CVP was monitored using a peripherally inserted central catheter (PICC) line (PowerPICC SOLO catheter, 4Fr. single-lumen, BARD Access Systems, Inc., Salt Lake City, UT, USA), which is clinical standard for CVP measurements at Umeå University Hospital. The PICC-line was inserted in the right median cubital (basilic) vein and was positioned in the right atrium (verified by a chest X-ray). A pressure sensor (PMSET 1DT-XX 1 Safedraw-P, Argon Critical Care Systems, Singapore) was connected to the PICC-line allowing for continuous reading of the CVP. The zero-level for the pressure sensor was the same as that of the ICP sensor. The reference level for the CVP measurements was chosen as the xiphisternal joint and at half the chest depth. All pressures were allowed to stabilize for 3 min at each posture, and the following 2 min were used for the pressure analysis (excluding the supine baseline measurement, where the stabilization period was longer). Hydrostatic distances from the level of the pressure sensors to the reference point for each pressure were measured in each posture using a laser sight mounted on a vertical rod, to correct for hydrostatic effects. The distances to the IJVs were also measured to assess when venous pressure had reached zero in these veins (also see the ultrasound section below). The IJVs were classified as inflated for positive IJV pressures and classified as collapsed once IJV pressure had reached zero.

**Ultrasound**

In papers II and III, the IJV cross-sectional area was measured by ultrasound using B-mode. The IJVs were measured at three different neck levels along a continuous segment of the veins, in order to more easily capture the collapse. These levels, from top to bottom, were referenced as the cranial, intermediate and caudal neck levels. As the top of the collapse was expected to be at the top of the neck, the cranial neck level was used as reference for the distance $L_{\text{collapse}}$ in Eq. 8 for the analysis of paper III, and the same level was also used as the
reference level for the IJV pressure. The ultrasound measurements were performed on both sides of the neck, yielding two IJVs per subject.

The measured cross-sectional area was assessed by manually drawing a region of interest (ROI) around the veins in the B-mode images (Figure 12 A). The average of the absolute maximum and minimum area for each ultrasound movie (i.e. image sequence) was used to represent the IJV area for each measurement. To ensure that the area represented the collapsed segment of the IJVs, the smallest area of the three IJV levels was used as $A_{\text{meas}}$ for each IJV. An ICC analysis for the inter-rater variability of the area measurements showed excellent agreement between raters ($r = 0.996$, with CI = $[0.963-0.999]$, N=20, $p<0.001$, for two-way random effects, absolute agreement and single rater/measurement).

For paper II, the ellipse factor $k$ and the IJV blood flow velocity $U_{\text{max}}$ also had to be assessed. The semi-major and semi-minor axes of the IJVs were acquired from the B-mode images to calculate the ellipse factor (Figure 12 B) and the IJV velocity was assessed using angle-corrected pulsed-wave ultrasound (Figure 13). The velocity was measured in the middle of the veins to closest represent $U_{\text{max}}$ within the veins. After the cross-sectional area was assessed at all three levels on one side of the neck, the velocity measurements directly followed before switching to the other side. This procedure was performed for each body position (tilt-angle). No flow was found in one of the IJVs, and since fluid continuity was necessary for the analysis of paper II, that IJV was excluded from the analysis (resulting in 33 IJVs from N=17 subjects). All ultrasound measurements were performed with a GE Vivid Eq ultrasound system with a 9L linear probe (4-8 MHz) (General Electric Healthcare, Chicago, IL, USA).

Figure 12. A: An example of the segmentation of the cross-sectional area of the IJVs acquired by ultrasound in paper II and III. B: An example of the semi-major and semi-minor axes used for calculating the ellipse factor $k$ in paper II.
Figure 13. An example of the velocity measurements within the IJVs performed by pulsed-wave ultrasound in paper II. The dashed blue line (red arrow) in the bottom of the figure represents the manual tracing of the velocity curve. In the top of the figure, the crossing between the green lines and the dotted yellow line marks the location of the velocity measurement in the IJV.

MAGNETIC RESONANCE IMAGING

Hydrostatic distances to the lamina cribrosa
In paper I, the distances between the auditory canal (reference point for ICP) and the LC, and the distance between the cornea and the LC, were measured to adjust for hydrostatic effects when relating the measured IOP and ICP to the LC. These distances were assessed from standard sagittal T2-weighted MRI images acquired with a 3T scanner (GE Discovery MR750; General Electric Healthcare, Waukesha, WI), and were combined with the tilt-angle to adjust the pressures for each investigated posture using basic trigonometry.

Aqueduct data acquisition
In paper IV, CFD simulations were used to calculate the pressure difference across the CA over the cardiac cycle in communicating hydrocephalus. The structural geometry of the ventricular system and the flow through the CA were required for use as input to the simulations, and this information was acquired through MRI. The structural data for the ventricular system was acquired by a Fast Imaging Employing Steady-state Acquisition Cycled Phases (FIESTA-C) sequence. This T2-weighted sequence provides excellent contrast between fluid-filled spaces and surrounding tissues [115], [116], which is needed to accurately capture the small CA. The repetition time/echo time was 6.5/2.5 ms and the flip angle was 55°. The spatial in-plane resolution was 0.39 mm x 0.39 mm, with a slice thickness of 0.6 mm. The slices were interpolated, resulting in a final resolution of 0.39 mm x 0.39 mm x 0.30 mm.
The velocity data were acquired by 2D-PCMRI with a plane positioned through the centre of the CA (Figure 14 A-B). The velocity encoding was 20 cm/s, and the spatial in-plane resolution was 0.35 mm x 0.35 mm, with slice thickness 4.0 mm. The repetition time/echo time was 8.8/4.6 ms, with 3 signal averages, and a flip angle of 6°. Retrospective electrocardiography gating was applied using a peripheral pulse detector, and data was reconstructed for 32 time frames over the cardiac cycle. Analyses of the PCMRI measurements were performed using Segment (version 2.1 R5960, http://segment.heiberg.se) [117] where a ROI was drawn around the cross-section of the aqueduct in the magnitude images. The average velocity magnitude of the pixels within the ROI was multiplied by the cross-sectional area to get the measured flow rate for each cardiac time frame. An ICC analysis was performed for the PCMRI measurements based on aqueductal pulsatility, here described by the volume of CSF passing the CA per cardiac cycle, i.e. the aqueductal stroke volume (SV). The ICC showed excellent inter-rater agreement ($r = 0.996$, with CI = [0.963-0.999], N=15, p<0.001, for two-way random effects, absolute agreement and single rater/measurement).

**COMPUTATIONAL FLUID DYNAMICS OF THE CSF**

All CFD simulations for paper IV were performed with COMSOL Multiphysics (COMSOL Multiphysics®, version 5.3a, www.comsol.com, COMSOL AB, Stockholm, Sweden). The Navier Stokes equations (Eq. 3) were solved for the velocity and pressure for each individual ventricular system using the high-resolution MRI data as input. The structural MRI data provided the geometrical shapes and the 2D-PCMRI data provided the flow rate. The density was set to $\rho=1000$ kg/m$^3$ and the dynamic viscosity to $\mu=0.9\cdot10^{-3}$ Pa·s [118] and laminar flow physics was applied. Transient (i.e. time-resolved) simulations were performed, where three cardiac cycles were calculated and the last one was used for the analysis. The time step used was 0.001 s. The simulations were run on an iMac (2.93 GHz Intel Core i7), with each simulation taking roughly 48 hours.

**Aqueduct geometry segmentation**

The structural MRI data was segmented from the FIESTA data. This was done in Synopsys’ Simpleware™ software (Version M-2017.06; Synopsys Inc., Mountain View, USA). The ventricular system was segmented manually and was then converted into a computational mesh, where the flow inlet and outlet boundaries were defined (Figure 14 C-D). Before mesh conversion, smoothing was applied to the segmentations where a built-in mask statistics function was used to ensure that the volume of the CA remained the same before and after smoothing. Finally, the constructed meshes were imported into the CFD software. The meshes were imported as volumes so that the mesh could be refined in the CFD software.
**Figure 14.** Illustration of the MRI flow measurements and mesh generation. A: The FIESTA acquired structural MRI data with indication for the PCMRI plane position (red line). B: The PCMRI (velocity) image in the plane across the aqueduct (CA marked by red arrow). C: Segmentation of the ventricular system (red). D: the constructed computational mesh with the defined flow boundaries (red arrows).

**Boundary conditions**
The foramen of Monro was set as an outflow boundary while the inlet was placed in the fourth ventricle above the foramina of Luschka and Magendie (Figure 14 D). The foramen of Monro was modelled as an open boundary, i.e. no normal stress at the boundary. The flow rates acquired from the PCMRI measurements in the CA were applied at the inlet in the fourth ventricle. The net flow was removed to only look at the contributions from the pulsations. All other boundaries were set to no-slip and the walls of the ventricles and CA were modelled as rigid. The finalised computational meshes of the ventricular system consisted of roughly 1 million elements and a minimum element quality of 0.1 ± 0.04 for the group.
**Post-processing**

The net pressure difference from the pulsations ($\Delta P_{\text{net}}$) was calculated as the time-average of the pressure difference $\Delta P$ across the CA over the cardiac cycle. The $\Delta P$ was defined as the pressure difference between the foramen of Monro and the fourth ventricle, i.e. the inlet and outlet of the geometry. The local pressures at the inlet and outlet boundaries were calculated as the spatial average for each point in time. The $\Delta P_{\text{net}}$ is the pressure difference corresponding to the transmantle pressure gradient.

**STATISTICS**

All statistics were calculated using MATLAB (version R2012b and version R2017b, The Mathworks, Natick, MA). Values are presented as mean±SD unless otherwise specified. A test was considered significant for $p<0.05$ throughout all studies.

In **paper I**, the comparisons of IOP, ICP and the TLCPD between postures were tested by two-tailed Student’s paired samples t-tests. The same test was used for the comparisons between measured and predicted ICP in **paper III**. The correlation between ICP in the supine and sitting positions in **paper I** was investigated using Pearson’s correlation coefficient.

For **paper II**, an equivalence test was used for comparing the measured ($A_{\text{meas}}$) and predicted ($A_c$) collapsed IJV cross-sectional area in the sitting position. The equivalence test consisted of the two one-sided t-tests (TOST) procedure [119], with equivalence limits of ±5 mm$^2$ and one test performed for each limit. The equivalence limit was based on the assumption of a measurement inaccuracy and physiological variability of 25 % in the measurement parameters.

In **paper IV**, a one-sample t-test was utilized to test for the occurrence of a non-zero $\Delta P_{\text{net}}$ across the cerebral aqueduct. Furthermore, a generalized linear model (GLM) analysis was performed to verify potential associations between $\Delta P_{\text{net}}$ and the different geometrical and flow rate characteristics of the cerebral aqueduct. $\Delta P_{\text{net}}$ was set as the dependent variable while CA cross-sectional area, SV and flow asymmetry were applied as random continuous predictor variables. The flow asymmetry was defined as the ratio of maximum outflow and maximum inflow through the CA ($Q_{O/I}$).
Results

PRESSURE DIFFERENCE BETWEEN EYE AND BRAIN

Table 2 shows the measured ICP and IOP for the healthy subjects of paper I. Both the ICP and IOP decreased when moving the subjects from the supine to the sitting position (p<0.001, N=11). Reversely, both pressures increased going from the (second) supine to the HDT position (IOP: p=0.003, N=11, ICP: p<0.001, N=7). No significant correlation was found between ICP in the sitting and supine posture (p=0.54). The ICP was more sensitive to changes in posture than the IOP, resulting in a strong postural dependence of the IOP-ICP pressure difference (supine to sitting: p<0.001, second supine to HDT: p=0.005) and the TLCPD (supine to sitting: p<0.001, second supine to HDT: p=0.002) presented in Table 3. Based on this data, the 24-hour time-average TLCPD was estimated to be 17.3 mmHg on earth and 6.8 mmHg in microgravity, assuming 16 hours in an upright position and 8 hours in the supine position on earth, corresponding to a difference of roughly 10 mmHg between the two gravity conditions.

Table 2. ICP and IOP for different postures from paper I (N=11).

<table>
<thead>
<tr>
<th>Posture</th>
<th>ICP [mmHg±SD]</th>
<th>IOP [mmHg±SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>10.5±1.5</td>
<td>17.2±1.8</td>
</tr>
<tr>
<td>Sitting</td>
<td>-0.8±3.8</td>
<td>14.5±2.3</td>
</tr>
<tr>
<td>Second supine</td>
<td>11.5±0.8†</td>
<td>16.0±1.9</td>
</tr>
<tr>
<td>9° HDT</td>
<td>15.8±1.3††</td>
<td>17.5±2.0</td>
</tr>
</tbody>
</table>

† N=8. †† N=7. The exclusions for ICP in the second supine and HDT positions were due to loss of CSF contact during the ICP monitoring in 3 and 4 subjects for the respective position.

Table 3. IOP-ICP and TLCPD for different postures from paper I (N=11).

<table>
<thead>
<tr>
<th>Posture</th>
<th>IOP-ICP [mmHg±SD]</th>
<th>TLCPD [mmHg±SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>6.8±2.3</td>
<td>12.3±2.2</td>
</tr>
<tr>
<td>Sitting</td>
<td>15.2±4.5</td>
<td>19.8±4.6</td>
</tr>
<tr>
<td>Second supine</td>
<td>4.0±1.8</td>
<td>9.4±1.9</td>
</tr>
<tr>
<td>9° HDT</td>
<td>1.6±2.5</td>
<td>6.6±2.5</td>
</tr>
</tbody>
</table>

† N=8. †† N=7.
POSTURAL CONTROL MECHANISMS OF ICP

For the ultrasound investigation of paper II, the measured IJV cross-sectional area is shown in Figure 15. Data for each of the parameters from the ultrasound measurements are shown in Table 4. The comparison between the measured collapse area \(A_{\text{meas}}\) and the predicted area required for viscous-hydrostatic pressure balance \(A_c\) based on Eq. 6 is presented in Figure 16. In the sitting position, the \(A_{\text{meas}}\) (6.5±5.1 mm\(^2\)) and \(A_c\) (8.7±5.2 mm\(^2\)) were found to be equivalent within the limits of ±5 mm\(^2\) (TOST: \(p=0.03, N=17, \text{number of IJVs}=33\)) with a median difference of -1.8 mm\(^2\). In addition, no statistically significant difference was found between \(A_{\text{meas}}\) and \(A_c\) \((p=0.14)\).

![Figure 15](image_url)

**Figure 15.** The measured IJV area for the healthy subjects in paper II in the supine, half-sitting, and sitting positions \((N=17, \text{Number of IJVs}=33)\). The values correspond to the area measured at the level of smallest area in the sitting posture. Markers indicate the group mean and the error bars the standard error of the mean.

**Table 4.** The ellipse factor \(k\), the blood flow velocity \(U_{\text{max}}\), the IJV area, and the estimated flow rate \(Q\) for the measurements of paper II \((N=17, \text{Number of IJVs}=33)\).

<table>
<thead>
<tr>
<th>Posture</th>
<th>IJV area [mm(^2)]</th>
<th>(k)</th>
<th>(U_{\text{max}}) [cm/s]</th>
<th>(Q) [ml/min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>94.5±53.3</td>
<td>1.2±0.3</td>
<td>18±19</td>
<td>429±298</td>
</tr>
<tr>
<td>Half-sitting</td>
<td>40.1±33.8</td>
<td>1.6±0.7</td>
<td>38±34</td>
<td>379±466</td>
</tr>
<tr>
<td>Sitting</td>
<td>6.5±5.1</td>
<td>2.1±1.0</td>
<td>89±39</td>
<td>165±129</td>
</tr>
</tbody>
</table>
The results for the validation of the full ICP model described by Eq. 7-8 (paper III) are presented in Figure 17, Figure 18 and Table 5. Figure 17 and Table 5 present the predicted vs. measured ICP on individual and group level, respectively. In seven of the eleven subjects, the measured and predicted ICP were in excellent agreement for all body positions (mean difference: -0.01±1.0 mmHg), see No. 1—7 in Figure 17. For two individual subjects, the ICP was underestimated after predicted IJV collapse (No. 8 & 9, Figure 17) and for the remaining two the ICP was instead overestimated (No. 10 & 11, Figure 17). The agreement between measured and predicted ICP on group level was excellent for all investigated body positions (Table 5).

The angle where collapse was predicted (based on an IJV pressure ≤0) agreed with the point of change between the faster and slower ICP decline (see the vertical dashed lines of Figure 17). The $A_{\text{meas}}$ of the IJVs also showed a two-phase behaviour similar to that of the ICP (Figure 18). With few exceptions, the IJVs classified as collapsed were smaller than those classified as inflated (based on IJV pressure) (Figure 18).

---

Figure 17. Predicted and measured ICP for each individual subject in paper III. Measured ICP (circles), predicted ICP (solid lines and triangles), and the tilt-angle where the IJVs were first estimated to be collapsed (i.e. IJV pressure was first ≤0) (dashed lines) are presented. The dotted lines for subjects 10-11 represent predicted ICP based on the top of the IJV collapse being located at the level of $A_{m}$ (which corresponded to the caudal neck level in these subjects) as opposed to the uppermost IJV neck level.

---

Table 5. Measured and predicted ICP (mean±SD) for the different tilt-angles of paper III (N=11).

<table>
<thead>
<tr>
<th>Tilt-angle [°]</th>
<th>Measured ICP [mmHg]</th>
<th>Predicted ICP [mmHg]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.4±1.5</td>
<td>10.4±1.5†</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>6.1±1.7</td>
<td>6.2±1.7</td>
<td>0.78</td>
</tr>
<tr>
<td>16</td>
<td>4.2±1.5</td>
<td>4.1±2.3</td>
<td>0.92</td>
</tr>
<tr>
<td>24</td>
<td>3.0±1.9</td>
<td>3.1±2.3</td>
<td>0.94</td>
</tr>
<tr>
<td>32</td>
<td>1.7±2.3</td>
<td>2.1±2.4</td>
<td>0.65</td>
</tr>
<tr>
<td>40</td>
<td>1.5±2.4</td>
<td>1.2±2.4</td>
<td>0.79</td>
</tr>
<tr>
<td>69</td>
<td>-0.9±3.5</td>
<td>-1.0±2.6</td>
<td>0.94</td>
</tr>
</tbody>
</table>

† Supine: The predicted and measured ICP are equal by definition.

Figure 18. The $A_{meas}$ in paper III. For each tilt-angle, each subject was grouped according to IJVs with pressure >0 or pressure ≤0, classified as inflated and collapsed respectively. The boxplots represent the first and third quartiles of the data and the bold midline represents the median. The whiskers correspond to the maximum and minimum values and the open circles are outliers.

PRESSURE DIFFERENCE OVER THE CEREBRAL AQUEDUCT

Figure 19 plots the calculated $\Delta P_{net}$ due to CSF pulsations in the patients investigated for communicating hydrocephalus in paper IV. The pulsations generated a non-zero pressure difference $\Delta P_{net}$ across the CA of 0.2±0.4 Pa ($p=0.03$), with higher pressure in the third ventricle (positive pressure difference). The range of $\Delta P_{net}$ was 1.4 to -0.4 Pa, and the magnitude was positive in two thirds of the subjects. The maximum systolic pressure difference across the CA was $\Delta P_{max}=20.3\pm11.8$ Pa. The results of the GLM analysis verified CA cross-sectional area and maximum flow asymmetry as significantly associated with $\Delta P_{net}$ ($p=0.01$ and $p=0.04$, respectively) while aqueductal SV was not ($p=0.35$). An example simulation is presented in Figure 20. PCMRI and FIESTA data for the group are presented in Table 6. There were 4/30 subjects that had a retrograde net flow (i.e. flow into the ventricles) through the CA.

![Figure 19](image-url)

*Figure 19.* The $\Delta P_{net}$ versus CA cross-sectional area for the group investigated for communicating hydrocephalus in paper IV.
Figure 20. The pressure and velocity distributions for a typical subject in paper IV. Upper: A sagittal slice of the pressure distribution for the point in time of largest pressure difference. The change in pressure occurs almost entirely over the CA, with only small changes in the third and fourth ventricle. Lower: Velocity streamlines during maximum outflow. The highest velocities were observed in the CA.
Table 6. Results of the PC-MRI and FIESTA measurements in the CA.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SD (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV [µl]</td>
<td>80±51</td>
</tr>
<tr>
<td>Cross-sectional area [mm²]</td>
<td>5.6±3.2</td>
</tr>
<tr>
<td>Net flow [ml/min]</td>
<td>0.74±0.71</td>
</tr>
<tr>
<td>Max flow-min flow [ml/min]</td>
<td>37.5±21.3</td>
</tr>
<tr>
<td>Maximum flow ratio (Qo/I)</td>
<td>1.32±0.28</td>
</tr>
<tr>
<td>Net flow direction [+/−] †</td>
<td>26/4</td>
</tr>
</tbody>
</table>

† Positive sign indicates flow out from the ventricles and negative sign indicates retrograde flow.
Discussion

This thesis presents observations that support the hypothesis that venous hydrostatics and venous collapse are key governing factors in the postural/gravitational control of ICP. Furthermore, a postural dependency of the IOP-ICP pressure difference was demonstrated. Computational fluid dynamic analysis revealed that the pulsations in communicating hydrocephalus generate a pressure gradient within the CSF system. In this chapter, the physiological importance of these findings is discussed, and the findings are related to previous studies. This is followed by the clinical relevance of the findings, relating to pathophysiology, diagnosis and treatment of diseases with suspected ICP disturbances. The chapter ends with thoughts on future research where remaining knowledge gaps are highlighted.

INTRACRANIAL PRESSURE CONTROL AND POSTURE

Pressure balance in the internal jugular vein
The results of paper II provide evidence that the viscous pressure gradient is comparable to the hydrostatic pressure gradient in the collapsed IJVs in upright humans (Figure 16). This pressure balance explains how the IJV pressure along the neck can be maintained close to the surrounding atmospheric pressure without requiring a total venous occlusion. The results thus unite previous findings that the IJVs are small but generally open in the upright posture [46], [63], [120] with the near atmospheric pressures measured at neck level in this position [60], [62], [121].

The results of paper II suggest that the surrounding tissue pressure in the neck determines the IJV pressure and thus the pressure reference for \( P_{\text{dural}} \) in the upright posture. The reason for this is that the driving force behind the internal pressure balance in the IJVs is a zero transmural pressure. Inter-individual variations in the surrounding pressure could thus introduce variations in this pressure reference between different individuals. This is supported by the fact that the surrounding pressure may vary between slightly negative and positive values [122], [123], which agrees with the IJV pressures measured internally [60], [62], [121].

It is worth noting that not all previous studies have indicated that the IJVs are open in the upright posture [47], [62]. This opens the possibility that the IJV collapse behaviour is heterogeneous, where the IJVs may be open in some subjects and occluded in others. However, the results of paper II, as well as several other IJV flow investigations [46], [63], [120], [124], support the notion
that most IJVs are likely open. In addition, forced occlusion of the IJVs (through applying the Queckenstedt manoeuvre [125]) has been shown to increase the cranial venous pressure in the upright posture [126], further supporting a potent flow in the IJVs in this position.

The data in Table 4 visualizes how the IJVs drastically decreased in size from nearly 100 mm$^2$ in the supine position, to 6.5 mm$^2$ in the sitting posture. Furthermore, the ellipse factors visualize how the IJVs were more elliptic in their shape in the sitting posture compared with the supine position. The estimated IJV flow rates in the sitting posture were comparable with that of previous measurements by MRI [46] and ultrasound [61], [63], [120], [124], supporting the assumption of a parabolic velocity profile.

**Venous collapse predicts postural changes in intracranial pressure**

The close agreement between the predicted and measured ICP in paper III revealed a strong link between postural ICP behaviour and venous dynamics. Not only did the inclusion of venous collapse predict the general behaviour of ICP for all upper-body tilt-angles (Table 5), but it also predicted the tilt-angle of the transition between the faster and slower phases of the ICP decrease with posture (see the vertical lines in Figure 17). The collapse is imperative for capturing this transition, as an open system would instead result in a predicted ICP close to -15 to -20 mmHg in the upright posture. The simultaneous ultrasound measurements verified that the IJV cross-sectional area also reflected this two-phase behaviour (Figure 18), which further substantiates the hypothesis. The observed changes in ICP in the healthy subjects of paper III (Table 5) were similar to that measured in previous postural ICP investigations, both those utilizing intracranially placed sensors [5], [6], [56], [111], [127] as well as lumbar puncture [7]. This similarity includes both the magnitude of the drop in ICP when going from supine to upright, as well as the two-phase behaviour of the changes in ICP.

In the description for ICP in paper III, only the pathway through the IJVs is in focus, regardless of the flow distribution through other potentially non-collapsible venous pathways. The rationale behind this is that the IJVs and the extra-jugular pathways form a parallel flow system between the dural veins and the heart, akin to a parallel electrical circuit (Figure 21). Regardless of the path taken along this parallel system, the cranial venous pressure and the CVP must be the same. The consequence of the IJVs being non-occluded is that the venous system retains fluid continuity through the IJVs in the upright posture. Thus, understanding the pressure regulation in the route through the IJVs should be enough to predict the dural venous pressure $P_{dural}$ (and by extension the ICP). If
the IJVs had been totally occluded the $P_{dural}$ would instead be determined by other venous outflow pathways (e.g. the vertebral veins [46]).

![Diagram of venous system and its relation to ICP](image)

**Figure 21.** Parallel circuit analogue of the venous system and its relation to ICP (through Davson’s equation for CSF absorption). Regardless of the route taken, $P_{dural}$ must be the same.

The results of papers II and III suggest that ICP in upright body positions is regulated through a passive mechanical process, i.e. the IJV collapse. This means that pressures interacting with the ICP, such as the arterial blood pressure driving blood flow through the brain, should actively change in tandem with the postural changes in ICP if homeostasis is to be maintained. A recent study utilizing simultaneous ICP and arterial blood pressure measurements have indicated that the cerebral perfusion pressure (i.e. the arterial blood pressure-ICP), referenced to the midbrain, can be maintained in the upright posture in the absence of ICP disturbances [6].

Written in the form of Eq. 1, Davson’s equation only describes absorption to the dural sinuses of the cranium, which is the classically referenced absorption route for the CSF [10]. However, as mentioned on page 4, CSF absorption likely also occurs through other routes, e.g. to the lymphatic system [24], [128] and by active fluid exchange [35], [36]. While the exact distribution of CSF through these different absorption routes has not been determined, our interpretation of the results of paper III is that regardless of where the CSF leaves the system, its underlying pressure reference is that of venous pressure.

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The subject-specific results show us that there were deviations in a few subjects in paper III (Figure 17). This could potentially be explained by variability in the extent of the collapse not accounted for by our assumption that the collapse occurs along the entire neck. This is supported by the dotted lines for subjects No. 10 & 11 in Figure 17, which shows a clear improvement in predicted ICP when using the level of smallest measured IJV area as the estimated top of the collapse (instead of using the uppermost neck level). Reversely, the underestimation of ICP in subjects No. 8 & 9 hint at a collapse that extends above the neck (i.e. intracranially). This warrants further investigations of the normal physiological variability of this variable. However, the near point-by-point agreement in subjects No. 1—7 does suggest that the top of the collapse is commonly located near the top of the neck.

GRAVITY AND THE PRESSURE DIFFERENCE BETWEEN EYE AND BRAIN

Paper I established a postural dependency of the IOP-ICP pressure difference, which remained when hydrostatically adjusting the pressures to the LC to calculate the TLCPD (Table 3). The small changes in IOP with posture were similar to those reported previously [76], [129]. The major contributions of paper I compared with previous assessments of the relationship between IOP and ICP were that both pressures were measured simultaneously in both a horizontal and an upright position, and that the pressures were also referenced to the lamina cribrosa. In previous studies, IOP and ICP have most often been assessed in different positions [70], [81], [130], which makes it difficult to compare estimations of the IOP-ICP pressure difference between studies. Overall, it is the addition of an upright ICP measurement that has been missing previously. The one study that measured both pressures in the upright posture was that of Morgan et al. [83] where nine neurosurgical patients were investigated (supine measurements were not included). This resulted in a mean IOP-ICP pressure difference of 10.7 mmHg in this posture, which is lower than the 15.2 mmHg found in the healthy subjects of paper I (Table 3). This may suggest that the IOP-ICP pressure difference varies between different groups of subjects. For estimation of the TLCPD, the previous studies did not hydrostatically correct the pressures to the level of the eye [70], [81], [130]. It may be worth noting that the TLCPD and the IOP-ICP pressure difference were not the same in any position investigated in paper I (Table 3), emphasizing the importance of hydrostatic effects for the TLCPD (even in horizontal body positions).

Both the IOP and ICP are modelled/defined by similar processes of fluid formation, outflow resistance, and fluid absorption to the venous system. Yet, ICP is more sensitive to postural changes than the IOP, although both pressures
are affected by changes in posture (Table 2). This suggests that the IOP and ICP do not share the same underlying pressure reference for all body positions. While collapse of the IJVs provide an explanation for the postural regulation of ICP (papers II and III), the eye appears to have additional mechanisms that prevent the IOP from falling too far below the supine value. Understanding these mechanisms is crucial for understanding the postural regulation of the IOP and how it differs from that of the ICP. A difference in the venous pressure of the absorption sites, i.e. the dural and episcleral veins, may contribute to these deviations.

The 24-hour average TLCPD in microgravity was estimated to be reduced compared with the TLCPD on earth. The original hypothesis for SANS was a decreased TLCPD through an elevated ICP in microgravity [13]. The postural dependency of the TLCPD revealed in paper I thus provides a possible physiological explanation for how microgravity can introduce a disturbance in this pressure difference, as the estimated TLCPD in microgravity is analogous to that of an increased ICP on earth. It is interesting to note that this reduction in TLCPD is not reliant on an actual increase in the ICP; it is instead a direct consequence of the complete removal of the ICP-lowering effects that the upright posture provides on earth. This may explain why the astronauts experience some, but not all of the symptoms typically associated with IIH patients on earth [15], [131].

The estimated TLCPDs assume that the ICP and IOP will not change in microgravity compared with the supine position. However, studies in acute microgravity during parabolic flights have indicated that ICP and CVP decrease slightly compared with the supine value [127]. This is also supported by measurements in actual microgravity (in space), where the CVP was reduced upon entry to space [132]. Reversely, IOP has been shown to increase during parabolic flights [76], again compared with the supine value. Taken together, these changes suggest that the TLCPD may actually increase slightly in microgravity compared with the supine position. While this would alter our simulated 24-hour TLCPD in microgravity, the estimated 24-hour TLCPD on earth would still be larger than that in microgravity.

All TLCPD calculations were based on a communicating CSF space all the way to the back of the eye. While the TLCPD is difficult to directly assess in humans, experimental dog models have shown that the correlation between ICP and the pressure at the back of the eye is high as long as ICP does not decrease below 0-3 mmHg [133], [134]. If this applies to the human physiology as well, it could mean that a separate mechanism prevents the eye from being subjected to large changes in TLCPD when moving to the upright posture. One such mechanism could be an occlusion of the CSF space around the optic nerve, possibly related
to the positive intra-orbital pressure surrounding the optic nerve as it exits the eye [135], [136]. Furthermore, studies of normal tension glaucoma patients have provided evidence of compartmentation of the subarachnoid space surrounding the optic nerve, which may suggest that the pressure communication to the optic nerve can also be altered by pathology [137]. These factors may thus affect the TLCPD and warrant further research on the pressure communication to the back of the eye.

Head down tilt (HDT) is commonly used as an analogue for simulating microgravity conditions on earth [138], [139]. In paper I, the simulated 24-hour average TLCPD of 6.8 mmHg in microgravity was very similar to that of the HDT position (Table 3). Thus, pressure-wise, the results support HDT as a fitting model for microgravity on earth. Long-term bed rest studies could be an alternative analogue for studying these effects, but such a state would be very sensitive to head position, as ICP is very sensitive to hydrostatic changes for small tilt-angles of the head (Table 5). It should be noted however, that studies of long-term HDT has indicated that the initial increase in ICP that is introduced with HDT might be remedied over time, likely by a decrease in CVP [127].

**PRESSURE GRADIENT IN COMMUNICATING HYDROCEPHALUS**

The direction of the $\Delta P_{net}$ observed in paper IV supported the occurrence of a transmantle pressure gradient across the CA derived from the pulsations in communicating hydrocephalus. The GLM analysis verified that the $\Delta P_{net}$ was associated with the asymmetries in flow rate, together with CA size, supporting that the hypothesis was sound from a fluid dynamic perspective. However, the magnitude was low (0.2 Pa on average). Looking at the results for all individuals, the maximum $\Delta P_{net}$ observed was roughly 1 Pa, and only two patients reached these pressure levels (Figure 19). What these two patients had in common was that they had very small CAs. This may suggest that only small CAs or CAs with partial obstructions, or narrowings, yield a $\Delta P_{net}$ of noteworthy magnitude. While the size of the transmantle pressure gradient needed for the ventricles to expand is not known, comparing 0.2 Pa to the several hundreds of Pa introduced in the ICP over each cardiac cycle [140] implies that it is unlikely that the effect size observed would contribute significantly to the ventriculomegaly in these patients.

The magnitude of the $\Delta P_{net}$ and $\Delta P_{max}$ were in agreement with that found in previous CFD case studies of communicating hydrocephalus [100], [141]. However, when comparing the results to that computed in a group of healthy volunteers [142], the magnitudes appeared to be roughly a factor 10 higher in
the hydrocephalic patients, which may suggest that there is a difference between these two groups, even though the magnitude is still small.

The results in paper IV neither confirm nor fully debunk the theory that altered CSF pulsatility may contribute to the ventricular enlargement in communicating hydrocephalus. However, the small magnitude of $\Delta P_{net}$ does indicate that any pronounced effect from the altered pulsations on the ventricles is likely acting through other mechanisms than a flow-related pressure difference over the CA. Still, as the patients were not investigated longitudinally in paper IV, we can only speculate on what the effects this small pressure difference may have on the ventricular system over time. The pulsatility in communicating hydrocephalus is a dynamically changing variable over time, as evident by changes in aqueductal SV, which has been shown to vary over the timeframe of several months after symptom onset [143]. Thus, the maximum observed pressure difference of $\sim 1$ Pa at least opens for the possibility that the $\Delta P_{net}$ may be larger during an early stage of the disease, and that the enlargement of the ventricles and CA subsequently compensate for these effects. To test this idea, $\Delta P_{net}$ for different stages of the disease would have to be determined.

CLINICAL IMPLICATIONS

Gravity’s importance in diseases of the eye

The estimated reduction in the TLCPD in microgravity suggests that the ICP pushes at the back of the eye, which is in agreement with the observed globe flattening and papilledema in space [15]. Experimental animal studies have shown that even small changes (a few mmHg) in the TLCPD can cause movement of the optic disc [144] and larger pressure changes may cause detrimental strains to the lamina cribrosa and neural tissue [145]. This means that the estimated 24h difference of roughly 10 mmHg could potentially explain the loss of vision acuity observed in the astronauts. To reach a conclusion regarding this hypothesis, measurements on-board the international space station are likely needed. Finally, it is important to note that not all signs and symptoms of SANS comply with the hypothesis of an altered TLCPD [14], [15], suggesting that other mechanisms may be involved.

The absence of a correlation between upright and supine ICP observed in paper I motivates studies of ICP in the upright posture in diseases with suspected TLCPD disturbances. This includes IIH, the disease on earth that most resembles SANS. Since it is logical to assume that the ocular changes in IIH are due to the increased ICP, the changes in ICP with posture is of special interest in this group of patients. In IIH it would be expected that the ICP is larger than
that of healthy subjects for all body postures, but so far, this postural behaviour has not been investigated. Another interesting TLCPD-related disease is that of normal tension glaucoma (NTG). In contrast to other types of glaucoma, NTG patients do not have an elevated IOP [146], [147]. Instead, a low ICP has been suggested as a potential cause of NTG, with some evidence providing support for this hypothesis [80], [82], [148]. These studies are based on measurements of ICP in the supine position and have not included the effects of postural changes. Very recently, one study did compare the postural behaviour in ICP between healthy volunteers and NTG patients, suggesting that postural ICP behaviour can be normal in NTG patients [149].

**Impairment in the intracranial pressure regulation**

As suggested by the results of papers II and III, venous dynamics, and specifically venous collapse, are related to the postural changes in ICP and may thus play a role in the pathophysiology of diseases with suspected disturbances in ICP. For example, a stiffening of the venous walls could result in an inhibition of the collapse, which may result in drastically lower pressures inside the dural veins of the cranium in the upright posture. Conversely, if the surrounding pressure is increased, e.g. due to edema or alterations of the surrounding tissue, it could lead to an increased cranial venous pressure and ICP in this posture. Thus, the results in papers I, II and III motivate investigations of both venous collapse as well as ICP behaviour in the upright posture in patient groups such as IIH INPH, and NTG. Progress has already been made on the front of ICP with regards to the latter [149] but data remain sparse. A connection between dural sinus stenoses and IIH has previously been observed [150]–[153], further supporting the importance of studying postural venous pressure changes in this patient group. For IIH and hydrocephalus, specifically, ICP measurements are performed routinely and an upright ICP measurement could be added to the measurement protocols. Studying upright ICP and venous dynamics may also provide important knowledge useful for improving the design of cerebrospinal fluid shunts, used for treatment in IIH and INPH, as over drainage is a common complication in the upright posture [154]–[156].

ICP control is crucial for traumatic brain injury (TBI) management, where the head of the bed is often raised to lower ICP [157], [158]. However, the optimal choice of tilt-angle is debated [2], [159]–[161]. Understanding the relation between ICP and venous collapse may provide some insight into the optimal choice of upper body positioning in TBI patients, as the transition between the faster and slower ICP decline could potentially be predicted by venous collapse. Based on the results in the healthy volunteers presented here (Figure 17 & 18) a tilt-angle >20 deg may be sufficient to transition into the phase of slower ICP-decline in most cases, i.e. to achieve most of the potential postural ICP decrease.
Communicating hydrocephalus

The most common choice of treatment for communicating hydrocephalus is a ventriculo-peritoneal shunt [4], [162]. Not all patients respond to this treatment however, and identifying responders is one of the main challenges in communicating hydrocephalus research (INPH patients specifically) [94]. Alternative treatments have been suggested and tested, such as third ventriculostomy, where the floor of the third ventricle is opened to allow for CSF to leave the ventricles through an alternative pathway than the CA [163], [164]. Regardless of treatment chosen, the small magnitude of $\Delta P_{net}$ observed in paper IV (Figure 19) indicates that any treatment approach based on simply bypassing the CA would most likely prove ineffective in symptomatic hydrocephalus, from the perspective of a flow-related pressure difference.

An alternative hypothesis to explain the ventriculomegaly in communicating hydrocephalus is that of a retrograde CA net flow, i.e. a net flow into the ventricles. Several PCMRI investigations of flow in the CA have supported this hypothesis, as a reversal of net flow has been found in INPH patients compared with healthy subjects [165]–[167]. This theory could not be substantiated by the study in paper IV, where only 4/30 subjects (3/15 INPH) had a retrograde net flow, and the group mean was caudally directed (Table 6), despite an MRI resolution that is far above the average [168]. A recent study by Spijkerman et al. [169] showed that net flow CA measurements can be confounded by respiratory effects, which further indicates that CA net flow assessed by PCMRI must be interpreted with caution. However, respiration does not seem to affect aqueductal SV [169], which motivates the choice in paper IV of looking at only the contribution from the pulsations, while removing the effects of net flow.

The study presented in paper IV is the largest CFD study of communicating hydrocephalus, where every measurement performed was optimized (highest resolution) to achieve the most accurate calculation possible of the pressure magnitudes. Considering the observed magnitude of $\Delta P_{net}$, it is not surprising that in vivo studies have yielded no gradient [16], [17]. Any clinical setup using pressure sensor systems would likely have an accuracy not capable of detecting such a small net pressure difference, further supporting the notion that assessment of pressure differences within the CSF system may indeed require other methods than in vivo measurements.

FUTURE RESEARCH

Based on the results of paper I, the next step in TLCPD research relevant for both SANS, IIH and normal tension glaucoma should be to verify whether or not the CSF is fully communicating all the way to the posterior of the eye, specifically in upright positions. This would test the validity of the TLCPD
calculations performed in the upright posture in this thesis and may be essential for understanding the relationship between IOP and ICP in this posture. However, in vivo assessment of CSF pressure at the LC is difficult due to the sensitivity and small size of the structures involved. Aiming for imaging modalities for visualizing the CSF in the upright posture, or non-invasive pressure measurement methods, may be more viable options. For SANS specifically, this knowledge should be complemented with ICP and IOP assessment in space. So far, no direct ICP measurements have been performed in humans in space.

As touched upon, the strong connection between venous collapse and the postural regulation of ICP (paper III) may have the potential to reveal new pathophysiological aspects and hypotheses related to diseases with ICP disturbances, as the link between pathophysiology and the postural ICP control is almost unexplored. Specifically, the venous collapse can easily be assessed using ultrasound when studying different groups of patients and may play a role in abnormal alterations in ICP in the upright posture.

Despite the fact that the results of paper III were strong, the small number of subjects may limit the generalisability of the results. Thus, additional studies with larger sample sizes are warranted. Specifically, it is important to identify if some subjects deviate from the model in similar manners, and to investigate the potential causes for such deviations.

While the IJV collapse at the level of the neck allowed for close predictions of ICP in the majority of the subjects (Figure 17), the possibility of a collapse that extends further cranially should be investigated to assess the physiological variability in the location of the top of the collapse. A thorough investigation of the extent of IJV collapse above the neck may be difficult to perform by ultrasound but could be investigated using other imaging modalities such as MRI, which can be performed in the sitting position [46].

With regard to communicating hydrocephalus the long-term effects of the transmantle pressure gradient observed in paper IV remains to be determined. To evaluate the consequences of this pressure gradient, a longitudinal study of communicating hydrocephalus would be needed, likely including pre-symptomatic hydrocephalus cases to catch the early development of the disease. A major challenge would be the detection of these pre-symptomatic hydrocephalus subjects, which would probably require large population studies.
Conclusions

In this thesis, it was shown that the pressure difference between eye and brain was posture dependent, due to larger postural changes in the intracranial pressure compared with the intraocular pressure. For comparisons of intraocular and intracranial pressure, the results emphasize the importance of assessing both pressures in the same body posture as well as accounting for hydrostatic effects, even in the supine position. The postural/gravitational dependency provides a possible physiological explanation for how the pressure difference between eye and brain can be altered in astronauts exposed to microgravity.

Ultrasound investigations of the collapsed internal jugular veins in the upright posture showed that self-adjustment of the vessel cross-sectional area created a balance between viscous losses and hydrostatic effects that could explain the near atmospheric pressures in these veins in this posture.

Furthermore, the link between venous dynamics and the postural regulation of intracranial pressure was demonstrated: Venous pressure sets the reference for intracranial pressure, and this reference is altered by the collapse, but not total occlusion, of the internal jugular veins in upright body positions.

A computational fluid dynamic analysis confirmed that the cerebrospinal fluid pulsatility does introduce a small transmantine pressure gradient in communicating hydrocephalus across the cerebral aqueduct, but additional mechanisms are likely needed to explain the ventriculomegaly in these patients.

In summary, application of fluid dynamic principles was able to further our knowledge of intracranial pressure control and local pressure distributions within the ventricular system. The results helped to fill knowledge gaps that may bear relevance for research on both microgravity physiology and earthbound neurological diseases with suspected ICP disturbances.
Acknowledgements

I would like to thank everyone who has helped and supported me during the work on this thesis. Friends, family, co-workers, co-authors and supervisors have all taken part in making the time spent on this project feel special. In particular I would like to thank:

Anders Eklund, my principal supervisor, who has been a constant source of encouragement and inspiration throughout this whole process. I am forever grateful for your support, insightful advice, and your treatment of other people. Your way of looking at research is truly inspiring. Just discussing theories and hypotheses with you has been among the most fun things I have had during these four years. Far from all PhD students have been so lucky.

Sara Qvarlander, one of my co-supervisors, for your never-ending support, brilliance and enthusiasm. Seldom have I met a more dedicated person, and I am constantly amazed at how you can tackle any type of problem regardless of its nature. You are a true problem solver, an incredibly competent researcher, and an inspiring person. You have taught me a lot and I have had a wonderful time working with you.

Jan Malm, my other co-supervisor, for encouragement and support, seemingly regardless of the hour. Your knowledge within the field of Neurology has helped me a lot, as has your help to ground my thesis in real-life medical problems. I am sure that your efforts at times must have been frustrating. I have really appreciated your advice, dedication and (last, but not least) your humour.

Khalid Ambarki who have been a great source of support during my first years of PhD studies. Your ability to find relevant literature is next to none. It has been great working with you, and to have someone to discuss football with.

Anders Wählin, for great cooperation in different research projects and for your constant optimism. Your positive outlook on life and the joy you emit is truly contagious.

Tomas Bäcklund, for all of your help with measurement equipment. Your vast knowledge in the field has been crucial for the work of this thesis.

Karen-Helene Støverud, for all the discussions on computational fluid dynamics, they have helped me greatly.
Thanks to all of my co-authors including Elias Johansson, Gauti Jóhannesson, Lars-Owe D. Koskinen and Nina Sundström for your vital contributions to this thesis.

Thanks to my fellow PhD students, especially Tora Dunås and Madelene Holmgren, for all your support and fun times. It has been great to share this experience with you and I wish you all good luck in your future endeavours.

Thanks to all my co-workers at MT-FoU. You are all great people and I have always felt at home at FoU thanks to you. Specifically, I would like to thank Tomas Bäcklund, Marcus Karlsson, Leif Nyström and Per Hallberg for helping me stay somewhat in shape, and the head of department Olof Lindahl for making MT-FoU a wonderful place to work.

Thanks to Kristin Nyman, Hanna Ackelind, and Sonja Edvinsson at the neurological department for all your invaluable assistance with measurements and patient correspondence. Without you this thesis could not have been done.

Thanks to Maria Wing and Margareta Marklund at the Department of Radiation sciences for all your administrative help.

Thanks to Umeå Centre for Functional Brain imaging, and specifically Rebeca de Peredo Axelsson, for making the MRI investigations possible.

I thank my friends and family (both my old and new one). Specifically I would like to thank my parents for their unconditional love and support, and my siblings Emme-Lie and Jonas for being the best sister and brother a person could have.

I would also like to specifically thank Åsa Holmner for being who you are. Even though you may not believe it you have been a rock for me to lean on during these past few years, a rock with the efficiency of a raging tornado:) I love you.

Finally, thanks to Trassel and Kajsa for always greeting me with extreme happiness whenever I come home, and for taking me out on my daily walks.

This thesis was financed by the Swedish National Space board, the Swedish Research council (grant number 2015-05616) and the Swedish Heart and Lung Foundation (grant number 20140592).
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