Cerebral blood flow and intracranial pulsatility studied with MRI

Measurement, physiological and pathophysiological aspects

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Umeå, Sweden, 2012
Abstract

During each cardiac cycle pulsatile arterial blood inflates the vascular bed of the brain, forcing cerebrospinal fluid (CSF) and venous blood out of the cranium. Excessive arterial pulsatility may be part of a harmful mechanism causing cognitive decline among elderly. Additionally, restricted venous flow from the brain is suggested as the cause of multiple sclerosis. Addressing hypotheses derived from these observations requires accurate and reliable investigational methods. This work focused on assessing the pulsatile waveform of cerebral arterial, venous and CSF flows. The overall aim of this dissertation was to explore cerebral blood flow and intracranial pulsatility using MRI, with respect to measurement, physiological and pathophysiological aspects.

Two-dimensional phase contrast magnetic resonance imaging (2D PCMRI) was used to assess the pulsatile waveforms of cerebral arterial, venous and CSF flow. The repeatability was assessed in healthy young subjects. The 2D PCMRI measurements of cerebral arterial, venous and CSF pulsatility were generally repeatable but the pulsatility decreased systematically during the investigation.

A method combining 2D PCMRI measurements with invasive CSF infusion tests to determine the magnitude and distribution of compliance within the craniospinal system was developed and applied in a group of healthy elderly. The intracranial space contained approximately two thirds of the total craniospinal compliance. The magnitude of craniospinal compliance was less than suggested in previous studies.
The vascular hypothesis for multiple sclerosis was tested. Venous drainage in the internal jugular veins was compared between healthy controls and multiple sclerosis patients using 2D PCMRI. For both groups, a great variability in the internal jugular flow was observed but no pattern specific to multiple sclerosis could be found.

Relationships between regional brain volumes and potential biomarkers of intracranial cardiac-related pulsatile stress were assessed in healthy elderly. The biomarkers were extracted from invasive CSF pressure measurements as well as 2D PCMRI acquisitions. The volumes of temporal cortex, frontal cortex and hippocampus were negatively related to the magnitude of cardiac-related intracranial pulsatility.

Finally, a potentially improved workflow to assess the volume of arterial pulsatility using time resolved, four-dimensional phase contrast MRI measurements (4D PCMRI) was evaluated. The measurements showed good agreement with 2D PCMRI acquisitions.

In conclusion, this work showed that 2D PCMRI is a feasible tool to study the pulsatile waveforms of cerebral blood and CSF flow. Conventional views regarding the magnitude and distribution of craniospinal compliance was challenged, with important implications regarding the understanding of how intracranial vascular pulsatility is absorbed. A first counterpoint to previous near-uniform observations of obstructions in the internal jugular veins in multiple sclerosis was provided. It was demonstrated that large cardiac-related intracranial pulsatility were related to smaller volumes of brain regions that are important in neurodegenerative diseases among elderly. This represents a strong rationale to further investigate the role of excessive intracranial pulsatility in cognitive impairment and dementia. For that work, 4D PCMRI will facilitate an effective analysis of cerebral blood flow and pulsatility.
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Original papers

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


IV. Wåhlin, A., Ambarki, K., Birgander, R., Malm, J., and Eklund, A. In healthy elderly the volumes of several brain regions are related to pulsatility in cerebral arteries and cerebrospinal fluid. *In Manuscript*.

V. Wåhlin, A., Ambarki, K., Birgander, R., Wieben, O., Johnson, KM., Malm, J., and Eklund, A. Measuring pulsatile flow in cerebral arteries using four-dimensional phase contrast magnetic resonance imaging. *In Manuscript*. 
1 Introduction

The adult brain is contained in a closed compartment constituted by the cranium and dura mater (Mokri, 2001). Inside this space cerebrospinal fluid (CSF) surrounds the entire central nervous system (Magendie, 1842). During each cardiac cycle arterial pulsatility causes a systolic increase in cerebral arterial blood volume (Greitz et al., 1992), something that can be observed during neurosurgery as a cyclic pulsation of the brain. To compensate for this volume increase, venous blood is forced out of the cranium and CSF is pushed down to the spinal canal (Enzmann and Pelc, 1991; Greitz et al., 1992; Enzmann and Pelc, 1993).

Recently, there has been increased attention on the pulsatility of cerebral arteries and CSF. Among elderly, an increased pulsatility in the arteries supplying the brain has been linked to cognitive impairment in several domains, including memory (Mitchell et al., 2011). It has been hypothesized that an age-related increase in pulsatility in the cerebral microcirculation is harmful for the brain (O'Rourke and Hashimoto, 2007). The CSF pulse pressure (Anile et al., 2010; Eide and Brean, 2010) and cardiac-related flow pulsatility have also been linked to the outcome following shunt surgery in subjects with communicating hydrocephalus (Bradley et al., 1996).

Moreover, although multiple sclerosis (MS) is commonly regarded as an inflammatory disorder caused by a complicated interaction between environmental and genetic risk factors (Compston and Coles, 2002), restricted venous flow (Zamboni et al., 2009b) and altered CSF flow (Zamboni et al., 2009c) were recently suggested to be parts of the disease pathophysiology. This controversial theory is appealing as restricted venous outflow potentially can be treated (Zamboni et al., 2009a).
Addressing hypotheses derived from these observations requires reliable investigational methods. It is also necessary to explore the normal physiological mechanisms associated with cerebral arterial, venous and CSF dynamics.

In this dissertation a biomechanical perspective on the interaction between cerebral arteries, veins and CSF was applied. With a theoretical model as a starting point, we probed the system from several angles while maintaining a critical evaluation of measurement reliability. Focus was on assessing the pulsatile waveforms of arterial and venous blood and CSF with phase contrast magnetic resonance imaging (PCMRI). These measurements were also combined with invasive CSF dynamic investigations, quantifying the magnitude of the CSF pulse pressure occurring in response to the vascular pulsations.
1.1 Arterial pulsatility

The left and right internal carotid artery (ICA) and vertebral artery (VA), respectively, are four arteries that supply the brain (Figure 1). Closer to the brain, the VA merge to form the basilar artery (BA) (Purves et al., 2011).

**Figure 1.** Arterial supply and venous drainage of the brain. ICA=internal carotid artery, VA=vertebral artery, BA=basilar artery, MCA=middle cerebral artery, ACA=anterior cerebral artery, SSS=superior sagittal sinus, IJV=internal jugular vein. The figure is based on a 4D PCMRI acquisition from Paper V.
At the circle of Willis, a hub connecting the major cerebral arteries, the ICA is divided into the anterior and middle cerebral artery (ACA and MCA, respectively). Here, the BA is also divided to form the posterior cerebral arteries. Blood from the ICA supplies a large part of the cerebrum. The VA and the BA supply the brain stem, cerebellum and posterior parts of the cerebrum (Hall and Guyton, 2010).

In young subjects with well functioning arterial systems, the arterial distensibility, or compliance, cushions the arterial pulse. This is sometimes referred to as the Windkessel effect (Westerhof et al., 2009). This absorption reduces the systolic pressure peak and smoothens the pulsatility of blood flow that reaches the capillaries (O’Rourke and Hashimoto, 2007). In general, for a higher cardiac stroke volume the compensating mechanisms of the arteries have to absorb a greater volume. The compliance of the arterial tree together with the cardiac stroke volume ultimately determine the magnitude of arterial pulse pressure (Hall and Guyton, 2010).

About 30 million heartbeats per year induce arterial fatigue and dilatation in the later stages of life (O’Rourke and Hashimoto, 2007; Bullitt et al., 2010). In parallel with atherosclerotic changes the artery is also hardened and less compliant, and a gradual decline in the Windkessel function is observed (Avolio et al., 1983). These interrelated changes are most prominent in the aorta and major proximal arteries and less prominent in the distal regions of the circulation. Consequently, a stiffer arterial system may result in increased pulsatility and cyclic distention of distal branches of the arterial system (Boutouyrie et al., 1992).

For most organs, the small arteries, arterioles and capillaries complete the transition of pulsatile blood flow into a steady flow. However, the high perfusion rate of the brain makes arterial pulsatility reach deeply towards the smallest vessels (O’Rourke and Hashimoto, 2007; Mitchell, 2008). Research regarding large arteries and their age-related stiffening have
promoted questions on what effects this might have on tissues and organs of the body (Mitchell, 2008). If aortic stiffness impedes appropriate cushioning of the arterial pulse, the pulsatile stress will extend deeper into the arterial tree. In this event the sites with the most dilated arterioles, e.g. the brain, may be at risk to damage caused by the increase in arterial pulsatility.

Research rationale

Recently, a large-scale evaluation focusing on elderly subjects demonstrated that cognitive performance in several domains, including memory, is negatively correlated with the amplitude of pulsatility in arteries supplying the brain (Mitchell et al., 2011). Based on these observations, it is relevant to evaluate if excessive pulsatility in cerebral arteries catalyze the aging of the brain, and possibly even pushes a subject into a degenerative dementia. It is essential to clarify if any specialized brain region is particularly susceptible to excessive pulsatile stress. Studies evaluating associations between regional brain volumes and intracranial vascular pulsatility may provide a first indication of which brain regions that may be harmed by such processes.
1.2 Restricted venous flow

In contrast to the arterial system, the cerebral venous drainage displays large individual variations (Doepp et al., 2004) and is easily influenced by external disturbances such as body position (Valdueza et al., 2000). Through bridging veins and deep cerebral veins the blood is transmitted to the venous sinuses, formed by the dura mater (Figure 1). The sinuses transport blood to the neck veins. In supine position, the major venous pathways of the neck are the left and right internal jugular vein (IJV) (Valdueza et al., 2000; Alperin et al., 2005). Commonly, the right IJV carries a dominant part of the total IJV outflow but individual variations of this distribution are large (Stoquart-ElSankari et al., 2009). In addition to the left and right IJV, extrajugular venous pathways contribute to the venous outflow. These include vertebral veins, epidural veins and deep neck veins. The large capacity of these veins indicates that they could take over the entire venous drainage of the brain if needed (Doepp et al., 2004).

Despite the extensive capacity of collateral pathways, a controversial hypothesis suggests that the development of MS is a manifestation of restricted venous flow. MS lesions often develop around a central vein (Tan et al., 2000), a rationale for suspecting venous involvement in the etiology of MS. Recently, the pattern of impaired cerebral venous outflow termed chronic cerebrospinal venous insufficiency (CCSVI) has been linked to MS (Singh and Zamboni, 2009; Zamboni et al., 2009b). The theory describes compromised venous outflow as a cause of accumulation of iron in the central nervous system, which may initiate the development of MS lesions. The IJV flow is reported as a central component in the hypothesis (Zamboni et al., 2009b). Stenoses or malformations have been suggested to be the primary cause of the restricted venous outflow. The restricted venous flow is also reported to bring about an abnormal CSF flow in the cerebral aqueduct (Zamboni et al., 2009c). Potentially, venous congestions of the CCSVI type
can be treated, improving the symptoms of MS patients (Zamboni et al., 2009a). Therefore, if proven accurate, this may represent a major therapeutic option for MS patients.

Research rationale

Because CCSVI potentially can be treated (Zamboni et al., 2009a), centers around the world are now offering endovascular procedures, i.e. angioplasty and stenting, to treat CCSVI. This has resulted in “medical tourism” where MS patients themselves seek help abroad. The scientific process needs to catch up with this potentially hasty development and the CCSVI theory needs to be evaluated by accurate, reliable and objective methods. The link between venous obstructions and MS was observed using ultrasound methods (Zamboni et al., 2009b). Because venous flow can also be quantified using PCMRI (Stoquart-ElSankari et al., 2009), it can be expected that the observations also will appear using this modality. Therefore, studies clarifying the PCMRI appearance of venous hemodynamics in MS are urgently needed.
1.3 CSF dynamics

The brain and spinal cord are surrounded by CSF (Figure 2). CSF is a clear fluid (99 % water) that is produced within the choroid plexus of the cerebral ventricles (Redzic and Segal, 2004) at a rate of approximately 7 µl/s (Ekstedt, 1978). In healthy elderly, the typical intracranial, ventricular and spinal CSF volumes have been measured to 195 ml (Tsunoda et al., 2002), 37 ml (Ambarki et al., 2010), and 85 ml (Edsbagge et al., 2011), respectively. CSF outflow is commonly thought to occur in the arachnoid villi located in the superior sagittal sinus (Figure 2), although at physiological pressure levels the significance of cerebral capillary fluid exchange may be more significant than previously recognized (Bulat and Klarica, 2011). The CSF production rate, outflow resistance and also venous pressure determine the CSF resting pressure (Davson et al., 1970; 1973).

The CSF has a role in clearing metabolic waste as well as providing mechanical support and buoyancy to the central nervous system (Irani, 2009). Furthermore, it provides the craniospinal system with the ability to compensate for a volume expansion. This function of the system is activated during every cardiac cycle, when CSF is redistributed upon the systolic increase in arterial blood volume (Enzmann and Pelc, 1991).

In the short time window of a cardiac cycle, the CSF outflow mechanisms are ineffective for dampening the CSF pulse pressure generated by the arteries. Instead the increased CSF pressure compresses the craniospinal venous bed, forcing venous blood out from the system (Greitz et al., 1992). This mechanism is a manifestation of craniospinal compliance. In addition, elasticity of dura mater, especially in the spinal compartment, is generally acknowledged to contribute to the overall capacity of craniospinal compliance (Martins et al., 1972; Tain et al., 2011).
Figure 2. Overview of the CSF system surrounding the entire central nervous system. CSF is produced within the ventricles, circulates and escapes to blood in the venous sinuses.
To describe craniospinal compliance, mathematical models have been developed. The relationship between pressure and volume of the craniospinal system can be approximated by a simple exponential function (Marmarou et al., 1975):

\[ P = P_r e^{kV} \]  

(1)

where \( P \) is the CSF pressure, \( P_r \) is the baseline pressure, \( V \) is the volume increase and \( k \) is the elastance coefficient. This model has been extended with a constant term to better match experimental observations (Avezaat and van Eijndhoven, 1986):

\[ P = P_1 e^{kV} + P_0 \]  

(2)

where \( P_o \) and \( P_1 \) are pressure constants with a sum that equals \( P_r \). \( P_0 \) has been linked to venous pressure (Löfgren et al., 1973; Avezaat and van Eijndhoven, 1986) and hydrostatic pressure gradients within the system (Raabe et al., 1999). Compliance is defined as the volume change per unit change in pressure \( (dV/dP) \), and for the craniospinal system the pressure dependent compliance becomes:

\[ C(P) = \frac{1}{k(P - P_0)} \]  

(3)

Usually, the term pressure volume index (PVI) is used instead of \( k \). The mathematical relationship between PVI and \( k \) is:

\[ \text{PVI} = \frac{1}{0.4343k} \]  

(4)

The PVI is therefore a factor describing the overall compensating capacity of the craniospinal system.
Research rationale

The concept of compliance and PVI also applies to arterial pulsations (Avezaat et al., 1979). A reduced PVI corresponds to a reduced ability of the craniospinal system to accommodate arterial pulsatility. A dysfunction of this type has been suggested to be present in Alzheimer’s disease and vascular dementia (Bateman et al., 2008). Moreover, the amplitude of the CSF pulse pressure has been shown to be important in predicting shunt outcome in idiopathic normal pressure hydrocephalus (Eide and Brean, 2006). Together these observations suggest that increases in arterial pulsations (often associated with increasing age) and impaired pulsation dampening may be involved in several degenerative neurological disorders among the elderly.

For this reason, it is important to develop accurate methods to measure PVI and remedy the gap in basic physiological knowledge regarding the magnitude and distribution of craniospinal compliance among healthy, non-demented elderly.
1.4 Structural magnetic resonance imaging

Magnetic resonance imaging (MRI) is based upon the interactions between nuclear spins, a fundamental property of all elementary particles, and external magnetic fields. Briefly, a powerful external magnetic field aligns all spins in the body. An external excitation radiofrequency pulse rapidly “tips” the spins in a prescribed volume (or slice). In their excited state the spins induce detectable signals in receiver coils, integrated within the system (Bloch, 1946; Purcell et al., 1946).

Spatial information is encoded to the spins by position-dependent phase and frequency modulation achieved by adding small magnetic field gradients to the static field. The detected signals can therefore be reconstructed into an image (Lauterbur, 1973).

The duration of the induced signal depends on the unique relaxation properties of the tissue. The difference in relaxation properties between tissues can be exploited to generate contrast in the images. The relaxation properties can be described by a longitudinal and transversal relaxation time (T1 and T2, respectively) and those two parameters differ between white matter, gray matter and CSF (Figure 3) (Bernstein et al., 2004).

The T1 and T2 contrast can be used to depict brain structures and also to delineate the intracranial compartment. Although the image intensity alone under many circumstances is not specific to a certain brain structure, e.g. the hippocampus and amygdala are inseparable by intensity alone (Fischl, 2012), the spatial information and surrounding pixels can be weighed in to the decision whether a pixel belongs to the brain structure. This methodology is being exploited in highly automated structural processing tools that are capable of providing an accurate segmentation of the entire brain. In this dissertation Freesurfer was employed. Freesurfer is a set of tools for automated structural processing that are based on probabilistic
models created from manually labeled brains (Fischl et al., 2002; 2004; Desikan et al., 2006). Freesurfer is capable of utilizing spatial relationships, e.g. the hippocampus is always behind and below the amygdala and never above and in front of amygdala (Fischl, 2012), in the automatic labeling of brain regions.

Figure 3. MRI appearance at different locations and weightings. In the T1 image CSF is black. In the T2 image CSF is white.
1.5 Flow sensitive magnetic resonance imaging

There are several techniques for measuring and visualizing motion using MRI. Typically, dynamic information such as flow or diffusion is acquired simultaneously as the spatial information. PCMRI is useful for flow rate and velocity quantification purposes (Bernstein et al., 2004).

PCMRI employs velocity encoding in a way analogous to spatial encoding (Moran, 1982). Because the angular frequency of a spin is proportional to the external magnetic field, a spin that travels in a magnetic field gradient (the velocity encoding gradient) will accumulate a different phase as compared to a stationary spin. Therefore, a bipolar gradient toggle rewinds stationary spins but induces a phase shift in moving spins (Figure 4).

![Figure 4. Velocity encoding principle of PCMRI. (a) The spin moves in the gradient direction during a bipolar gradient toggle, G+ and G-. (b) The phase evolution over time for the spin. Note the resulting phase shift.](image-url)
Phase wrapping occurs at shifts of $\pi$ and -$\pi$. To avoid this, the magnitude of the velocity encoding gradient is prospectively adjusted according to the maximum velocity expected in the vessel of interest. The velocity encoding parameter corresponds to the velocity where phase wrapping occurs (Bernstein et al., 2004).

The first moment of a gradient field determines the velocity sensitivity of the acquisition. In two-dimensional (2D) PCMRI, two acquisitions with different first moments are required to quantify flow in one direction. This way, a subtraction or complex conjugate multiplication between the two acquisitions allows removal of unwanted phase shifts that do not depend on velocity. The relationship between velocity and phase shift can be described as:

$$\phi = \tilde{v} \cdot \gamma \Delta \tilde{M}_1$$  \hspace{1cm} (5)

where $\phi$ is the phase shift, $\tilde{v}$ is the velocity, $\gamma$ is the Larmour frequency constant and $\Delta \tilde{M}_1$ the difference in first moments of the velocity encoding gradients.

When quantifying flow in all three spatial directions, a series of three or four acquisitions together with a reference scan can be utilized to shorten the scan time (Wigström et al., 1996; Johnson and Markl, 2010). The velocity can be obtained from solving:

$$\tilde{\phi} = \gamma A \tilde{v}$$  \hspace{1cm} (6)

where $A$ is the encoding matrix containing the differences in first moments in analogy to equation 5. Commonly, time resolved quantification of flow in all three directions is referred to as four-dimensional (4D) PCMRI.
Figure 5. 2D PCMRI images at three time points during the cardiac cycle. 
(a1-3) Blood flow at cervical level in the systolic, intermediate and diastolic cardiac phase, respectively. (b1-3) Spinal CSF flow. Black and white represents flow from and towards the cranium, respectively. (c1-3) Aqueduct CSF flow. Black and white represents flow towards and from the fourth ventricle, respectively.
The PCMRI sequence can be used to quantify arterial, venous and CSF flow waveforms of the cardiac cycle (Figure 5 and 6) (Nayler et al., 1986; Greitz et al., 1992; Enzmann and Pelc, 1993). To achieve this, an ECG or a peripheral pulse is recorded by equipment integrated with the MRI system, allowing the sequence to be prospectively or retrospectively gated (Bernstein et al., 2004). In prospective gating, the data acquisition is initiated by a trigger signal. This technique is robust even in mild arrhythmia but a small fraction of the cardiac cycle, where the sequence waits for the next trigger, is not acquired. In retrospective gating, continuously acquired data is sorted into an average cardiac cycle. This technique provides the flow waveform of the complete cardiac cycle, although some temporal smoothing may occur as a result of heart rate variability (Lotz et al., 2002).

![Figure 6. Blood and CSF flow waveforms. In these acquisitions 32 image frames represent the cardiac cycle. Positive values represent flow in the caudal-cranial direction.](image-url)
Research rationale

There are many factors that potentially degrade the quality of the PCMRI quantification. Partial volume effects (Tang et al., 1995) cause flow rate overestimations. Misalignment errors influence the observed velocity (Wolf et al., 1993). Moreover, physiological variability adds to the uncertainties associated with a measurement.

Net flow rate quantifications have been thoroughly validated, both for 2D (Spilt et al., 2002) and 4D PCMRI (Gu et al., 2005; Chang et al., 2011). However, less is known about the repeatability when quantifying the volume of cerebral arterial, venous and CSF pulsatility. Therefore, to meet with the increased interest in intracranial pulsatile hemodynamics and CSF flow it is necessary to evaluate the stability of PCMRI measurements.
1.6 Quantification of CSF pulse pressure

The CSF system dynamics can be investigated invasively by inserting two needles in the spinal lumbar subarachnoid space (Eklund et al., 2007). One needle is used to infuse artificial CSF and the other is used to determine the pressure response. Lumbar infusion tests are commonly used to investigate the CSF outflow resistance in cases of suspected normal pressure hydrocephalus (Andersson et al., 2005; Sundström et al., 2010; Malm et al., 2012), but the technique is also useful for investigating compliance related parameters of the craniospinal system (Juniewicz et al., 2005). Various infusion patterns are available and they can be divided into two categories, those regulating the CSF pressure to predetermined levels (Ekstedt, 1977) and those employing a predetermined rate of infusion (Hussey et al., 1970; Katzman and Hussey, 1970).

![Figure 7. CSF pressure during a constant pressure infusion test. The CSF pressure is regulated to six levels (each given its own color) above baseline pressure (yellow).](image-url)
The constant pressure regulated infusion pattern (Figure 7) is designed for estimations of CSF outflow resistance and does not provide estimations of PVI (Andersson et al., 2005; 2010). However, in the pressure signals recorded from a lumbar infusion test it is evident that physiological activity such as arterial cardiac-related pulsatility influences the CSF pressure. During an infusion test it can be observed how the CSF pulse pressure, caused by arterial pulsatility, increases linearly as the average pressure in the system is raised (Figure 8) (Avezaat et al., 1979; Avezaat and van Eijndhoven, 1986). This is a manifestation of a gradual decrease in compliance.

![Figure 8](image)

**Figure 8.** CSF pulse pressure versus average CSF pressure. The colors correspond to different levels of regulated pressure.
Research rationale

Although the relationship between CSF pressure and pulse pressure is related to the compliance properties of the craniospinal system, i.e. PVI, it is also related to the volume of cerebral arterial pulsatility, which cannot be estimated solely from CSF pressure measurements. Interestingly, the volume of arterial pulsatility can be estimated from PCMRI measurements. Therefore, bringing together data from CSF infusion measurements and PCMRI acquisitions can potentially provide estimations of the craniospinal PVI.
2 Aims

The overall aim of this dissertation was to explore cerebral blood flow and intracranial pulsatility using MRI, with respect to measurement, physiological and pathophysiological aspects.

The specific aims for Papers I-V were to:

I. Assess 2D PCMRI measurement repeatability for quantifications of the pulsatile waveforms of cerebral arterial, venous and CSF flow.

II. Combine lumbar CSF infusion tests with 2D PCMRI flow measurements to assess PVI and its distribution between the intracranial and spinal compartments.

III. Test the most vital part of the CCSVI hypothesis by comparing IJV flow as well as CSF dynamics between healthy and MS subjects.

IV. Assess relationships between regional brain volumes and arterial and CSF pulse pressure and the volume of cerebral arterial and CSF pulsatility.

V. Evaluate 4D PCMRI for assessing pulsatility of large cerebral arteries.
3 Materials and methods

3.1 Subjects

The regional ethical review board approved all separate studies. Informed consent was obtained from all participants. The subject groups for all studies are listed in Table 1. All healthy young (HY) subjects were normal as determined from anatomical MRI scans. The healthy elderly (HE) passed a neurological examination, had a mini mental state examination score of at least 28 and did not suffer from advanced vascular disease (previous stroke, myocardial infarction, diabetes). The MS group had the relapsing-remitting disease course with a median disease duration of five years.

Table 1. Overview of subjects enrolled in the five studies. HY=healthy young, HE=healthy elderly, MS=multiple sclerosis.

<table>
<thead>
<tr>
<th>Paper</th>
<th>No. of subjects</th>
<th>Male / female</th>
<th>Age (mean ± SD)</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>20 HY$^a$</td>
<td>12/8</td>
<td>33±8</td>
</tr>
<tr>
<td>II</td>
<td>37 HE$^b$</td>
<td>15/22</td>
<td>71±6</td>
</tr>
<tr>
<td>III</td>
<td>20 HY$^a$, 21 MS</td>
<td>12/8, 8/13</td>
<td>33±8, 34±10</td>
</tr>
<tr>
<td>IV</td>
<td>37 HE$^b$</td>
<td>13/24</td>
<td>71±6</td>
</tr>
<tr>
<td>V</td>
<td>10 HY</td>
<td>7/3</td>
<td>36±9</td>
</tr>
</tbody>
</table>

$^a$Same subjects. $^b$34 subjects were shared.
3.2 Magnetic resonance imaging

For Paper I-IV MRI measurements were performed on a 3T Achieva scanner (Philips Healthcare, Best, the Netherlands) using an 8-channel head coil. Routine anatomical sequences were performed to confirm a healthy status. A 3D T1 weighted turbo field echo sagittal scan with good gray/white matter contrast was used for automated regional brain volume quantification (echo time 5.0 ms, repetition time 10 ms, acquisition resolution 0.5 x 0.6 x 1 mm³). An axial T2 weighted turbo spin-echo (echo time 80 ms, repetition time 3000 ms, acquisition resolution 0.5 x 0.5 x 3.3 mm³) was used for manual delineation of the intracranial space.

For Paper I-IV three 2D PCMRI protocols were used to assess blood and CSF flow pulsatility. The tree protocols measured:

1. ICA and VA flow (level between second and third cervical vertebrae)
2. Spinal CSF flow (level between second and third cervical vertebrae)
3. Aqueduct CSF flow

The scanning parameters for sequences 1 / 2 / 3 were: encoding velocity 70 / 7 / 20 cm s⁻¹, flip angle 15 / 10 / 10 degrees, repetition time 9.6 / 16 / 15 ms, echo time 5.8 / 11 / 10 ms, voxel size 0.9 x 0.9 x 6 / 1.2 x 1.2 x 5 / 1.2 x 1.2 x 5 mm³ and two signal averages.

In Paper I five repeated measurements of the three sequences were performed in the 20 HY subjects. An aqueduct measurement with increased resolution (0.7 x 0.7 x 0.7 mm³) was also added to evaluate potential influence of partial volume effects. For paper II and IV the first two 2D PCMRI protocols were utilized (34 HE were shared between the studies).
In Paper III, 21 MS subjects underwent the first and last 2D PCMRI protocols, and the values were subsequently compared with the first repetition of the same sequences performed on the HY group of Paper I.

In Paper V measurements on 10 HY subjects were performed on a 3T Discovery MR 750 scanner (General Electric, Waukesha, WI, USA) with a 32-channel head coil. Measurements started with a 3D time of flight acquisition for vessel localization. Secondly, a 4D PCMRI measurement was made using a phase contrast vastly undersampled projection imaging (PCVIPR) sequence (Frydrychowicz et al., 2010), covering the entire intracranial space. The resolution was 0.7 x 0.7 x 0.7 mm, velocity encoding 110 cm s⁻¹, repetition time/echo time 6.5 / 2.7 ms, flip angle 8 degrees. Besides velocity images for 20 time positions of the cardiac cycle, a time averaged complex difference image was reconstructed to provide anatomical localization of the vascular system.

After the 4D PCMRI acquisition, five 2D PCMRI scans were performed. These measured flow in:

1. ICA and BA
2. Right MCA (M1 segment)
3. Left MCA (M1 segment)
4. Right ACA (A1 segment)
5. Left ACA (A1 segment)

The encoding velocity for protocol 1 / 2 / 3 / 4 / 5 was 80 / 110 / 110 / 90 / 90 cm s⁻¹. The additional 2D PCMRI parameters were: repetition time/echo time 7.6-8.5 / 4.1-5.0 ms, 15 degrees flip angle, resolution 0.5 x 0.5 x 3.0 mm³, six views per segment and two signal averages. Thirty-two phases were retrospectively reconstructed.
3.3 Volume of arterial and CSF pulsatility

For all 2D PCMRI acquisitions, arterial, venous and CSF lumen segmentations were performed manually using the free software ImageJ (National Institute of Health, Bethesda, MD)(Paper I-IV) and Segment (http://segment.heiberg.se)(Paper V). All measurements were systematically reviewed and corrected for phase aliasing if needed. The total arterial flow waveform was calculated from the sum of ICA and VA flow. Total internal jugular blood flow was calculated from the sum of left and right IJV flow (Paper III). The venous waveforms were also normalized by the total arterial inflow (Paper III). An IJV reflux was registered if, during any time of the cardiac cycle, the flow was in the caudo-cranial direction.

For the 4D PCMRI segmentations in Paper V, in-house software was developed (Figure 9). The software enabled the user to rotate, zoom and visualize flow in the 4D PCMRI data. The segmentation was initiated by selecting a reference pixel in the vessel of interest (a mouse click in a maximum intensity projection of the complex difference image). The software included neighboring pixels with values of at least 18 % of the maximum of the complex difference image. An additional requirement was used to limit the segmentation to the branch of interest:

\[
\frac{|\vec{r}_i \cdot \vec{v}_0|}{\|\vec{v}_0\|} \leq \frac{l}{2}
\]

(7)

where \(\vec{r}_i\) is a vector from the reference pixel to the \(i:\)th pixel, \(\vec{v}_0\) is the vessel direction estimated by the velocity direction (temporally averaged) in the reference pixel and \(l\) is desired segment length. The segment length \(l\) was fixed at five pixel widths (similar to the slice thickness of the 2D PCMRI scans). The value 18 % was selected from a pre-calibration series indicating that this threshold provided complete vessel coverage.
In this dissertation flow pulsatility was described in terms of volume. This concept is natural considering that cerebral arterial, venous and CSF volumes interact as a result of the limited intracranial volume. The volume of pulsatility ($\Delta V$) was calculated using an identical procedure for arteries, veins and CSF (Figure 10) (Paper I-V). After subtraction of the net flow rate, cumulative integration was used to estimate the volume variation associated with the remaining waveform. $\Delta V$ was defined as the difference between the maximum and minimum of the integrated waveform.

**Figure 9.** A maximum intensity projection of the complex difference image. Flow rates from the colored arterial segmentations were compared with the 2D PCMRI data.
Figure 10. Arterial waveforms from a 4D PCMRI measurement. (a) The flow rate during the cardiac cycle for right ICA, MCA and ACA as well as the basilar artery. (b) Cumulative integral of the ICA waveform after subtracting the net flow rate. The volume ($\Delta V$) of ICA pulsatility was defined as the maximum minus minimum of this waveform.
3.4 CSF pulse pressure

Lumbar CSF pressure and pulse pressure were measured with the subject in a supine position (Paper II and IV). A special bed, exposing the region for needle insertion, enabled access to the lumbar space. The highly automated investigational method has previously been described in detail (Andersson et al., 2005; Malm et al., 2011). After 10-15 minutes of rest, with the needles in place, the CSF pressure was sampled for 5 minutes at 100 Hz.

After the resting pressure measurement the CSF pressure was regulated to six predetermined pressure levels using infusion of artificial CSF. In a few exceptions, pressure elevation was performed using a constant rate of artificial CSF infusion.

![Figure 11](image)

**Figure 11.** The $\Delta P$ for each regulated pressure level (colored dots) was defined as the median CSF pulse pressure (gray dots). The colors correspond to the pressure levels in Figure 8. The line represents the relationship between $\Delta P$ and $P$ determined from a linear regression.
In the post-processing step the slow pressure variations, not related to the cardiac cycle, were eliminated using a high-pass filter. After this operation, pressure pulses were estimated by analyzing the difference between maximum and minimum pressure in successive 1.5 second time intervals. For each regulated pressure level, a $\Delta P$ value was calculated as the median value of all pulse pressures. Resting pressure $\Delta P$ was used for Paper IV. In Paper II a linear regression was used to estimate the relationship between $\Delta P$ and $P$, as a step in calculating PVI (Figure 11). In Paper IV, baseline $\Delta P$ could not be assessed for three subjects because of needle obstruction. In addition to these measurements a standard automated blood pressure monitor, Omron M5-I (Omron Health Care, Kyoto, Japan) was used to assess left upper arm mean arterial pressure and arterial pulse pressure.

### 3.5 Mathematical model

In Paper II, a way to calculate PVI from PCMRI and CSF infusion data was presented. Here, the craniospinal model (equation 2) was adapted to suit the combination of measurements. The response in pressure following an increase in arterial volume can be written as:

$$P + \Delta P = P_1 e^{k(V + \Delta V)} + P_0$$

Where $\Delta V$ is the cyclic increase in intracranial arterial blood volume and $\Delta P$ is the CSF pulse pressure. This can be rewritten to:

$$\frac{\Delta P}{P - P_0} = e^{k\Delta V} - 1$$

where the left hand is the mathematical expression of the slope between CSF $\Delta P$ and $P$ that can be determined from an infusion test (as described in the previous section and Figure 11), with $P_0$ as the intersection between the regression line and the pressure axis.
Consequently, using both a CSF infusion measurement and a measurement of $\Delta V$, the elastance coefficient can be calculated as:

$$k = \ln\left(\frac{\Delta P}{P - P_0} + 1\right) / \Delta V$$

(10)

To comply with common nomenclature, the elastance coefficient was translated into PVI according to equation 4.

3.6 Intracranial volume

The post-processing software QBrain (version 2.0; Medis Medical Imaging Systems, Leiden, the Netherlands) was used to segment the intracranial volume of each subject in Paper IV. This was performed by manual delineation in T2 weighted images using a threshold based drawing tool (Ambarki et al., 2010; 2011).

3.7 Regional brain volumes

In Paper IV cortical and subcortical structures were segmented using FreeSurfer 5.0 (available online at http://surfer.nmr.mgh.harvard.edu). The software utilizes probabilistic models treating relationships between characteristic magnetic resonance appearances and spatial orientations (Figure 12) (Fischl et al., 2002; 2004; Desikan et al., 2006).

An experienced neuroradiologist verified the accuracy of the segmentations of the 13 brain regions extracted for the analysis (Figure 12). Paper IV originally included 38 subjects, but one subject had too severe atrophy for the automated segmentation, which ended with unacceptable errors. This subject was excluded from all analyses.
Figure 12. Result from brain segmentation (Paper IV). (a) Cortical subdivisions. (b) Subcortical structures. Besides these structures the insula, cerebral white matter and cerebellum white matter were included in the analyses.
3.8 Statistics

For Paper I the within-subject and between-subject standard deviations were calculated (SD_{intra} and SD_{inter}, respectively). SD_{intra} describes the variation over the five repetitions and is thus a measure of repeatability. To put this value in proportion to the population distribution, an intraclass correlation coefficient (ICC) was calculated as $SD_{inter}^2/(SD_{intra}^2+SD_{inter}^2)$. An ICC above 0.80-0.85 is generally regarded as sufficient repeatability for isolated measurement. Differences between the results from the two aqueduct measurements with different resolution were assessed using the Wilcoxon signed rank test. The Pearson correlation coefficient was used to assess the relationships between pulsatility measures.

Analysis of variance for repeated measurements was used to assess systematic differences between the repetitions performed in Paper I. The association between total arterial $\Delta V$ and the sum of cervical CSF and IJV $\Delta V$ was investigated using the Pearson correlation coefficient.

Group differences were assessed by 2-sided $t$-tests or Mann-Whitney tests where appropriate (Paper II-III). The chi-square test was used for comparing prevalence of IJV reflux between HY and MS groups (Paper III).

In Paper IV, multiple linear regression was used to assess relationships between regional brain volumes and CSF pulse pressure, arterial pulse pressure, the volume of spinal CSF pulsatility, the total volume of VA pulsatility (left plus right artery) and the total volume of ICA pulsatility (left plus right artery). The partial correlation coefficient was used to describe the strength of identified relationships.

In Paper V, differences between 2D and 4D PCMRI derived measures were investigated using 2-sided paired samples $t$-tests. In all studies, a p-value $<0.05$ was regarded as significant.
4 Results

4.1 Repeatability

Results from repeated 2D PCMRI measurements in Paper I are displayed in Table 2. For all measures, the ICC was above 0.85, except for the volume of right and left ICA pulsatility (ICC=0.80 and ICC=0.84, respectively) and net flow in the aqueduct (ICC=0.41). Estimations of the volume of aqueduct CSF pulsatility were lower for the high-resolution sequence than for the low-resolution sequence (0.03 ml versus 0.05 ml, p<0.001). The difference between the sequences decreased for larger sizes of the cerebral aqueduct, as determined from the high-resolution sequence (p=0.031).

There was a significant decrease in the volume of total arterial pulsatility and net flow rate between repetitions (p=0.017 and p=0.024, respectively). Intra-subject variations in the volume of total arterial pulsatility correlated with changes in heart rate (r=-0.51, p<0.001). When removing linear trends between measurements, i.e. taking away the systematic decrease in pulsatility that occurred between repetitions on group level, the repeatability for the volume of both left and right ICA pulsatility increased to ICC>0.85.

A second analysis was aimed towards assessing the relationship between pulsatility in arteries, veins and CSF. Analyzing the flow into and out of the cranium showed that the volume of total arterial pulsatility correlated with the volume of summed spinal CSF and IJV pulsatility (r=0.75, p<0.001). This relationship is visualized in Figure 13.
**Table 2.** Results from repeated ΔV measurements. Blood and spinal CSF flows were quantified at cervical C2-C3 level.

<table>
<thead>
<tr>
<th>Location</th>
<th>ΔV (ml)</th>
<th>Net flow (ml/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean±SD_{inter}</td>
<td>SD_{intra}</td>
</tr>
<tr>
<td>ICA (R)</td>
<td>0.56±0.14</td>
<td>0.07</td>
</tr>
<tr>
<td>ICA (L)</td>
<td>0.57±0.15</td>
<td>0.07</td>
</tr>
<tr>
<td>VA (R)</td>
<td>0.20±0.08</td>
<td>0.03</td>
</tr>
<tr>
<td>VA (L)</td>
<td>0.30±0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>Total arterial</td>
<td>1.60±0.35</td>
<td>0.15</td>
</tr>
<tr>
<td>IJV (R)</td>
<td>0.64±0.39</td>
<td>0.11</td>
</tr>
<tr>
<td>IJV (L)</td>
<td>0.36±0.23</td>
<td>0.08</td>
</tr>
<tr>
<td>Total IJV</td>
<td>0.97±0.49</td>
<td>0.16</td>
</tr>
<tr>
<td>Aqueduct CSF</td>
<td>0.045±0.023</td>
<td>0.005</td>
</tr>
<tr>
<td>Spinal CSF</td>
<td>0.77±0.23</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Figure 13. The volume of total arterial pulsatility versus the volume of summed spinal CSF and total IJV pulsatility. The line represents equality.

4.2 Craniospinal compliance

Paper II provided values on the magnitude and distribution of craniospinal compliance among healthy elderly. The volume of total cerebral arterial pulsatility (ICA+VA) measured at cervical level was $1.98 \pm 0.43$ ml. This was significantly larger than in the younger group of Paper I ($p<0.001$). The volume of spinal CSF pulsatility was $0.68 \pm 0.23$ ml. The craniospinal PVI calculated from combined 2D PCMRI and pressure data was $11.8 \pm 9.0$ ml. The volume of spinal CSF pulsatility was 35 % of the volume of total arterial pulsatility. For comparison the corresponding value for the younger group of Paper I was 49 %. This difference was significant ($p<0.001$).
4.3 Restricted venous flow

The balance between left and right IJV net flow rate for the MS and control groups of Paper III are visualized in Figure 14. No clear difference between the groups could be observed. There were no differences in total, left or right IJV net flow (p=0.38, p=0.51 and p=0.38, respectively). Five MS subjects and five controls displayed an IJV reflux during the cardiac cycle (p=0.93). There were no significant differences regarding aqueduct CSF net flow or volume of pulsatility (p=0.75 and p=0.14, respectively).

Figure 14. Normalized blood flow of the left and right internal jugular veins. Encircled subjects indicate those with IJV reflux.
4.4 Intracranial pulsatility and brain volumes

In healthy elderly, the volumes of several gray matter structures were negatively related to CSF pulse pressure and the volume of ICA and CSF pulsatility (Figure 15 and Table 3). The strongest relationships concerned the temporal cortex and hippocampus. In agreement with these observations, the ventricular volume increased for larger pulsatility. The volume of VA pulsatility and arterial pulse pressure were not correlated to the volume of any brain region.

Figure 15. Partial correlation coefficients between regional brain volumes and pulsatility variables. Correlation values are stacked on each other for visibility. All significant relationships are also presented in Table 3. GM=gray matter, WM=white matter. *Significant at $\alpha=0.05$, **Significant at $\alpha=0.01$
Internal relationships between the measures of pulsatility were also assessed. The volume of ICA pulsatility was related to the volume of spinal CSF pulsatility as well as CSF pulse pressure, but only after adjusting for net ICA flow (\(p=0.01\) and \(p=0.05\), respectively). The volume of spinal CSF pulsatility and CSF pulse pressure were not significantly correlated with each other.

**Table 3.** Partial correlations between regional brain volumes and pulsatility measures. \(\Delta V\) ICA was calculated from the sum of the left and right ICA waveforms.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>(\Delta V) ICA(^a)</th>
<th>(\Delta V) CSF(^b)</th>
<th>(\Delta P) CSF(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal cortex</td>
<td>(p=0.404)</td>
<td>(p=0.017)</td>
<td>(p=0.008)</td>
</tr>
<tr>
<td></td>
<td>(r=-0.41)</td>
<td>(r=-0.48)</td>
<td></td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>(p=0.003)</td>
<td>(p=0.006)</td>
<td>(p=0.028)</td>
</tr>
<tr>
<td></td>
<td>(r=-0.51)</td>
<td>(r=-0.47)</td>
<td>(r=-0.40)</td>
</tr>
<tr>
<td>Cerebral White Matter</td>
<td>(p=0.062)</td>
<td>(p=0.043)</td>
<td>(p=0.698)</td>
</tr>
<tr>
<td></td>
<td>(r=-0.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>(p=0.003)</td>
<td>(p=0.040)</td>
<td>(p=0.679)</td>
</tr>
<tr>
<td></td>
<td>(r=-0.50)</td>
<td>(r=-0.36)</td>
<td></td>
</tr>
<tr>
<td>Ventricular System</td>
<td>(p=0.011)</td>
<td>(p=0.110)</td>
<td>(p=0.008)</td>
</tr>
<tr>
<td></td>
<td>(r=0.44)</td>
<td></td>
<td>(r=0.47)</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for net ICA flow, age, sex, intracranial volume and mean arterial pressure, \(n=37\). \(^b\)Adjusted for age, sex, intracranial volume and mean arterial pressure, \(n=37\). \(^c\)Adjusted for age, sex, intracranial volume and mean arterial pressure, \(n=34\). \(r=\)partial correlation coefficient.
4.5 Four-dimensional flow measurements

The comparison in Paper V showed that 2D and 4D PCMRI produced highly correlated results for the volume of arterial pulsatility as well as for net flow (r=0.86 and r=0.95, respectively, n=69 vessels). These values improved further (r=0.93 and r=0.97, respectively) when excluding measurements with more than a 5 % variation in heart rate between the 4D and 2D acquisitions (n=31 vessels). The correlation between all vessel segments is illustrated in Figure 16.

Significant differences between 4D and 2D PCMRI were found for ICA and MCA net flow (p=0.004 and p<0.001, respectively) as well as for the volume of MCA pulsatility (p=0.006), n=69 (Table 4 and 5). However, these differences were attenuated when excluding measurements with large variations in heart rate (n=31 vessels).

**Table 4. Comparison between 2D and 4D PCMRI measurements of arterial ΔV. Values are given in ml.**

<table>
<thead>
<tr>
<th>vessel</th>
<th>n</th>
<th>ΔV 4D mean±SD</th>
<th>ΔV 2D mean±SD</th>
<th>2D-4D mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA</td>
<td>10</td>
<td>0.20±0.08</td>
<td>0.21±0.08</td>
<td>0.01±0.05</td>
<td>0.504</td>
</tr>
<tr>
<td>ICA</td>
<td>20</td>
<td>0.35±0.10</td>
<td>0.36±0.10</td>
<td>0.01±0.06</td>
<td>0.656</td>
</tr>
<tr>
<td>MCA</td>
<td>20</td>
<td>0.23±0.05</td>
<td>0.20±0.05</td>
<td>-0.03±0.04</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>ACA</td>
<td>19</td>
<td>0.14±0.08</td>
<td>0.12±0.08</td>
<td>-0.02±0.05</td>
<td>0.102</td>
</tr>
</tbody>
</table>
Figure 16. 2D versus 4D PCMRI derived $\Delta V$ for major cerebral arteries. The line represents equality. The correlation coefficient for the entire ensemble of vessels was $r=0.86$.

Table 5. Comparison between 2D and 4D PCMRI measurements of arterial net flow. Values are given in ml/s.

<table>
<thead>
<tr>
<th>vessel</th>
<th>n</th>
<th>Net flow 4D mean±SD</th>
<th>Net flow 2D mean±SD</th>
<th>2D-4D mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA</td>
<td>10</td>
<td>2.15±0.58</td>
<td>2.18±0.49</td>
<td>0.03±0.34</td>
<td>0.787</td>
</tr>
<tr>
<td>ICA</td>
<td>20</td>
<td>3.72±0.70</td>
<td>4.02±0.62</td>
<td>0.29±0.40</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>MCA</td>
<td>20</td>
<td>2.54±0.36</td>
<td>2.26±0.34</td>
<td>-0.28±0.29</td>
<td>&lt;<strong>0.001</strong></td>
</tr>
<tr>
<td>ACA</td>
<td>19</td>
<td>1.47±0.52</td>
<td>1.44±0.49</td>
<td>-0.02±0.21</td>
<td>0.627</td>
</tr>
</tbody>
</table>
5 Discussion

This dissertation focused on cardiac-related intracranial pulsatility using a unique combination of multi-modal MRI and invasive lumbar infusion tests. The analysis provided insight into the pulsatile forces exerted on the brain, and how the compensating mechanisms of the CSF system and venous blood cooperate in attenuating these rapid excitations. The approach taken in this dissertation has improved the understanding of the stability of PCMRI measurements, the mechanisms involved in intracranial pulsatility and how intracranial pulsatility may be related to pathophysiology.

5.1 Measurement aspects

Paper I investigated the repeatability of 2D PCMRI net flow and pulsatility measurements of cerebral arterial, venous and CSF flows (Table 2). The volume of arterial pulsatility was sensitive to variations in heart rate and decreased as the subject remained in the MRI machine. This could be related to a decrease in anxiety and blood pressure as the subject gradually adapted to the unusual environment. This favored standardization of the acquisition order, e.g. always performing the PCMRI measurements last in the MRI protocol.

The 2D PCMRI net flow measurements were reproducible for the ICA, VA and IJV. The volume of spinal and aqueduct CSF pulsatility also had sufficient precision. This indicated that aqueduct stroke volume measurements for selecting shunt candidates in normal pressure hydrocephalus (Bradley et al., 1996; Kahlon et al., 2007) are adequate from a measurement repeatability perspective. However, the small size of the aqueduct makes the measurements susceptible to partial volume overestimations, whereby as high resolution as possible should be used. The net aqueduct CSF flow showed high variability between measurements and interpretations based on single measurements of this quantity should be avoided (Table 2).
Nevertheless, the average aqueduct net CSF flow reported in Paper I is similar to invasive estimations (Ekstedt, 1978) and a previous 2D PCMRI study (Huang et al., 2004). Besides limitations associated with the measurement technique, slow changes in cerebrovascular caliber related to physiological and neuronal activity likely causes slow oscillations of CSF at the aqueduct, which will also will be reflected as variability in the measurements. Therefore, the stability in this measure may be improved by longer acquisition times.

The 4D PCMRI measurements produced estimations of the volume of arterial pulsatility (Figure 16) and net flow consistent with results from 2D PCMRI (Paper V). This supports using a single 4D PCMRI measurement to assess pulsatility in many intracranial arteries, despite using a velocity sensitivity adapted for vessels containing high velocities, such as the MCA.

The increase in 2D and 4D PCMRI correlation when excluding measurements with large differences in heart rates (Paper V) indicated that a large part of the random differences between measurements is a result of actual physiological variations. This is in agreement with the results from Paper I where it was demonstrated that physiological variability influences the repeatability.

The standard deviation of the difference between 2D and 4D PCMRI for the volume of ICA pulsatility and net flow was 0.06 ml and 0.40 ml/s, respectively (Paper V), which agreed with the corresponding values provided from repeated 2D PCMRI measurements of Paper I (0.07 ml and 0.32-0.33 ml/s, respectively, Table 2). This indicated that 2D and 4D PCMRI were associated with the same level of measurement variability, supporting that 4D PCMRI can replace 2D PCMRI, at least for the ICA.

Interestingly, the 2D PCMRI measurements of ICA net flow and the volume of ICA pulsatility in Paper V were smaller than corresponding values from
Paper I (approximately one sixth and one third lower for net flow and pulsatility, respectively). Machine dependence may have contributed to this discrepancy. However, phantom measurements indicated that for large vessels, such as the ICA, the accuracy was better than 10% for both the Philips (Paper I) and GE system (unpublished data). The large relative difference in ICA pulsatility could originate from differences in measurement location. In Paper I, ICA measurements were made more proximally, whereby the arterial pulsatility likely was less attenuated by arterial compliance. This is in line with previous observations regarding the dampening of arterial pulsatility along the ICA (Schubert et al., 2011). Additionally, the true temporal resolution of the 2D PCMRI sequence used in Paper V is lower than the sequence in Paper I-IV (a consequence of employing multiple views per segment) (Lotz et al., 2002). This smoothens the reconstructed arterial waveform, something that potentially decreases the estimated volume of arterial pulsatility.

The 4D PCMRI workflow required minimal prospective planning. This is very different from 2D PCMRI where skillful observations and interpretations are needed to place the measurement section perpendicular to the vessel of interest. Moreover, the 4D PCMRI analyses were highly automated (Figure 9), and only required basic anatomical knowledge from the user. This simplification in the PCMRI workflow will make the technique more accessible for future research projects, aiming to determine cerebral hemodynamics in multiple cerebral vessels.

### 5.2 Physiological aspects

In Paper I the correlation between arterial pulsatility and the sum of venous and cervical CSF pulsatility supported the notion that venous blood and CSF escapes the cranium in response to an increased arterial volume (Figure 13). This finding was in line with the Monro-Kellie principle and previous analyses (Enzmann and Pelc, 1993; Greitz, 1993; Balédent et al., 2001; Kim
et al., 2007). Essentially, this emphasizes the role of venous blood, as an important part of craniospinal compliance, in absorbing intracranial pulsatility.

The PVI is a factor describing the magnitude of craniospinal compliance (Marmarou et al., 1975; Shapiro et al., 1980). It describes how well arterial volume pulsations are absorbed at a certain pressure within the system (Avezaat and van Eijndhoven, 1986). Different infusion methods produce disparate PVI values (Tans and Poortvliet, 1989; Juniewicz et al., 2005; Sundström et al., 2010) whereby new methods are desirable. The method dependence in the PVI estimate may in part be a consequence of slow vasogenic responses to the infusion (Fridén and Ekstedt, 1983) that complicate the time series analysis used in the calculation. The presented method to assess PVI avoids the time series analysis by utilizing the pulsatile CSF dynamics, averaged over many cardiac cycles, both for infusion and MRI data. This quantification is likely less prone to slow vasogenic responses, but can still be obtained regardless of infusion pattern. We note that the measurement stability for the volume of arterial pulsatility was poorer (Paper I) than assumed in Paper II. The effect will be a less reliable estimate of PVI. Given the observations from Paper I, a possible improvement could be obtained from modeling effects of physiological variability such as heart rate. Alternatively, several measurements can be averaged to obtain a more stable value.

The PVI value provided in Paper II was the first estimation in healthy subjects based on the lumped parameter model in equation 2. The value is lower than previously reported in adult subjects (Shapiro et al., 1980). We hypothesize that this difference is related to the inclusion of the constant term in the mathematical model of the CSF system. Indeed, the studies using the constant term (Czosnyka et al., 2001; Juniewicz et al., 2005) have produced lower PVI estimates than studies without the constant term (Shapiro et al., 1980; Maset et al., 1987).
Venous compression was treated as part of the craniospinal compliance. This is important since otherwise the venous waveform should be subtracted from the arterial waveform when calculating the volume of the excitation. This calculation would yield the cyclic change in cerebral blood volume, i.e. the part of the arterial volume increase that is not directly compensated by venous outflow. The different approaches have been the subject of controversy as the method applied in Paper II indicated that the capacity of the spinal compliance is less than that of the intracranial compartment. This result has been argued not to conform with anatomical considerations, i.e. that the spinal dura mater is not as strictly confined in bone as the dura mater in the cranium (Tain et al., 2011), and with previous observations in subjects with a cervical block (Magnaes, 1989). However, by considering that the volume of spinal CSF pulsatility was approximately one third of the volume of total arterial pulsatility, it is clear that the dominating compensating mechanism, for processes in the time frame of a cardiac cycle, was located intracranially.

Interestingly, the proportion of spinal compliance appeared different between young and elderly subjects (Paper I and II). In elderly subjects a larger part of the total arterial pulse was absorbed by intracranial compensating mechanisms. The volume of total arterial pulsatility was also higher among elderly, something that may be a reflection of reduced aortic compliance in the elderly, inducing larger pulsatility in distal intracranial arteries.

5.3 Pathophysiological aspects

With focus on IJV flow in the supine position there were no signs of altered venous hemodynamics specific to MS (Paper III). The great variability in the lateralization of the IJV flow appeared similar between cases and controls (Figure 14). In most cases and controls, the right IJV conducted the major
part of the internal jugular drainage, which is in accordance with the literature (Stoquart-ElSankari et al., 2009).

We were unable to find a difference in the aqueduct CSF flow between MS and controls. Here, it is important to note that the aqueduct measurements were associated with partial volume overestimations (Paper I). However, because only results from sequences with identical settings were compared, this limitation hardly caused any group specific biases in the CSF waveform.

An IJV reflux was only observed in vessels carrying small flow rates, and only during a fraction of the cardiac cycle. As CCSVI has been described, with IJV insufficiency in 94 % (33 of 35) of relapse-remitting MS cases (Zamboni et al., 2009b), and almost never present in controls, this case-control evaluation should have had the ability to detect a difference. The failure to do so challenges the view of CCSVI as an important factor in MS.

Paper III was one of the first scientific evaluations of CCSVI ever performed. Today, there is accumulating evidence that the role of IJV congestion does not have a causative role in MS (Doepp et al., 2010; Centonze et al., 2011; Doepp et al., 2011; Zivadinov et al., 2011). Nevertheless, although the association between CCSVI and MS is weaker than initially reported, more research is required to exclude a role of altered venous hemodynamics in the MS etiology.

Paper IV investigated relationships between intracranial pulsatile stress and regional brain volumes. The sizes of several vital brain structures were related to arterial and CSF pulsatility (Figure 15). The volumes of the frontal cortex, temporal cortex, hippocampus and ventricles were related to two or more measures of intracranial cardiac-related pulsatility (Table 3). These brain regions are reported to have rapid age-related structural alterations (Tisserand et al., 2004; Fjell et al., 2009a; 2009b), stressing the importance of adjusting for age in the statistical analysis performed in this study.
Although we studied healthy subjects, the array of anatomical features that were related to large pulsatility resembled features linked to Alzheimer’s disease, i.e. small hippocampus and large ventricles (Fjell et al., 2009a). The findings should encourage investigating intracranial cardiac-related pulsatile stress as a potential risk factor that may cause or contribute to cognitive impairment and dementia.

There are no previous studies on arterial and CSF pulsatility and regional brain volumes. However, cortical thickness correlates with risk factors for cerebrovascular disease (Leritz et al., 2011). Surprisingly, the pattern of age-related tissue reduction may appear without reduction in local cerebral perfusion rates (Chen et al., 2011). Furthermore, in Alzheimer’s disease, where vascular risk factors are increasingly being recognized, the spatial distribution of gray matter thinning is associated with a matching pattern of hyperperfusion consistent with the paths of large cerebral vessels and their early divisions (Alsop et al., 2008). These paradoxical relationships may be explained if cardiac-related intracranial pulsatile stress harms the brain. In this scenario, high tissue perfusion rates and proximity to a large artery likely increases the risk of damage (O’Rourke and Hashimoto, 2007).

The cortical regions with volumes related to intracranial pulsatility were located near large cerebral vessels and their first branches, where vascular pulsatility likely is more intense. Still, the unique relationship between frontal cortex size and CSF pulsatility suggests that other mechanisms than pure intravascular damage might be active. Additionally the finding of a relationship between CSF $\Delta P$ and ventricular volume further emphasizes the potential importance of intracranial pulsatility in normal pressure hydrocephalus.

It is relevant to summarize the factors shaping intracranial pulsatility. The magnitude of the cardiac stroke volume and compliance of the aorta and pre-cranial arteries determine the magnitude of cerebral arterial pulsatility.
Therefore, large vessel stiffness may induce increased intra-vascular pulsatile stress. The craniospinal compliance determines the corresponding rise in CSF pressure, which constitutes a force of extra-vascular pulsatile stress inside the cranium.

The volume of CSF pulsatility and CSF pulse pressure were both related to the volume of ICA pulsatility, but they were not related to each other. This was a manifestation of the variability in magnitude and distribution of craniospinal compliance, in agreement with Paper II. This indicated that although all measures of pulsatility were related to the same phenomena, each variable held a considerable amount of unique information, supporting the choice to run correlation analyses between regional brain volumes and all available measures related to intracranial cardiac-related pulsatile stress (Paper IV).

Given the results of Paper IV, it is important to further study the mechanism behind the relationships between regional brain volumes and intracranial cardiac-related pulsatility. Potentially, this provides one additional piece of evidence of the link between arterial and cerebral aging. Furthermore, it may open an avenue of new treatment options aimed towards cognitive decline. In perspective of the aging population (Lutz et al., 2008) it will be increasingly important to evaluate factors contributing to cerebral aging, something that starts earlier than previously believed (Singh-Manoux et al., 2012). This dissertation suggests that PCMRI may be an important tool for that work.
6 Conclusion

We found that 2D PCMRI was a feasible tool to study the pulsatile waveform of cerebral arteries, veins and CSF. However there were differences between measurements that largely depended on physiological variability in the parameters of interest. To reduce the impact of this limitation, all flow quantifications should be performed last in the MRI protocol, so that the patient can adapt to the potentially stressful environment.

The volume of summed cerebral venous and spinal CSF pulsatility was related to the volume of intracranial arterial pulsatility. This verified the exchange in volume that occurs between the main intracranial constituents during the cardiac cycle, and also supported the view that intracranial veins contribute to craniospinal compliance.

We showed how PCMRI and CSF infusion tests could be combined to estimate PVI. The intracranial contribution to the overall craniospinal compliance was larger than previously thought. The distribution of craniospinal compliance was also different between age groups.

Using 2D PCMRI we were not able to reproduce the findings associated with the vascular MS hypothesis, CCSVI. If CCSVI is an entity associated with MS, the association is likely weaker than previously reported. Importantly, this did not support endovascular procedures in the veins of MS subjects.
Among elderly, CSF pulse pressure and the volume of arterial and CSF pulsatility were related to the sizes of several vital brain structures. The anatomical features associated with cardiac-related intracranial pulsatility resemble features that are strongly linked to Alzheimer's disease. This finding should stimulate further research exploring intracranial cardiac-related pulsatility as a contributing factor to cognitive decline and dementia.

4D PCMRI provided a viable methodology to estimate cerebral arterial pulsatility. The results were consistent with 2D PCMRI estimations. The workflow required minimal prospective planning and the output allowed comprehensive analysis of intracranial hemodynamics. Therefore, 4D PCMRI is an important tool for future investigations of altered intracranial hemodynamics and associated disorders.
7 Acknowledgements

I wish to express my sincere gratitude to:

Anders Eklund, my main supervisor, for giving me the opportunity to work in this captivating field. You have been a great source of inspiration and I am forever grateful for your dedicated mentorship. Jan Malm, my supervisor, for your enthusiasm and commitment to push our research field further. Richard Birgander, my supervisor, for sharing and teaching your expertise regarding complex neuroanatomy. Khalid Ambarki, a great colleague and a close friend. Working with you has been so much fun. My co-authors, Jon Hauksson, Peter Sundström, Noam Alperin, Kevin Johnson and Oliver Wieben. Kristin Nyman, Sonja Edvinsson, Hanna Ackelind and Ann-Catrine Larsson for skillful measurements and for always being helpful. My colleagues in the group as well as fellow PhD candidates, Kennet Andersson, Anders Behrens, Tomas Bäcklund, Gabriel Granåsen, Hanna Isarelsson, Niklas Lenfeldt, Sara Qvarlander and Nina Sundström. The staff at the biomedical engineering and radiophysics departments. Anna Wernblom, for administrative support. Olof Lindahl, Ronnie Lundström and the late Stefan Karlsson for leading the department and providing a nice environment to conduct research in. Anders Garpebring and Greger Orädd for fun experiments, interesting discussions and good collaboration. Göran Mannberg, for #!/bin/bash and your helpfulness. The staff at AMI centre, for the angiogram on the cover. All my friends that make the spare time fun. My relatives (including those I count as relatives) and especially my grandmother. You are all so supportive and kind. My mother and father. You are true role models and continue to inspire me. My wife, Mirjam, for your constant support and encouragement.
This project was supported by the Swedish research council; VINNOVA; and the Swedish Foundation for Strategic Research through their common initiative: ‘Biomedical engineering for improved health’; Swedish research council Grant No. 621-2011-5216; EU, Objective 2 Norra Norland, CMTF; The County Council of Västerbotten; and the Swedish Heart and Lung Foundation.
8 References


