MAGNETIC RESONANCE IMAGE-BASED HYDRODYNAMIC ANALYSIS OF CEREBROSPINAL FLUID MOTION IN TYPE I CHIARI MALFORMATION

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MAGNETIC RESONANCE IMAGE-BASED HYDRODYNAMIC ANALYSIS OF CEREBROSPINAL FLUID MOTION IN TYPE I CHIARI MALFORMATION

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ABSTRACT

Type I Chiari malformation (CMI) is a complex disorder of the craniospinal system that is estimated to effect as many as 1:1000 adults in the US. In CMI, the fluid space near the craniovertebral junction becomes compressed and the tonsils of the cerebellum become stretched downward through the foramen magnum (FM), creating a partial blockage to the motion of cerebrospinal fluid (CSF) in the subarachnoid spaces. Diagnosis of the disorder is difficult because the most commonly used diagnostic criterion, cerebellar tonsil descent (CTD) >3-5 mm past the foramen magnum does not correlate well with patient symptom severity.

Because of the hydrodynamic component of the disorder, subject-specific computational modeling of cerebrospinal fluid dynamics may have utility in identifying biomechanical parameters to (1) quantify the severity of CMI and (2) quantify the changes to the CMI-affected spinal canal created by corrective surgery. In the first study presented in this work, magnetic resonance image based computational models of the cervical spinal canal were used of CSF dynamics showed that longitudinal impedance (LI) to CSF motion was elevated in a group of CMI patients compared to healthy volunteers and did not correlate well with CTD.

In the second study, a similar modeling methodology was used to compare pre-surgery CMI patients, post-surgery CMI patients, and healthy volunteers. LI was compared against CTD, cross-sectional area, hydraulic diameter, gradients at peak systole, peak diastole, and peak-to-peak pressure gradient. LI was found to decrease
significantly post-surgery on average, but remained significantly higher than in healthy volunteers. LI was found to be sensitive to small average changes in the cross-sectional geometry of the SSS, but only correlated weakly with changes to CTD. However, because of the preponderance of female patients in the study, pre-surgery and post-surgery LI data may have been biased low.

Finally, velocity fields at the foramen magnum and C2 level of the spinal canal were compared to validate the subject-specific models against physical measurements from 2D phase-contrast MRI. Peak velocities and through-plane velocity profiles compared poorly between CFD and 2D pcMRI. CFD showed a trend of underestimating the peak velocities observed in 2D pcMRI at both the FM and C2 levels of the spinal canal. CFD velocity profiles at C2 lacked the anterior flow dominance and heterogeneous velocity distributions typically seen in 2D pcMRI measurements. Thus, while the data presented here was useful for analyzing difference between velocity fields in CMI-affected spinal canals and healthy spinal canals, CFD velocity fields could not be validated using 2D pcMRI.
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CHAPTER I

INTRODUCTION

1.1 Type I Chiari Malformation and Diagnostic Problem

Type I Chiari malformation (CMI) is a complex disorder of the craniospinal system that is estimated to effect as many as 1:1000 adults in the US [1]. In CMI patients, the fluid space in the cisterna magna becomes compressed and the tonsils of the cerebellum become stretched downward through the foramen magnum (FM), creating a partial blockage to the passage of cerebrospinal fluid (CSF) between the lower cranial and upper spinal subarachnoid spaces. Specifically, cerebellar tonsil descent (CTD) of greater than 3-5 mm has typically been used as the quantitative anatomical criterion for CMI. However, this criterion has become problematic for two reasons. The first problem is that the extent of CTD does not necessarily correlate with the severity of the associated neurological symptoms or level of patient disability. The range of symptoms in CMI can be wide and often overlaps with the symptomatology of other neurological disorders [2, 3], making CMI difficult to differentiate. The second problem is that incidental observation of cerebellar tonsil herniation has become more common [4] with the increased use of magnetic resonance imaging (MRI) in head and neck injury examinations. Thus, clinicians and researchers have a need for new and better pathophysiology metrics to quantify the severity of CMI.
1.2 Cerebrospinal Fluid Dynamics

One approach to analyzing CMI pathophysiology that has recently seen an increase in interest is the analysis of cerebrospinal fluid (CSF) dynamics near the craniovertebral junction (CVJ). During the cardiac cycle, a small but measurable amount of CSF is displaced from the lower cranial subarachnoid space (SAS) to the spinal SAS to maintain pressure and volume equilibrium in the cranium. The partial flow blockage near the CVJ created by cerebellar TD causes elevated CSF pressure gradients, which can lead to a problematic increase in hydraulic pressure on nervous tissue. In hydrodynamic terms, alterations to CSF pressure gradients are likely related to alterations in impedance to CSF motion [5, 6], CSF velocities and velocity patterns [7-15], neural tissue motion [16-18], and craniospinal compliance [19-22]. Though the bulk of research in CSF dynamics in CMI to this point has been concerned with velocimetric analysis, it is possible that alterations to multiple or all of the aforementioned parameters may be useful to quantify changes to the biomechanical environment near the CVJ in CMI.

1.3 In Vivo Imaging and Subject-Specific Modeling

Because of increased interest in CSF dynamics, some of the focus in CMI research has shifted to the development of MRI protocols for direct in vivo measurement of CSF hydrodynamics or the development of subject-specific computational fluid dynamics (CFD) models to simulate CSF hydrodynamics. The goal of both is to non-invasively provide useful information which may help objectively evaluate CMI patients by the severity of the biomechanical alterations to their craniospinal system. Such approaches could potentially improve the care and treatment of CMI patients if they were found to be clinically translatable. To date, many studies have employed in vivo imaging
or CFD techniques to conduct variational velocimetric analysis. However, only a few have focused on parameters such as impedance or compliance. Thus, there exists a need to further investigate these parameters and assess their potential utility in being a quantitative metric of CMI severity.

1.4 Current Study Objectives

The objective of this study is to use MR image-based hydrodynamic measures of resistance and compliance to investigate differences between (1) adult CMI patients pre- and post-decompression surgery and (2) CMI patients and healthy control subjects. Specifically, longitudinal impedance (LI) to CSF motion will be investigated and compared against static morphometric or geometric measurements and more conventional hydrodynamic measures, such as pressure and velocity.

1.5 Dissertation Overview

The remainder of this dissertation is comprised as follows:

- Chapter 2 presents a brief background of the CSF circulation, normal mechanism of CSF motion, and normal craniospinal anatomy before discussing the changes that occur with CMI and the surgical technique typically used in attempting to correct those changes.

- Chapter 3 contains a review of past studies that have used engineering analysis to examine cerebrospinal fluid hydrodynamics in the cranial and spinal subarachnoid spaces, which was originally published as a review paper in 2011 and has been updated to include discussion of more current relevant studies.
• Chapter 4 describes a study where CFD modeling and longitudinal impedance analysis were used to show that impedance to fluid motion in the spinal subarachnoid space was elevated in CMI patients compared to healthy volunteers and did not correlate with CTD.

• Chapter 5 describes a study where CFD modeling and longitudinal impedance analysis was used to show that impedance to fluid motion in the spinal subarachnoid space decreases significantly as a result of decompression surgery.

• Chapter 6 describes a study where CSF velocities obtained from the CFD models from Chapter 5 were compared against the 2D phase-contrast MR images used to formulate model boundary conditions to assess whether physical measurements match the computational models.

• Chapter 7 draws conclusions from the combined results of each preceding chapter and discusses possible implications and future research directions.
CHAPTER II
BACKGROUND

In attempting to analyze CSF hydrodynamics, it is first useful to have a basic understanding of the anatomy and physiology of CSF, the craniospinal anatomy through which it moves, and the mechanism which causes CSF motion. This chapter discusses each of those topics.

2.1 Cerebrospinal Fluid Circulation and Motion Mechanism

In the craniospinal system, the brain and spinal cord are suspended in CSF. Functionally, the purpose of CSF is two-fold: (1) to buffer the brain and spinal cord from impact with the walls of the cranium and vertebrae and (2) to transport nutrients toward and metabolic waste away from nervous tissue. CSF is a filtrate of blood plasma, secreted by the choroid plexus in the four ventricles of the brain at a net rate of ~0.35 ml/min. Secretion occurs when sodium ions are transported through the epithelial cells lining the choroid plexus, which in turn draws chloride ions through the same lining. The high sodium-chloride concentration then causes osmosis of water through the epithelial lining, supplying the clear fluid constituent of CSF [23]. Proteins and monoamines are also transported into the CSF, giving it a dilute macromolecular content. The macromolecules have only a small effect on the density and viscosity of the CSF though. In fact, CSF viscosity has been measured to be ~0.008 Poise (range 0.007-0.01 Poise) and
CSF density measured to be 1.0 gm/cm$^3$ at normal body temperature (~37°C) [24], which are similar to the properties of water at the same temperature.

At any point in time, the amount of CSF in the craniospinal system of an adult human is ~140 ml, but may range from 110-160 ml depending on stature. However, the rate of secretion is thought to be relatively constant. Pressure-volume balance in the craniospinal system is regulated by structures known as arachnoidal villi. Arachnoidal villi are primarily located in the superior cranial subarachnoid space and act as a passive pressure valve system. When a threshold pressure gradient of ~1.5 mmHg between the CSF and venous blood is reached, the vesicular passages in the arachnoidal villi allow free flow of CSF into the venous drainage system [23].

Once secreted and prior to draining, CSF navigates the complex ventricular system of the brain to reach the subarachnoid space (SAS). Figure 2.1.1 shows an idealized diagram of the CSF circulation pathway in the cranium and cervical spine. From the blood stream through the ventricular system and into the SAS, the circulation pathway is as follows:

- CSF is secreted by the choroid plexus into each lateral ventricle of the brain.
- CSF flows through the foramen of Monro into the lower third ventricle.
- The choroid plexus in the third ventricle adds more CSF to the circulation.
- CSF flows down the aqueduct of Sylvius to the fourth ventricle.
- The choroid plexus in the fourth ventricle adds more CSF to the circulation.
• CSF exits the ventricular system from apertures (foramina of Luschka and Magendie) in the fourth ventricle and enters the cisterns surrounding the cerebellum in the inferior cranial SAS; some CSF remains in the fourth ventricle and continues into the central canal of the spinal cord.
Figure 2.1.1: Diagram of CSF circulation pathway in the cranium and cervical spine. [25]
In contrast to the passive movement of CSF into and out of the craniospinal circulation the movement of CSF within the ventricular system and SAS is relatively dynamic. Of particular interest in this study is the motion of CSF between the lower cranial cisterns and the spinal SAS, which is pulsatile in nature. Several mechanisms have been suggested for the origin of the pulsation which causes CSF motion [25-27], though the primary mechanism has been shown to be the expansion of the brain resulting from changes in intracranial blood volume during the cardiac cycle. Brain expansion is the result of a phase difference between the inflow of arterial blood to and outflow of venous blood from the cranium created by capillary resistance. From the Monro-Kellie hypothesis [27], it is assumed that the volume of space in the cranium is fixed and its contents are incompressible. It follows that the cranium, blood, CSF, and brain tissue must maintain a state of volume equilibrium such that an increase in the volume of one component is compensated by a decrease in volume of another. With a net increase in cranial blood volume during systole, volume equilibrium is maintained by displacement of CSF and sometimes brain tissue caudally through the foramen magnum. Also, as blood volume increases in the cranium, so too does intracranial pressure, which creates a caudal-directed pressure gradient in the SAS and also contributes to caudal-directed CSF motion during systole. Likewise, when cranial blood volume decreases during diastole, CSF moves in the cranial direction (Figure 2.1.2).
An early study by Feinberg and Mark [29] hypothesized that vascular-driven movement of the entire brain may act as a pump for the CSF circulation, which was consistent with the Monro-Kellie hypothesis. CSF motion in the spinal SAS has been studied extensively, particularly since the advent of phase contrast MRI (pcMRI), which allows for non-invasive measurement of CSF velocity. Additionally, studies have also examined brain and spinal cord motion and the relationship between fluid and tissue motion. Several more in-depth pcMRI-based studies of the source of CSF motion were subsequently undertaken to expand on these findings.

A series of studies of tissue motion in the cranium were conducted by Greitz et al. [27, 30] using pcMRI methods with the goal of characterizing the CSF pumping mechanism. The first of these studies hypothesized that the expansion and retraction of
the brain during systole and diastole acts similar to a piston and causes the large CSF pulsations observed in the cervical spinal SAS. A second study concluded that arterial expansion was the driving mechanism behind pulsatile brain movements, which lead to a morphological change in the inferior part of the brain and consequent caudal-directed CSF motion. Henry-Feugeas et al. [31] drew similar conclusions in a later study, noting specifically that arterial expansion in the cerebellar tonsils appeared to be the primary initiator of systolic CSF flow and added that pulsations in the spinal vasculature may also contribute to the CSF pumping mechanism.

Levy and DiChiro [32] characterized normal CSF flow by detailing flow phenomena in a region ranging from the skull to the thoracic spine using pcMRI in a mid-sagittal plane. The onset of caudal-directed CSF flow was observed slightly earlier in the posterior SAS than in the anterior SAS. Oppositely-directed flows were observed in the anterior SAS and the posterior SAS for short periods during flow reversal in early systole and early diastole. This study also found a measurable caudal-directed velocity of the spinal cord during cranial-directed CSF flow, which suggested that spinal cord motion precedes CSF flow reversal and reinforced the view that CSF flow results from the pumping action created by systolic brain expansion. Both Levy and DiChiro [32] and Enzmann, et al. [33] found that, in general, CSF velocities were highest in the cervical region of the spine and gradually decreased with distance from the foramen magnum.
2.2 Normal Craniospinal Anatomy

This section describes the normal anatomy of bone and nervous structures in the craniospinal system. It is included here for the benefit of the reader.

2.2.1 Bony Anatomy

Once CSF exits the brain ventricular system, the boundary of its circulation becomes the cranium, vertebral column, and meninges. The cranium, or skull, is comprised of 22 bones connected by immobile fibrous suture joints. Of those, eight are the flat irregularly shaped bones that form the smooth, dome-like cranial cavity, which encases and protects the brain and sensory organs. The base of the cranium is essentially a three-tiered basin which follows the contour of the inferior surface of the brain. From superior to inferior, these basin tiers are: the anterior cranial fossa, which accommodates the frontal lobes of the brain; the middle cranial fossa, which accommodates the temporal lobes of the brain; the posterior cranial fossa, which accommodates the cerebellum. Though the cranial bones are contoured to the inferior surface of the brain, brain tissue does not directly contact the cranial bones. In addition to the layer of CSF, the brain is also buffered from direct contact with bone by the meninges, which are described below. Though the volume of a typical adult human cranial cavity is 1300-1350 ml in adult humans [34] only 100-150 ml of that volume is occupied by CSF. The remainder is occupied by the brain, brain stem, and spinal cord. At the base of the skull is the foramen magnum, which serves as a passage into the spinal column for the spinal cord and CSF.

The spinal column (Figure 2.2.1) is comprised of 33 vertebrae connected by fibrocartilaginous discs, which are classified into five subsets by region. Cranial to caudal, these subsets are the cervical vertebrae (C1-C7), thoracic vertebrae (T1-T12),
lumbar vertebrae (L1-L5), sacral vertebrae (5), and coccygeal vertebrae (4) [34]. In adults, the sacral and coccygeal vertebrae are fused to form the sacrum and coccyx. The cervical, thoracic, and lumbar vertebrae are all capable of relative movement, whereas the sacral and coccygeal are not. The fibrocartilaginous discs act as spacers between vertebrae and serve to dampen shock to the spinal column.

The function of the spinal column is two-fold: (1) to form a mechanical linkage to support the weight of the upper body and (2) to act as a protective casing for the spinal cord. Each of the vertebrae between C3 and L5 has two main bony components, the vertebral body and arch, which are linked to form a circular opening, called the vertebral foramen, through which the spinal cord and CSF pass. The functions of the vertebral body are to protect the delicate internal structures, allow flexibility, and support the surrounding body weight. The function of the vertebral arch is to provide a site for attachment of muscles and ligaments.
Figure 2.2.1: Anatomical diagrams of the C1, C2, C3-C6, and C7 vertebrae (left) showing the variation in bony anatomy and vertebral foramen shape along the spinal column (right). [Public domain images from Gray’s Anatomy]
The membranous meningeal layers which line the inside of the cranium and spinal column buffer nervous tissue from direct contact with bone. From superficial to deep, these layers are the dura mater, arachnoid mater, and pia mater [34]. In the cranium, the dura mater is comprised of an outer periosteal layer and an inner meningeal layer. The two layers of the dura mater separate at certain points and support the dural venous sinuses, which facilitate drainage of blood toward the heart. Only the meningeal layer continues into the spinal column, where it is separated from the surface of the vertebral foramen by a layer of epidural fat. The meningeal layer is tough and inflexible and acts as a sort of sac to contain the CSF. The arachnoid mater lines the inside of the meningeal dura mater and acts a network of connective fibers between the dura mater and pia mater. The pia mater serves as a protective sheath around the nervous tissue. In both the cranium and the spine, CSF flows between the arachnoid mater and the pia mater, hence the term “subarachnoid space” (Figure 2.2.2).

Figure 2.2.2: Cross-sectional diagram of an idealized spinal SAS showing the spatial relation of the meningeal layers, nerve branches, and spinal blood vessels. [Public domain images from Gray’s Anatomy]
2.2.2 Anatomy of the Cerebellum, Brain Stem, and Spinal Cord

In the lower cranial cisterns and spinal SAS, the nervous structures comprising the inner boundary for the CSF circulation are the cerebellum, brain stem and spinal cord. The cerebellum is a large lobular structure that forms the largest part of the hindbrain. Whereas the spinal cord is mainly a signal transducer, the cerebellum is responsible for higher functions, such as muscular coordination, cognitive functions such as language comprehension and attention, and emotional functions such as responses to fear and pleasure [34]. The cerebellum does not initiate movement, but does contribute to coordination, precision, and accurate timing. It receives input from sensory systems and other parts of the brain and spinal cord to coordinate motor activity. Because of this coordination function, damage to the cerebellum does not cause paralysis, but instead produces disorders in fine movement, equilibrium, posture, and motor learning. Interestingly, the cerebellum contains more neurons than all the other parts of the brain combined, but only accounts for 10% of the total volume of the brain [16].

The brain stem and spinal cord form a long, tube shaped neural structure which extends from the base of the cerebrum to the L1-L2 vertebral region. On average, the spinal cord has a diameter of ~1.8 cm and is ~45 cm long in normal adult humans. At the end of its length, the spinal cord splits into the cauda equina (horse’s tail). Thirty one nerve pairs branch out from the spinal cord between individual vertebrae into various locations in the body and are bundled together into tracts. Nerve tracts can be sub-classified into ascending or descending tracts. The ascending tracts transmit signals from proprioceptors and other sense receptors. The descending tracts contain motor nerves, which transmit signals from the brain that control muscle contraction. Pressure at certain
points along the spinal cord can produce various dysfunctions. The cord itself is composed of white matter, from which the nerve tracts originate, and gray matter, which is composed of nerve cells. In addition to the small vessels in the spinal cord’s pia mater sheath, many blood vessels run longitudinally along the length of the spinal cord.

2.3 Type I Chiari Malformation

This section details the pathophysiology of CMI. It also briefly describes the typical surgical treatment method used by neurosurgeons.

2.3.1 CMI Pathophysiology

As mentioned in previously, CMI has historically been defined in morphological terms. The distinguishing pathoanatomical features of CMI are thought to be cerebellar tonsil descent (CTD) of more than 3-5 mm past the foramen magnum as diagnosed by anatomical MRI and crowding of the fluid space in the cisterna magna [2, 35-37]. Figure 2.3.3 illustrates the difference between the anatomy of a healthy subject and one with CMI. However, CTD may trigger a feed-forward pathophysiological cascade which makes cause and effect difficult to differentiate. This mechanism is discussed in more detail in Chapter 3.

One reason for the problematic understanding of CMI is that its etiology is not well-understood. For example, several hypotheses have arisen regarding other pathological conditions that may cause cerebellar herniation and has led to the recognition of clinical subgroups of CMI patients. One such subgroup is that of patients with an underdeveloped posterior cranial fossa. Several studies have shown that, on average, CMI patients have a smaller posterior cranial fossa volume than normal, in
addition to abnormalities in the dimensions of bony landmarks [2, 38]. A small posterior cranial fossa volume was noted as being particularly prevalent in CMI patients who also had concomitant SM. This characteristic is not present in all CMI patients, though.

Figure 2.3.1: Diagrams (top) and MR images (bottom) illustrating the difference between the craniospinal anatomy of a healthy subject and one that is affected by CMI.
Another subgroup of patients that has recently been identified is that of patients who may have developed CMI due to tethering at the base of the spinal cord. Royo-Salvador et al. [39] proposed that abnormally high tension on the terminal filum (long fiber that provides longitudinal support to the spinal cord) may result in acquired CMI. Abel et al. [40] found radiological evidence of acquired CMI resulting from a fatty terminal filum. Similarly, Tubbs et al. [41] found a high number of instances of CMI associated with lipomyelomeningocele (fatty mass on the spinal cord). However, a cadaver-based study by Tubbs et al. [42] demonstrated that traction force applied to the base of the spinal cord was dispersed before the level of the foramen magnum or cerebellum. Thus, high tension on the terminal filum may not always result in acquired CMI.

Milhorat et al. [43] identified a subset of CMI patients with hereditary connective tissue disorders. The authors hypothesized that hypermobility of the joint at the craniocervical junction in combination with connective tissue disorders may cause cranial settling and some amount of CTH. However, 45% of the patients in the study were prior surgical failures and may have had some craniocervical instability resulting from the bone removal during the surgical procedure.

There is evidence of a subgroup of CMI patients characterized by the presence of altered hydrodynamics due to the presence of neurological pathologies such as hydrocephalus or intracranial hypertension (also referred to as pseudotumor cerebri or PTC) [44-46]. For example, Johnston et al. [44] found that ~14% of patients in a series treated for PTC were found to have acquired CTH at re-evaluation, though only 6% had the level of CTH characteristic of CMI in pre-treatment evaluation. Though the authors
conceded that pretreatment MRI may have been inadequate, the rate of incidence was far
greater than the general incidence rate (0.77%) for CTH proposed by Meadows et al.
[47]. Bejjani et al. [46] added that PTC and certain cases of CMI may just be slight
variants based on overlapping symptomatology and concomitant incidence rates.

Finally, syringomyelia (SM), which is characterized by the development of a fluid
syrinx (or cyst) in the center of spinal cord, has been observed in up to 81% [48] of
symptomatic CMI cases in certain patient series. SM may result from CTH, but CTH
may also result from SM. Syringes are known to form caudal to CSF flow obstructions
such as CTH, vary in length and diameter, and can expand, destroying nerve fibers
adjacent to the spinal cord. Syringes may also form as the result of flow obstruction from
post-traumatic arachnoidal scarring (e.g. from whiplash). Depending on the position of
the syrinx, the altered local hydrodynamics may also induce CTH. SM associated with
CMI can result in a multitude of additional symptoms, including loss of sensation in the
extremities, bladder and bowel dysfunction, and flaccid paralysis [49].

2.3.2 CMI Symptomatology

Another complication in CMI diagnosis is that the neurological symptoms of CMI
are typically diverse and vague in presentation, often overlapping with symptoms of other
neurological disorders and making accurate diagnosis a long and difficult process. The
most common symptoms observed in CMI patients have been documented as the
following:

- Severe sub-occipital headache, exacerbated by physical exertion or straining
- Dizziness that worsens when lying down or with sudden posture change
- Rapid-movement-induced disequilibrium
• Difficulty sleeping due to pain, difficulty breathing when lying down, etc.
• Neck pain
• Numbness or tingling feeling in the upper extremities
• Unrelenting fatigue
• General body weakness
• Blurred vision
• Tinnitus
• Dysphagia

Mueller and Oro found that 95% of patients in a prospective study of 265 reported five or more symptoms and 49 distinct symptoms were identified by two or more patients [3], ergo why diagnosis based on neurological evaluation can be so difficult. One commonality is that physically traumatic events are often cited as a symptom trigger, though it is largely unclear as to why certain symptoms may present at seemingly random points in time. More detailed discussions of the symptomatology associated with CMI can be found in studies by Milhorat et al. [2] and Mueller and Oro [3].

The complicated symptom presentation of CMI can result in a delay of several years before accurate diagnosis is made, and in a significant number of cases patients are actually referred for psychological care before being found to have CMI. The limited utility of standard MRI in linking complicated and diverse symptoms to tonsillar herniation means that the diagnosis of symptomatic CMI in many cases is made subjectively, which can result in missed or misdiagnosis [50]. The development of an
objective, quantitative measure associated with symptoms or symptom severity of CMI could have a positive impact on patient outcomes and experiences.

2.3.3 CMI Treatment Method

For symptomatic CMI patients, the primary method for surgical treatment is decompression of the craniovertebral junction, which is designed to create more space around the compressed cerebellar tonsils and brain stem and restore the natural flow of CSF. Generally speaking, there are two parts to the procedure. First, a small portion of the occipital bone (suboccipital craniectomy) and sometimes the posterior arch of the C1 vertebra (C1 laminectomy) are removed to allow the cisterna magna and subarachnoid spaces near the CVJ to expand. Second, the dura is sometimes opened to view the cerebellar tonsils and determine if resection of the cerebellar tonsils is necessary. If the dura is opened, it must then be patched and sealed closed. This patch may enlarge the dura and create a small amount of additional space near the CVJ. Figure 2.3.2 shows a diagram of a typical decompression procedure.
Though decompression surgery is the standard surgical treatment method, surveys of neurosurgeons have shown significant disagreement regarding when surgery should be recommended and what techniques should be employed. For example, one survey found disagreement regarding the extent of bone removal, whether opening of the dura mater was necessary and, if so, what type of dural patch should be used to close it, and whether brain tissue should be removed [51]. Further, surgical success in published patient series tends to be poorly defined and subjective in nature, relying on patients’ anecdotal reports of symptom improvement and the surgeon’s judgment as to whether enough space has been created at the CVJ. For example, Mueller and Oro [52] found that decompression surgery significantly improved the quality of life for patients ~80% of the time and McGirt et al. [53] found mild to moderate symptom recurrence in more than 20% of patients over time. In these cases, it was not clear if the surgery was initially successful,
but then failed over time, or whether the initial success was overstated due to the subjective nature of the outcome measures and possible influence of a placebo effect.
CHAPTER III
REVIEW OF CEREBROSPINAL FLUID DYNAMICS STUDIES IN TYPE I CHIARI MALFORMATION

This chapter discusses past studies that have used dynamic imaging, modeling, and/or simulation methods to investigate cerebrospinal fluid hydrodynamics in cranial and spinal subarachnoid spaces in both healthy humans and those affected by Type I Chiari malformation. It is based on a review paper published in 2011 [54], but has been revised and expanded to include several newer studies of engineering analysis applied to CSF dynamics and one key study [5] in which the author was co-author on the paper.

3.1 Introduction

Type I Chiari Malformation (CMI) has historically been described as a change in the morphology of the hindbrain, characterized by cerebellar tonsil descent (CTD) of more than 3 to 5 mm past the foramen magnum as diagnosed by magnetic resonance imaging [2, 36, 37]. CTD results in reduced cross-sectional area of the subarachnoid space near the foramen magnum [36] (Figure 3.1.1). Thus, at first glance the problem appears to be geometric in nature. However, the dynamic nature of CSF and tissue motion may make the problem more complex and the cross-sectional blockage may trigger a pathophysiological cascade making cause and effect difficult to decipher. Up to
present, it remains unclear whether the changes in morphology associated with CMI result more consistently from genetic or mechanical factors [2, 55, 56].

Figure 3.1.1: T2-weighted sagittal magnetic resonance images of the head and cervical spine (above) and three-dimensional reconstruction of the cervical spinal subarachnoid space near the foramen magnum (below). (A) Healthy subject; (B) Patient with symptomatic CMI.
From a mechanical perspective, the present understanding of the pathophysiological cascade in CMI is as follows (Figure 3.1.2):

- Morphological changes to the cerebellum crowd the SAS near the foramen magnum [38, 57, 58].
- Crowding of the local SAS results in obstruction of CSF flow pulsations.
- The obstruction of CSF flow pulsations results in increased resistance and abnormal CSF velocities [8, 11].
- Because the driving pressure (arterial pressure) of the pulsation is much larger than intracranial pressure, the same volume of CSF is forced out of the cranium (assuming no reduction in the volume of CSF displaced).
- An increased pressure gradient is required to push the same volume of CSF from the cranial to the spinal SAS with an obstruction present.
- The increased CSF pressure gradient may also displace brain tissue, resulting in further alteration to the morphology of the cerebellum and producing abnormal biomechanical forces on the nervous tissue and vasculature [27].
The abnormal pressures acting on nervous tissue may be at the root of the neurological symptoms associated with CMI [59]. Chronic changes in pressure may also alter the elasticity, permeability, and water content of nervous tissue over time. All these factors in combination produce a flow problem that is more complex than a geometric change alone. Because some of the etiological factors appear to be hydrodynamic in nature, hydrodynamic analysis of CSF motion may be a useful tool to improve understanding of the pathophysiology in CMI.
3.2 Existing CMI Diagnostic Methods: Static versus Dynamic

While many MRI techniques are available to analyze the craniospinal system, only static anatomic imaging has fully translated to clinical use. Unfortunately, static anatomic measurements have correlated poorly with patient response to treatment. In particular, the widespread adoption of static anatomic MRI in diagnosis has called into question the relevance of the classical definition of CMI. For example, Milhorat et al. [2] found no correlation between cerebellar tonsil descent (CTD) and the level of disability in patients with CMI. Further studies have shown that patients can exhibit CMI-like neurological symptoms with minimal CTD and be asymptomatic with large CTD [47, 57, 60-62].

Part of the difficulty in establishing useful diagnostic criteria for symptomatic CMI, and perhaps why many different diagnostic methods are being explored, is that its etiology is not well understood. CTD may result from multiple anatomical factors including genetic disorders [55, 56], underdevelopment of the posterior cranial fossa, and tethering of the spinal cord due to the presence of a fatty or tight terminal filum. Studies have used computed tomography imaging to show that, on average, patients with CMI have a smaller posterior cranial fossa volume than normal subjects [63], and thus insufficient space for a normally developed hindbrain, in addition to other dimensional abnormalities in the posterior fossa and brain. However, these abnormalities are not universally present in CMI patients [2, 38, 64]. Similarly, studies have demonstrated high incidence of CMI concomitant with lipomyelomeningocele [41] and an acquired version resulting from a fatty terminal filum [40]. However, one study [42] demonstrated that traction force applied to the spinal cord at the terminal filum is dispersed before the
foramen magnum and may not have a tethering effect on the cerebellum. Therefore, a
diagnostic technique to assess spinal cord tension may not have any relevance.

Perhaps the discrepancies between the classical definition of CMI and
contradictory clinical findings can be attributed to the disorder being more dynamic than
previously thought, particularly in terms of CSF hydrodynamics. At present, it is unclear
if the symptomatology and tissue damage resulting from CMI are more the result of
altered neural anatomy or altered CSF hydrodynamics or both (Figure 3.2.1). Parameters
such as resistance to flow and craniospinal compliance are dynamic components of the
biomechanical environment in the craniospinal system that are not measurable by static
evaluation techniques. Hydrodynamic measurements could provide clinicians with more
complete information in order to determine which patients will have progressive
symptoms and would respond to treatment best. Further, it may also be possible to gauge
the success of surgical treatment if such parameters could be normalized and shown to
change significantly after decompression surgery.
Figure 3.2.1: CMI is characterized by both the altered neural anatomy and cerebrospinal fluid (CSF) dynamics. Presently, it is unclear which of these directly cause the symptoms and/or nerve tissue damage which patients experience.

A number of different dynamic MRI tools are available for evaluating different aspects of CMI, though none of these have yet translated to standard clinical use. The most well-researched of these dynamic tools is phase-contrast MRI (pcMRI). pcMRI has been used for a number of applications, including measurement of CSF velocity in 2D [7-10, 13, 17, 65-71] and 4D [14, 15, 72], measurement of CSF pulse wave velocity [73], measurement of cerebellar tonsil motion [16, 27], and quantification of craniospinal compliance [22, 74]. Recent advancements have also introduced new MR measurement modalities to quantify different aspects of craniospinal disorders. These modalities include techniques such as MR diffusion tensor imaging to measure the direction, alignment, and structural integrity of nerve fiber tracts [75, 76], MR elastography to
measure brain elasticity [77, 78], and MR spectroscopy to measure metabolite levels in the brain [79].

3.3 In Vivo CSF Velocity Measurements

pcMRI has been widely explored in CMI research, as it provides *in vivo* measurement of velocity that can be valuable to understanding the CSF environment. However, it has yet to translate to use in standard clinical scenarios for several reasons. First, pcMR imaging requires specific scanning protocols that are often only available at research-class hospitals. Second, interpretation of time-varying velocity field data is more complex than static CTD measurements obtained from standard anatomical MRI. Finally, research studies have focused on analyzing peak CSF velocities, but have yet to establish a reliable quantitative criterion (e.g. similar to the 5 mm criterion for CTD) for distinguishing between CMI patients and healthy controls. Nonetheless, many groups have undertaken studies to investigate the potential clinical utility of measuring CSF velocity with pcMRI. Menick [80] reviewed many early articles describing methods for obtaining and interpreting qualitative and quantitative CSF velocity and cerebellar tonsil motion data. Several more recent studies are summarized in Table 3.1 and discussed here.
Table 3.1 Summary of *in vivo* pcMRI measurements of CSF velocities in healthy (H) and CMI patient (P) cases.

<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging Sequence</th>
<th>Subject (N) (H)Healthy / (P)Patient</th>
<th>Spinal Region</th>
<th>Peak V_{WS} (cm/s)</th>
<th>Peak V_{MA} (cm/s)</th>
<th>Qualitative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haughton et al.[7]</td>
<td>2D pcMRI</td>
<td>H (10)</td>
<td>FM</td>
<td>2.4 ± 0.2</td>
<td>2.8 ± 0.3</td>
<td>Uniform profiles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P (8)</td>
<td>FM</td>
<td>3.0 ± 0.4 (Pre)</td>
<td>4.0 ± 0.3 (Pre)</td>
<td>Jetting, bi-directional in-plane velocities</td>
</tr>
<tr>
<td>Dolan et al.[9]</td>
<td>2D pcMRI</td>
<td>P (8)</td>
<td>FM</td>
<td>3.4 (Pre)</td>
<td>6.9 (Pre)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C1</td>
<td>2.4 (Pat)</td>
<td>3.9 (Pat)</td>
<td></td>
</tr>
<tr>
<td>Iskandar et al.[10]</td>
<td>2D pcMRI</td>
<td>H (1)</td>
<td>FM</td>
<td>0.8 ± 0.3</td>
<td>0.1 ± 0.3</td>
<td>Uniform profiles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P (4)</td>
<td>FM</td>
<td>5.2 ± 0.6 (Pre)</td>
<td>9.7 ± 0.8 (Pre)</td>
<td>Jetting, bi-directional in-plane velocities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C1</td>
<td>3.5 ± 0.2 (Pat)</td>
<td>6.6 ± 0.7 (Pat)</td>
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</tr>
<tr>
<td>Quigley et al.[8]</td>
<td>2D pcMRI</td>
<td>H(10)</td>
<td>FM</td>
<td>---</td>
<td>---</td>
<td>Uniform profiles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P(8)</td>
<td>FM</td>
<td>---</td>
<td>---</td>
<td>Jetting, bi-directional in-plane velocities</td>
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<tr>
<td>Sakas et al.[11]</td>
<td>2D SPAMM</td>
<td>H(11)</td>
<td>Cervical SAS</td>
<td>2.8 ± 0.3</td>
<td>---</td>
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<tr>
<td></td>
<td></td>
<td>P(15)</td>
<td>Cervical SAS</td>
<td>2.1 ± 0.4 (Pre)</td>
<td>4.2 ± 0.5 (Pat)</td>
<td>---</td>
</tr>
<tr>
<td>McGirt et al.[13]</td>
<td>2D pcMRI</td>
<td>P(14)</td>
<td>Cervical SAS</td>
<td>---</td>
<td>---</td>
<td>Decreased posterior or anterior-posterior flow compared to healthy controls</td>
</tr>
<tr>
<td>Shah et al.[67]</td>
<td>2D pcMRI</td>
<td>P(17)</td>
<td>FM-C2</td>
<td>5.6 ± 0.6</td>
<td>3.5 ± 0.1</td>
<td>Higher peak velocities with distance from FM.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>C4-C5</td>
<td>7.5 ± 0.6</td>
<td>4.7 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Krueger et al.[68]</td>
<td>2D pcMRI</td>
<td>P(14)</td>
<td>FM</td>
<td>6.3 ± 0.7 (Sym)</td>
<td>4.5 ± 0.5 (Sym)</td>
<td>Jetting, bi-directional in-plane velocities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.9 ± 0.7 (Asym)</td>
<td>4.1 ± 0.4 (Asym)</td>
<td></td>
</tr>
<tr>
<td>Bunck et al.[14]</td>
<td>2D/4D pcMR</td>
<td>H (10)</td>
<td>FM</td>
<td>3.6 ± 0.6</td>
<td>---</td>
<td>Uniform profiles</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C1</td>
<td>3.6 ± 0.3</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C2</td>
<td>4.5 ± 0.3</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P(2)</td>
<td>C2/C3</td>
<td>19.7 ± 0.1</td>
<td>---</td>
<td>Jetting, bi-directional in-plane velocities</td>
</tr>
<tr>
<td>Bunck et al.[15]</td>
<td>4D pcMR</td>
<td>H (10)</td>
<td>FM</td>
<td>3.2 ± 0.3</td>
<td>---</td>
<td>Uniform profiles</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C1</td>
<td>3.6 ± 0.3</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C2</td>
<td>4.0 ± 0.3</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P(20)</td>
<td>FM</td>
<td>7.6 ± 1.1</td>
<td>---</td>
<td>Jetting, bi-directional in-plane velocities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C1</td>
<td>12.8 ± 2.3</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C2</td>
<td>8.4 ± 1.9</td>
<td>---</td>
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</tr>
</tbody>
</table>
Haughton et al. [7] compared systolic and diastolic CSF velocities in CMI patients and volunteers using pcMRI and found that average peak systolic velocity in pre-surgical CMI patients was significantly higher than in healthy volunteers (3.1 vs. 2.4 cm/s). The study also noted inhomogeneous flow patterns in patients compared to blunt flow patterns in healthy volunteers as a significant finding and perhaps a characteristic feature of the CMI. Similar phenomena were observed in studies of adult CMI patients by Quigley et al. [8] and pediatric CMI patients by Iskandar et al. [10], which each found fluid jets and synchronous bidirectional flow (large cranial-directed velocities in the anterior subarachnoid space, lower caudal-directed velocities in adjacent regions) in the anterior subarachnoid space of CMI patients, and plug-like flow in healthy volunteers.

Studies by Iskandar et al. [10] and Dolar et al. [9] examined differences in systolic and diastolic velocity in CMI patients before and after decompression surgery and found that mean peak caudal-directed velocities (5.2 to 3.5 cm/s [10], 3.4 to 2.4 cm/s [9]) and mean peak cranial-directed velocities (9.7 to 6.6 cm/s [10], 6.9 to 3.9 cm/s [9]) decreased as a result of decompression surgery. The adult study [9] also noted that peak cranial-directed velocities varied widely pre-surgery (2.5-14.6 cm/s) and to a lesser extent post-surgery (2.1-5.4 cm/s), which supported the theory that CMI is associated with abnormal CSF velocities. Though the study showed that decreases in CSF velocity correlated with clinical improvement, this result was only qualitative.

Continuing with the theme of identifying homogeneous flow patterns in CMI patients, a study by Shah et al. [67] imaged CMI patients at several levels of the spine from FM to C4 to examine the caudal reach of flow inhomogeneities. Peak velocities at the FM were found to agree well with prior results (6.0 [67] vs. 5.3 [81] cm/s at peak
systole and 3.4 [67] vs. 2.8 [81] cm/s at peak diastole). More importantly though, the study found that peak systolic and diastolic velocities attenuated with distance from the FM in healthy controls, whereas they did not attenuate in CMI patients. Finally, though prior studies found that peak CSF velocities had utility for differentiating CMI patients from healthy volunteers, Krueger et al. [66] found that peak CSF velocities were similar in symptomatic and asymptomatic CMI patients.

In a novel study that utilized high-speed midsagittal 2D pcMRI, CSF velocity wave speed (VWS) in the spinal subarachnoid space of three healthy subjects was calculated to be 4.6 m/s by Kalata et al. [73]. As velocity wave speed is known to relate to the material properties of a flow conduit, the study proposed that it may provide an estimate of tissue stiffness in the craniospinal system when measured in the spinal subarachnoid space. Further, as increased tissue stiffness is known to result from chronically increased pressures, the authors of the study proposed that the VWS technique may be useful in quantifying stiffness differences in the spinal subarachnoid space of healthy subjects and patients with CMI. Though only the VWS in systolic acceleration was found to be linear in the study, mean VWS during acceleration compared favorably to cerebrospinal fluid pressure wave speed (PWS) in the spinal subarachnoid space obtained in several in vitro simulations [82, 83] and estimated based on in vivo measurements [84-86].

Recently, researchers have begun to use 4D pcMRI to capture more complex flow phenomena such as secondary flow and vortex strength [87]. Bunck, et al [14] found that CSF velocities measured with both 4D pcMRI and transverse 2D pcMRI showed good agreement in healthy control subjects. However, the same group also found that higher
peak velocities were found in CMI patients using 4D pcMRI measurements compared to 2D pcMRI [15]. Though 4D pcMRI is not as well-validated as transverse 2D pcMRI, these studies nonetheless reinforce the theory that elevated CSF velocities may be a characteristic feature of CMI.

3.5 Modeling and Simulation to Understand Cerebrospinal Fluid Hydrodynamics

To date, several computational studies of varying levels of complexity (Figure 3.5.1) have been used to study CSF hydrodynamics in the spinal SAS. Those studies are summarized in this section (Table 3.2). Loth, et al. [62] conducted the first CFD simulation of CSF motion in a 2D, geometrically idealized, rigid wall model of the spinal SAS. In this study, inertial effects were shown to dominate the flow field under normal physiological flow rates. Peak instantaneous Reynolds numbers were estimated to be in the range of 150-450 and peak instantaneous Womersley numbers were estimated to be in the range of 5-17, suggesting that CSF motion is laminar, but highly oscillatory. These findings were validated by the additional finding of blunt velocity profiles at peak flow in both the CFD model and pcMRI analysis of CSF motion in a healthy spinal SAS.

Using a similar geometry model (elliptical annulus), Stockman [63] further developed the 2D, rigid wall model of the spinal SAS by analyzing the influence of small structures in the SAS, such as nerve roots, arachnoidal trabeculae, and perivascular blood vessels, using a lattice Boltzmann methodology. However, the study only found that the introduction of small structures into the geometry model did not have a significant impact on velocity or pressure profiles when spacing of the structures was symmetric. As a result of this study, it has generally been assumed that the small structures in the spinal SAS have a negligible impact on bulk CSF hydrodynamics.
Figure 3.5.1: Examples of existing computational models of the spinal SAS shown in decreasing order of anatomical complexity [68, 69, 72, 88-90].
Table 3.2: Summary of existing spinal canal CFD studies and results. Note: wave propagation studies used to study syringomyelia are not included.

<table>
<thead>
<tr>
<th>Study</th>
<th>Technique</th>
<th>Geometry</th>
<th>Boundary Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loth et al. [68]</td>
<td>Reduced Navier-Stokes</td>
<td>2D concentric ellipse</td>
<td>Pulsatile flow from MRI</td>
<td>CSF motion is inertia-dominated in the SSS</td>
</tr>
<tr>
<td>Stockman [90]</td>
<td>Lattice Boltzman</td>
<td>2D annulus, idealized microstructures</td>
<td>Pulsatile body force</td>
<td>Microstructures did not have significant impact on.</td>
</tr>
<tr>
<td>Roldan et al. [91]</td>
<td>Boundary Element Method</td>
<td>3D subject specific</td>
<td>Steady</td>
<td>Peak CSF pressure gradient is elevated in CMI</td>
</tr>
<tr>
<td>Gupta et al. [88]</td>
<td>CFD, rigid wall</td>
<td>3D subject specific</td>
<td>Pulsatile subject-specific</td>
<td>Dimensions and permeability of porous media impact pressure gradients, net CSF flow in SSS is negligible.</td>
</tr>
<tr>
<td>Linge et al. [89]</td>
<td>CFD, rigid wall</td>
<td>3D idealized</td>
<td>Pulsatile flow, idealized</td>
<td>Spatial flow variations from CFD resembled those in pCMI, laminar flow, uniform longitudinal pressure variation.</td>
</tr>
<tr>
<td>Linge et al. [92]</td>
<td>CFD, rigid wall</td>
<td>3D idealized</td>
<td>Pulsatile flow, idealized</td>
<td>Cerebellar tonsils cause pressure gradients and complexity of flow patterns to increase.</td>
</tr>
<tr>
<td>Linge et al. [93]</td>
<td>CFD, rigid wall</td>
<td>3D idealized</td>
<td>Pulsatile flow, idealized</td>
<td>Pressure gradient magnitudes increased significantly with increased pulse frequency</td>
</tr>
<tr>
<td>Linge et al. [94]</td>
<td>CFD, rigid wall</td>
<td>3D idealized</td>
<td>Pulsatile flow, idealized</td>
<td>Geometry changes simulating surgical defects decreased CSF velocities and pressures.</td>
</tr>
<tr>
<td>Rutkowska et al. [69]</td>
<td>CFD, rigid wall</td>
<td>3D subject specific</td>
<td>Pulsatile flow, idealized</td>
<td>CMI patients had greater peak velocities and pressure gradients.</td>
</tr>
<tr>
<td>Helgeland et al. [95]</td>
<td>CFD, rigid wall</td>
<td>3D subject specific</td>
<td>Pulsatile flow, idealized</td>
<td>Geometric complexity of CMI-affected spinal canal may cause flow instabilities</td>
</tr>
<tr>
<td>Clarke et al. [71]</td>
<td>CFD, rigid wall</td>
<td>3D subject specific</td>
<td>Pulsatile flow, subject-specific</td>
<td>Peak CSF pressure higher in CMI without syringomyelia than without syringomyelia.</td>
</tr>
<tr>
<td>Cheng et al. [70]</td>
<td>CFD, rigid wall</td>
<td>3D subject specific</td>
<td>Pulsatile flow, subject-specific</td>
<td>Arachnoiditis increases resistance to CSF flow.</td>
</tr>
<tr>
<td>Cheng et al. [96]</td>
<td>Coupled CFD/FEA</td>
<td>3D subject specific</td>
<td>Pulsatile flow, subject-specific</td>
<td>Spinal cord motion has a negligible effect on CSF pressure.</td>
</tr>
<tr>
<td>Yiallourou et al. [72]</td>
<td>CFD, rigid wall</td>
<td>3D subject specific</td>
<td>Pulsatile flow, subject-specific</td>
<td>CFD underestimates CSF velocities observed in 4D pcMRI</td>
</tr>
<tr>
<td>Pahlavian et al. [97]</td>
<td>CFD, rigid wall</td>
<td>3D subject specific with nerve roots</td>
<td>Pulsatile flow, subject-specific</td>
<td>Nerve roots produce CSF velocity fields closer to 4D pcMRI than [72].</td>
</tr>
<tr>
<td>Martin et al. [5]</td>
<td>CFD, rigid wall</td>
<td>3D subject specific</td>
<td>Pulsatile flow, subject-specific</td>
<td>Longitudinal impedance higher in CMI patients and decreases after surgery.</td>
</tr>
<tr>
<td>Shaffer et al. [6]</td>
<td>CFD, rigid wall</td>
<td>3D subject specific</td>
<td>Pulsatile flow, subject-specific</td>
<td>Longitudinal impedance higher in CMI patients and doesn’t correlate with CTD.</td>
</tr>
</tbody>
</table>
Expanding to 3D, Linge et al. [89, 92-94] produced similar results in a series of studies using geometrically idealized models of the posterior cranial fossa and cervical spine. The first study [89] examined the effect of anatomic variation on normal CSF hydrodynamics and found that flow patterns resembled those observed in in vivo MRI studies (e.g. synchronous bi-directional flow) and the simulated pressure pulse (0.75 mmHg peak-to-peak amplitude) compared favorably with in vivo CSF pulse pressure measurements in healthy subjects (1-2 mmHg). The second study [92] found that the introduction of cerebellar tonsil geometry into the model caused pressure gradients and flow pattern complexity to increase. The third study [93] found that pressure gradient magnitudes also increased with flow pulse frequency. The fourth [94] used the spinal canal geometry from the second study modified to simulate varying levels of CMI decompression surgery. Though geometry models were again quasi-idealized, it was found that peak systolic CSF velocities and pressure gradients were generally lower in post-operative models.

Recently, Helgeland et al. [95] used a subject-specific spinal canal geometry model and quasi-idealized CSF flow waveform to assess whether the geometric complexity of the CMI-affected spinal canal could cause flow to become transitional or turbulent. Analysis of the distribution of local Reynolds number in the model showed pockets of flow instabilities that the authors hypothesized represented CSF flow just below the threshold of transitional flow.

With advent of better imaging and geometry modeling capabilities, several recent studies have begun to use patient-modeling for both SSS anatomy and/or CSF motion. Roldan et al. [64] simulated CSF flow in rigid, subject-specific SSS geometries based on
the spinal canal of a CMI patient and a healthy volunteer. The study employed the boundary element method, which neglects inertial effects, to solve the Navier-Stokes equations. As a consequence of that solution methodology, peak systole and peak diastole had to be modeled separately as steady flow. Because of the influence of CTD on the spinal SAS geometry, both peak pressure and the pressure gradient between the inlet and outlet in the CMI model were found to be higher than in the healthy model. In both models, flow fields were heterogeneous with fluid jets observed anterolaterally to the spinal cord, which was qualitatively similar to results from several pcMRI studies [8-10].

Rutkowska, et al [66] compared cyclic CSF flow patterns in subject-specific 3D models of the spinal SAS to velocimetric measurements taken with 2D pcMRI for CMI patients and healthy controls. In general, the findings of the study were that peak pressures and velocities in the CMI patient models were elevated compared to those observed in the healthy controls. In a similar study, Clarke et al [71] simulated CSF flow in CMI patients with and without concomitant syringomyelia and found that peak CSF pressure in the spinal canal was higher in the patient without syringomyelia. Investigating the possible impact of syringomyelia further, Cheng et al showed that resistance, and thereby pressure, increased when the spinal canal was modeled to have arachnoiditis [70], but spinal cord motion had only a negligible effect [96].

In a unique study that introduced the notion of modeling the SAS as porous media rather than an open conduit, Gupta et al. [68] conducted a study to simulate CSF motion near the CVJ using a uniformly distributed anisotropic porous media model to represent the arachnoidal trabeculae. The results of this study showed that the density and
dimensions of the mock arachnoidal trabeculae had a large impact on pressure gradients, which agree with the findings by Cheng et al [70].

Taking the CFD-pcMRI comparison study to a new level of complexity, Yiallourou et al. [72] compared CSF flow patterns in subject-specific 3D models of the entire cervical spine to 4D pcMRI measurements taken at the level of each intervertebral disc in the cervical spine. The study showed that the subject-specific CFD models underestimated peak CSF velocities compared to the 4D pcMRI measurements at all locations. Likewise, it was also shown that peak velocities were much more concentrated in the anterior spinal SAS of the 4D pcMRI measurements compared to the CFD models. Taken together these results suggested that the subject-specific CFD models were missing some element (e.g. arachnoidal trabeculae) to account for the difference between the models and the 4D pcMRI measurements.

Expanding on the previous study, Pahlavian et al [67] added realistic 3D nerve roots and denticulate ligaments to the models developed by Yiallourou et al and again compared the results to 4D pcMRI measurements taken at all the intervertebral levels in the cervical spine. The results showed that peak velocities in the more anatomically complex 3D models had better agreement with 4D pcMRI measurements than did the models assuming a completely open conduit. However, the CFD models still underestimated peak velocities compared to 4D pcMRI measurements.

Several studies have used LI analysis to quantify the impact of CTD on the geometry of the SSS near the CVJ. An early study by Kalata [98] used CFD modeling to show that that impedance in models of the SSS from two CMI patients (Figure 3.5.2) decreased by a large amount (>30%) in post-surgery CMI patients compared to pre-
surgery, but was still much higher than that observed in a healthy volunteer (Figure 3.5.3). These results were expanded by Martin et al. [5]. Though these results were promising, there was no statistical power to the data.

Figure 3.5.2: Meshed 3D reconstructions (sagittal view) of the SSS geometries used for the CFD simulations in a healthy volunteer and two CMI patients before and after decompression surgery in [5, 98].
Figure 3.5.3: LI (denoted $Z_{L(1-8HZ)}$ in this figure) for the five SSS models used in [5, 98].

The author’s Master of Science thesis [99] also investigated LI in the SSS using CFD modeling. The main finding of the work was that LI was a useful analysis metric to stratify symptomatic CMI patients, asymptomatic CMI patients, and healthy volunteers, even though subject sample sizes were disproportionate (Figure 3.5.4). The study also found that LI had a strong linear correlation with the mean cross-sectional area ($A_{CS}$) and mean hydraulic diameter ($D_H$) in the SSS models (Figure 3.5.5), which showed that constriction in the SSS was reflected by LI. Though the data in this study was also promising, it suffered from lack of statistical power and mixing adult and pediatric CMI patients. It should also be noted that subject-specific boundary conditions were not used in this study, though they were not necessary for LI analysis as will be shown in Chapter IV.
Figure 3.5.4: LI for the 20 SSS models used in [99].

Figure 3.5.6: Relationship between LI and 1/Acs (left) and 1/Dh (right) showing a strong linear relationship between LI and SSS geometry [99].
Considerable interest has also been given to in silico and in vitro models of CSF hydrodynamics in the spinal SAS affected by SM. A full review of these model studies is given by Martin et al. [69]. Bilston et al. [70] simulated CSF movement in the perivascular spaces of the spinal cord given different phase delays between CSF and arterial pulsations. These simulations demonstrated that, given certain phase delays between the CSF and arterial pulsations, adverse pressure gradients could occur which would move perivascular fluid into the syrinx. Fluid-filled coaxial elastic tube models of the spinal SAS with SM were constructed by Carpenter et al. [60], Berkouk et al. [71], Bertram et al. [58, 59], and Cirovic [72]. An electrical circuit equivalence model was developed by Chang et al. [73]. Bilston et al. [74] formed a model of SM with spinal arachnoiditis modeled as a porous obstruction. Martin et al. [69, 75, 76] conducted in vitro experiments to examine the importance of spinal stenosis and presence of a non-communicating syrinx on spinal CSF hydrodynamics. Those experiments highlighted the importance of mechanical properties of the neural tissue such as compliance and permeability and the complex fluid-structure interaction involved with CSF flow obstruction and neural tissue. Overall, experimental work with SM hydrodynamics have been helpful to detail the spatial pressure and flow environment, but have employed significant simplifications and need further comparison and validation with In vivo measurements. In addition, the experiments have not revealed a reason why a syrinx commonly forms caudal to CSF flow blockage, such as that observed at the craniovertebral junction in CMI.
3.6 Hydrodynamic Parameters Affected by CMI

Currently, the focus of CMI research is developing MR imaging protocols for direct measurement of CSF hydrodynamics by imaging methods or indirect calculation of hydrodynamic parameters through the use of computational models. The goal of examining these parameters is to provide clinically useful information to improve care and treatment for patients with CMI. Some challenges to clinical translation of direct or indirect hydrodynamic parameters include:

a. Typical values of hydrodynamic parameters are not well-established, as evidenced by the wide range of CSF velocities discussed previously. Many physiological data can vary significantly with age, sex, weight, and other factors. Thus, establishing indices for normal versus pathological hydrodynamics is problematic. One possible solution could be to develop parameters that are based on subject specific diagnostic tests rather than direct comparison to healthy subjects. These tests could be performed on a case by case basis to examine how the cerebrospinal fluid system responds to a particular stimulus. Such a type of test would be analogous to diagnostic techniques for assessment of stroke, coronary artery disease, and hypertension by vasodilation [100].

b. Computational models require many assumptions in order to be workable. These assumptions will introduce some amount of error into parameters calculated from models. Some assumptions are realistic, such as assuming that CSF behaves like water [24]. However, other assumptions such as rigid, impermeable conduit...
boundaries and homogenous tissues could be an oversimplification. It is difficult to conclude when and which assumptions are valid, as these measurements are difficult to make *in vivo*.

c. MRI measurements have resolution limits. It is possible that the current imaging limitations are one of the confounding factors behind seemingly contradictory data in CSF velocimetric studies. Additionally, the accuracy of the simulations can only be as good as the boundary conditions used. Thus, boundary condition sensitivity analysis is an important step before making any conclusions on hydrodynamics.

d. Parameter interpretation is complex. While imaging and simulation studies have provided many hydrodynamic data for assessment of CMI, better fundamental understanding CSF dynamics is needed to correctly interpret what influence these parameters have on the global dynamics. Additional complexities are also involved in correlation of parameters with clinical results such as symptom improvement, which is highly subjective.
At present, the hydrodynamic parameters of interest are 1) craniospinal geometry, 2) velocity and volume flow, 3) compliance and tissue mechanical properties, 4) resistance/impedance, and 5) pressure. The following discussion details each of these parameters in light of the current findings and challenges involved in their determination.

Craniospinal Geometry

While CTD has proven to be a poor sole criterion for diagnosis of CMI and has not been satisfactorily correlated with the severity of neurological symptoms, it is clear that the geometry of the spinal canal is altered by the cerebellar deformity. In turn, those geometric changes could impact velocity, compliance, resistance, and pressure. However, the sequence in which these properties become altered is unclear. For example, it is possible that the mechanical properties of nervous tissue or craniospinal blood vessels become altered, which can then lead to slight brain settling and consequential CTD. Brain settling may then cause increases in CSF velocity and resistance to flow, which could in turn create larger pressure gradients that may further alter the compliance of the craniospinal system [59]. The success of decompression surgery to alleviate symptoms has made geometry appear to be the likely root cause of the problem. In fact, Tubbs et al. [42] stated “It is so likely that Chiari decompression will resolve the situation that an inadequate clinical outcome most always is because of an inadequate decompression.” But while surgery alters the geometry of the subarachnoid space, it may also alter compliance in the craniospinal
system, leading researchers to question if geometry or compliance is really at the root of the problem.

Obtaining an accurate representation of the cerebrospinal fluid system geometry is difficult with the pre-processing workflow required to perform CFD simulations. To perform these simulations, the geometry images need to be segmented and smoothed to form the numerical geometry which involves difficult interpretation of the fine and complex anatomical structures in the cerebrospinal fluid system contained within the images. At present, the precision of image-based geometry measurements are on the sub-millimeter level with varying levels of repeatability and accuracy. The dimensions of the subarachnoid space in a patient with CMI can be small near the cerebellar tonsils with complex morphology, which could translate into significant errors when simulating fluid flow. In particular, the pressure gradients required to move cerebrospinal fluid are highly sensitive to dimensions. For steady flow in straight circular pipe, the pressure gradient \( \frac{dP}{dz} \) required to cause flow \( Q \) is proportional to the inverse of the diameter \( D \) of the pipe to the fourth power along with fluid viscosity \( \mu \) and flow \( \frac{dP}{dz} = \frac{128 \mu Q}{\pi D^4} \). Gap dimensions for CMI patients can be as small as one millimeter. Errors in these gap dimensions due to image resolution could easily be 20-50%, which would lead to large errors in pressure gradient calculations. In addition, hydrodynamic simulations are typically limited to local regions of the cranial, cervical, thoracic or lumbar subarachnoid space. This is a product of the limitations in magnet strength and scanning time.
An added complexity in evaluating craniospinal geometry is that tissue moves during the cardiac cycle. At present, it is unclear how influential tissue motion is on the hydrodynamic environment. This motion has been reported as small but detectible and may not always be negligible given the importance of gap size. Brain displacements as measured by phase-contrast imaging have been described to be 0.1 to 0.2 mm with velocities in the range of 1-2 mm/s [27, 101, 102]. In addition, spinal cord motion has been measured in healthy subjects and velocity values were even greater (12.4±2.9 mm/s [32] and 7.0±1.4 mm/s [103]). Alperin et al. [22] reported maximum bulk spinal cord displacement for healthy control volunteers and CMI patients to be 0.33 and 0.39 mm, respectively.

Velocity

Abnormal velocity distributions in the axial plane have been consistently observed in CMI patients and are thought to be characteristic of the disorder. However, studies have drawn different conclusions about which velocity field features are indicative of severity. Presence and location of simultaneous velocity jets and regions of stagnant flow can indicate the extent of crowding at the foramen magnum due to CTD. However, there may be instances where velocity appears to be uniformly low when crowding is significant. For example, in presurgical evaluations of patients, Dolar et al. [9] observed velocity jetting in the anterior cervical SAS where Sakas et al. [11] observed reduced velocities in the same region. Though neither study examined what fraction of the subarachnoid space in the foramen magnum was open to flow, this contradiction suggests that it
may be necessary to analyze fluid velocity in the context of the subarachnoid space geometry.

Additionally, the importance of high cerebrospinal fluid velocities in relation to nerve damage, which is thought to contribute significantly to the symptomatology of CMI, is not well-established. Elevated velocities may imply higher pressure gradients and a greater adverse effect on the nervous tissue in the system may be expected. The contribution of other forces imparted by fluid flow, such as wall shear stress, to nerve damage is as yet unexplored.

While investigating intracranial compliance, Alperin et al. [22] demonstrated that volume flow analysis may offer more insight to the altered biomechanical environment than velocity field analysis. Results in that study showed that peak volume flow rate measured at the C2 level was higher in volunteers (215 ml/min) than in CMI patients (190 ml/min). However, the net volume of fluid displaced during the cardiac cycle was similar between the two cases (0.57 ml healthy vs. 0.56 ml patient). This implies that while increased resistance due to CTD may affect velocity magnitudes throughout the cardiac cycle, flow rate may not be affected in the same way. Pressure gradients in the spinal canal (dP/dz) would then be forced to increase to maintain volume flow in the presence of increased resistance. Prolonged pressure elevation may then affect the elastic properties of the tissue in the craniospinal system and, thus, change the compliance of the system.

pcMR image-based velocity measurements may also have significant error and could be improved in many ways. Measurements are limited to velocity in a
single direction (i.e. through-plane or in-plane velocity in a single direction) at approximately 30 time points during the cardiac cycle. Possible sources of error are signal noise, breathing artifacts, and difficulty in selection of velocity encoding value, since cerebrospinal fluid velocities may vary widely. Further, cerebrospinal fluid velocities difficult to measure in regions where flow is particularly low and the influence of breathing on fluid motion is maximal. Cerebrospinal fluid velocities are also difficult to measure in regions with complex flow patterns when significant portions of the velocity are not in the direction of velocity encoding, such as at the foramen magnum in CMI. In these measurements, integration of velocity to determine hydrodynamic parameters such as flow volume can also introduce error since the region of interest in the subarachnoid space cross-section needs to be interpreted. In the context of CMI, velocity can be greatest in the narrow regions and thus the region of interest selection can have a critical impact. Techniques that may help improve fluid velocity measurement, and thereby calculation of hydrodynamic parameters from phase-contrast images, include reduction of signal noise from breathing, automatic optimization of velocity encoding values, better selection and optimization of the region of interest for flow measurement, greater temporal resolution, and velocity measurement in multiple directions within an entire volume of cerebrospinal fluid.
Compliance and Tissue Mechanical Properties

It has been hypothesized that, under normal conditions, the healthy spinal subarachnoid space could act as a sort of notch filter to dampen incoming cerebral blood flow pulsations to supply smooth blood flow to the neural tissue by Madsen et al. [104] and Luciano et al. [105]. Thus, any disruption to the system that alters compliance, such as an obstruction to CSF motion, could reduce the damping effect on cerebral blood flow pulsations. A reduction in damping of the cerebral blood flow pulsations would then result in abnormal biomechanical forces acting within the craniospinal, arterial, or venous system. A number of studies have sought to understand craniospinal compliance based on the relation of arterial, venous, and CSF flow at the foramen magnum [106, 107]. For example, Sivaramakrishnan et al. [20] showed increased intracranial compliance in CMI patients after decompression surgery. Presently, other non-invasive methods of measuring compliance and tissue mechanical properties in the spinal subarachnoid space are being developed. These include MR imaging techniques that allow calculation of compliance in the spinal subarachnoid space from CSF velocity wave speed [73] and magnetic resonance elastography to measure brain elasticity [77, 78] and local material properties.

A major reason for the focus on non-invasive compliance measurement methods is that there are many complexities to physically obtaining and measuring material properties of tissues \textit{ex vivo} that may affect compliance assessment of the craniospinal system. Some of these complexities include 1) differences in material testing techniques can produce varying results, 2) testing
direction and orientation can have a large impact on measurements of anisotropic tissues [108-111], and 3) removal and separation of each tissue component is not straight-forward, easily repeatable, or always complete [111]. In addition, the time after harvesting, subject age, and preservation methods may influence tissue properties.

Resistance/Impedance

CTD likely increases resistance to CSF flow from the cranial to the spinal subarachnoid space. However, further research is necessary to quantify this resistance and assess its importance in CMI patients. Such quantification is difficult as the pressure gradient across the blockage requires either invasive pressure measurements or computational simulations. While resistance can be increased by changes in geometry such as CTD, the impact on CSF hydrodynamics can follow two different scenarios. First, if the pressure gradient in the subarachnoid space increases greatly, the CSF flow rate (i.e. the volume of fluid leaving the cranium) may be maintained. However, if the pressure gradient in the subarachnoid space remains unchanged, the flow rate would decrease correspondingly. pcMRI measurements of velocity could be greater or smaller for an obstructed versus an unobstructed subarachnoid space due to the two possible scenarios as well as velocity jetting in the obstructed subarachnoid space.

Increased resistance due to CTD may initiate a cascade of hydrodynamic abnormalities such as reduction in spinal subarachnoid compliance. Some patients may experience similar abnormalities due to factors unrelated to resistance such
changes in tissue mechanical properties due to other diseases or aging. The occurrence of Type 0 Chiari malformation [61, 62], which has similar symptomatology to the Type I malformation but without tonsil descent, is an example of a case in which resistance to CSF motion might not be the problem.

Pressure

*In vivo* pressure measurements indicate that pressure magnitudes and gradients have an impact in CMI in terms of symptoms and severity. While MR imaging methods have provided information about velocity and geometry of the cerebrospinal fluid system, they are unable to measure pressure. Invasive measurements of pressure are possible but require creation of an access point to the subarachnoid space which alters the system and may not permit accurate measurements. Nevertheless, CSF pressure has been quantified in a limited number of invasive studies to be 7 to 15 mmHg in the supine position and 0 to 10 mmHg in the vertical position in healthy subjects [112, 113]. Pressure in healthy subjects and patients with CMI has been measured in a number of ways including craniospinal pressure dissociation, which is obtained by measuring instantaneous pressure differences between ventricular and lumbar cerebrospinal fluid pressure, a technique introduced by Williams [114, 115]. Williams’ measurements indicated that pressure differences between the ventricles and spinal subarachnoid space are greater in patients with CMI than in healthy subjects. In another study by Sansur et al. [116], it was found that CSF pressure measured during coughing
was elevated in patients with headache in comparison to patients without headache and healthy volunteers.

Pressure gradients in the CSF system are the driving forces that cause tissue and CSF motion and may be the cause for nerve damage in CMI [59]. Local CSF pressure magnitude could also cause damage to the neural tissue by disrupting the normal flow of blood, interstitial, and/or lymphatic fluid within the tissues. Thus, a detailed understanding of the pressure within the CSF, blood, interstitial, and lymphatic fluid would be helpful toward understanding the pathophysiology of CMI and related craniospinal disorders such as syringomyelia.

Many structural and communicating factors may influence cerebrospinal fluid system pressure dynamics. Structural factors include the mechanical properties of neural tissue and of structural layers, such as the vertebrae, skull, brain, spinal cord, dura, pia, and arachnoid membrane, that each have complicated anisotropic, non-linear, and poroviscoelastic properties. Further, the cerebrospinal fluid system communicates with the cardiovascular system through the veins and arteries supplying blood to the neural tissue [107, 117]. In particular, pressure in the venous system may have a significant impact on cerebrospinal fluid pressure, as pressure in the venous vascular bed is normally only slightly lower (1-3 mmHg) than in the cerebrospinal fluid, with the veins only held from collapsing by their structural rigidity [118]. Communication between the cerebrospinal fluid and intrathoracic pressure due to postural changes [119, 120], coughing [116], valsalva and Queckenstedt’s test, and abdominal pressure [121] has been well documented elsewhere [114-116, 122].
Cerebrospinal fluid pressure dynamics are difficult to simulate due to the complexities detailed above. Even if the pressure boundary conditions for computational simulations are measured invasively, the simulated results are suspect due to the necessity to simplify and decouple different parts of the cerebrospinal fluid and communicating systems. For example, decoupling of the spinal and cranial cerebrospinal fluid systems has been common in the existing studies and could make anomalies in the approximated flow field (e.g. seemingly random pressure or velocity fluctuations) difficult to justify in the context of only one part of the system [123].

3.7 Conclusion

Careful examination of CSF hydrodynamics in CMI offers potential for better understanding of pathophysiology and clinical utility. Key parameters are geometry, velocity, compliance, resistance, and pressure. It is unclear which parameter is most important and it is likely that a combination of parameters is necessary to assess a pathological state. However, studies of CSF hydrodynamics in CMI are as yet sparse, with the exception of clinical pcMR imaging studies of velocity. Engineering-based models may help identify more parameters that could be evaluated to assess clinical significance, which could in turn assist current research efforts that are focused on developing magnetic resonance imaging protocols with an eye toward clinical applications.
CHAPTER IV
CEREBROSPINAL FLUID FLOW IMPEDANCE IS ELEVATED IN TYPE I CHIARI MALFORMATION

This chapter describes a study [6] that used subject-specific computational modeling to investigate longitudinal impedance (LI) as a parameter to assess CMI in terms of impedance to cerebrospinal fluid motion near the craniovertebral junction and its relation to cerebellar tonsil herniation (referred to as cerebellar tonsil descent elsewhere). It was originally published as an invited paper in the Journal of Biomechanical Engineering and is partially based on the authors Master of Science thesis [99].

4.1 Introduction

Type I Chiari malformation (CMI) is a complex disorder of the craniospinal system that has historically been radiologically defined by cerebellar tonsillar herniation (CTH) greater than 3-5 mm below the foramen magnum (FM) into the spinal subarachnoid space (SSS) (Figure 4.1.1) [2, 35, 36]. Patients with CMI can have a variety of neurological symptoms and pain ranging from mild to severe [2]. It is thought that these symptoms result from abnormal pressure acting on the spinal cord, brain stem and/or cerebellum due to crowding of the tissue in the posterior cranial fossa and craniovertebral junction (CVJ) [54, 124, 125]. However, large retrospective clinical
studies have shown that CMI symptom severity does not always correlate with CTH depth [47]. Patients with large CTH may present with mild neurological symptoms and vice versa.

Figure 4.1.1: (a) Midsagittal MRI image of the cervical spine of a CMI patient showing the McRae line, CTH measurement (approximately 7.4 mm for this case), and planes where pressure drop was calculated; (b) transverse MRI image from the plane used to demarcate the model top, highlighting the separation between the cerebellar tonsils and body of the cerebellum. Note: patient tonsils for this case are asymmetric with greater CTH on the left side.
As such, clinicians have sought additional objective measurements to assist in the diagnostic process. In clinical practice, the diagnostic process can vary widely; clinicians have differing views on the importance of CTH alongside many factors such as symptom history, neurologic deficit, degree of craniocervical “crowding”, bony landmark positions, and cisterna magna volume. CTH greater than 3-5 mm as a marker for CMI has been established as a ‘rule of thumb’ over time. This is problematic, as incidental observation of CTH has become more common with increases in the use of magnetic resonance imaging (MRI) for head and neck injury examinations. Recent research has shown that as much as 3% of the pediatric population, 2% of the adult female population, and 1% of the adult male population have greater than 5 mm CTH [126, 127] and CTH varies throughout life (Figure 4.1.2).

![Figure 4.1.2: CTH as a function of age (in decade range, e.g. 1st decade 0-10 yrs.) and sex for healthy subjects showing a parabolic trend with females having greater CTH values throughout life. Positive CTH values are in the caudal direction to the FM (Data based on Smith et al. [126]). CMI patients, not shown, would have positive CTH values greater than 3 mm.](image-url)
In hydrodynamic terms, CTH creates a stenosis near the CVJ that partially blocks the pulsatile motion of cerebrospinal fluid (CSF) between the cranial and spinal subarachnoid spaces. Although the pulsatile CSF stroke volume is only ~1 cc with each cardiac cycle [128, 129], the partial stenosis near the CVJ causes elevated CSF pressure gradients [114, 115] that can result in severe neurologic consequences. At present, MRI techniques are being developed to measure CSF pressure gradients non-invasively[130], but these methods are not in standard use and have not been validated. In principle, changes in CSF pressure gradients are related to alterations in impedance to CSF motion, CSF velocities [7-11, 13-15], neural tissue motion [16-18], and craniospinal compliance [19, 20, 22]. We suspect that alterations in each of these biomechanical parameters could prove useful to quantify the biomechanical environment near the CVJ in CMI.

Of interest in this study is longitudinal impedance (LI), or the impedance to the pulsatile component of CSF motion, in the cervical SSS near the CVJ [5]. While CTH is typically indicative of a blockage, it only accounts for one linear dimension, depth, and does not consider the three-dimensionality of the stenosis (e.g. the girth of the blockage) at the CVJ (Figure 1) or the dynamic changes to the biomechanical environment caused by the stenosis. In contrast, LI is a pressure-based parameter (ratio of pressure drop to volume flow) that is dependent on the complex conduit geometry. By quantifying the severity of the stenosis in terms of LI, rather than by a single geometric dimension such as CTH, LI may provide a better parameter to assess the pathoanatomy of CMI. Martin et al. [5] demonstrated the utility of LI to quantify CMI blockage in a pilot study with one healthy subject and two CMI patients before and after surgery. LI was found to be elevated in patients compared to a healthy subject and to decrease after surgery, but the
limited number of subjects analyzed did not permit statistical analysis. The aim of the present study was to utilize the methods of Martin et al. [5] to analyze LI in a larger patient and control group to determine statistical differences, if any, and understand the relation of LI and CTH. Our hypothesis was that LI would be higher in CMI patients than in healthy volunteers due to the stenosed CVJ and would increase with CTH.

4.2 Materials and Methods

This section presents a brief description of the planned methods for obtaining image data, CTH measurement, and reconstruction of 3D SSS models. The computational method for simulating flow is then briefly outlined. Finally, the statistical model to be used for data analysis is discussed.

4.2.1 Ethics Statement

MRI data acquisition was performed at the University of Wisconsin (UW), the Cleveland Clinic Foundation (CCF), and Emory University (EU). The study was approved by the institutional review board of each institution. Prior to scanning, written informed consent was obtained for all subjects. All MRI data was anonymized before being transferred for analysis.

4.2.2 Study Population

Fifteen adult CMI patients (age 17 or older) volunteered to participate in the study (6 at UW, 9 at CCF). Consistent with the conventional definition of CMI, the inclusion criterion was CTH greater than 3-5 mm below the FM. Among these fifteen patients were ten symptomatic CMI patients and five “asymptomatic” CMI patients. Patients were classified as symptomatic based on the presence of sufficiently severe neurological
symptoms to warrant corrective craniocervical decompression surgery. Patients were classified as “asymptomatic” that had only mild symptoms or symptoms that weren’t attributable to CTH and were not recommended for corrective surgery. Although patients in this group can have symptoms, neurosurgeons commonly refer to this group as “asymptomatic”. Patients were excluded that had secondary causes of CTH, such as hydrocephalus, had undergone previous decompression surgery, or had implanted CSF shunts. A group of eight healthy volunteers with no history of neurological disorder or spinal trauma volunteered for the control group (2 at UW, 5 at CCF, 1 at EU).

4.2.3 **MR Imaging**

The cervical spine of each subject was imaged using a 3D balanced steady-state free precession (SSFP) gradient echo sequence on a 3T scanner [GE Medical Systems, Milwaukee, WI or Siemens Healthcare, Malvern, PA]. The result of each scan was a set of axial T$_2$-weighted images of the lower cranial and upper cervical SSS. The sequence was optimized to provide high contrast between the CSF and surrounding tissues. Additional image parameters were as follows: slice thickness = 0.8-1.0 mm with no inter-slice spacing, FOV = 260x260 mm or 210x280 mm, and matrix size = 320x320 or 240x320.

Phase-contrast MRI (pcMR) images were obtained for only 15 of the subjects at sites where the sequence was available. Images were acquired in a transverse plane at the caudal end of the C2 vertebra using a retrospective peripheral pulse-gated sequence with a velocity encoding of 10 cm/s. Each pcMR scan yielded a set of 20 images over the cardiac cycle. Additional image parameters were as follows: TR = 49.3 ms, FA = 15°, FOV = 240-180 mm, matrix size = 256 x 192, and slice thickness = 6 mm.
4.2.4 CTH Measurement

Measurement of CTH was performed independently by two neurosurgeons using the high-resolution T2-weighted anatomy images. The procedure for measurement of CTH was as follows: (1) select the sagittal slice with greatest tonsillar descent, (2) identify the basion and opisthion within the selected slice, (3) draw the McRae line between the basion and opisthion, and (4) measure the length of a second line that is perpendicular to the McRae line and ends at the tip of the cerebellar tonsils. Inter-operator variability was assessed by computing the intra-class correlation coefficient (ICC) between measurement sets.

4.2.5 Anatomy Modeling and Meshing

3D geometric models of the SSS were reconstructed for each subject over the first 40-50 mm caudal to the FM by a single operator. The boundary of the SSS was segmented using the level-set edge detection feature of the freely available Segment software [Medviso, Sweden]. The top (cranial end) of each model was positioned in-line with the z-plane of the MRI image set at the most cranial location where the SSS could still be considered an annular conduit. That location was found by identifying the first image where the body of the cerebellum was only visible in a separate cavity from the SSS (Figure 1b). This was generally in close proximity to the McRae line at the FM. The bottom of each model was chosen to be 40-50 mm caudal to the top.

Each of the 3D segmentations was converted to an STL surface and smoothed to remove pixilation artifacts using Geomagic [Geomagic Inc, Morrisville, NC]. The inlet and outlet faces of each model were extruded 2-5 hydraulic diameters normal to the plane of each face to create entry and exit lengths and minimize the influence of boundary
effects in the anatomical section of the geometry. Models were then converted to non-uniform rational Bezier spline (NURBS) surfaces for better compatibility with the meshing software. All models were meshed for CFD analysis using ICEM CFD [Ansys Inc, Canonsburg, PA]. The meshing process comprised the following steps: applying an unstructured tetrahedral mesh to the entire volume using the Octree algorithm, smoothing the mesh using the Delaunay algorithm, splitting the mesh near the model wall to create a layer of prismatic boundary layer cells, splitting the prismatic layer to create five smaller prismatic layers of linearly increasing aspect ratio, and re-smoothing the tetrahedral core using the Delaunay algorithm. Depending on the size of the original SSS model and length of the model extensions, this procedure yielded meshes of 1-2 million cells.

4.2.6 Flow Waveforms

For those subjects who were imaged at a site where pcMR was available, subject-specific CSF waveforms were obtained from pcMR measurements at the caudal end of the C2 vertebra (15 of 23 cases). A custom MATLAB graphical user interface was developed to allow manual masking of pixels within the SSS that had cardiac-like pulsatile velocity profiles. Volume flow waveforms were then computed from the sum of pixel velocity multiplied by pixel area for each pixel in the mask in each phase image. Flow waveforms were scaled by area of the top face of each anatomy model to create an average velocity waveform, which was used as the inlet boundary condition for CFD modeling.

4.2.7 CFD Model Setup

Walls of the SSS were modeled as rigid with the model top specified as a velocity inlet and the model bottom specified as a zero-pressure outlet. CSF was modeled as
water at 37 °C (ρ = 1.0 gm/cm³, µ = 0.01 P) [24]. The distribution of instantaneous Reynolds number at peak systole for each model was calculated using the relation Re_{SYS} = (4*Q_{SYS}) / (P_{WET}*v), where Q_{SYS} was volume flow rate at peak systole, P_{WET} was the wetted perimeter at each slice in the segmented image stack, and v was the kinematic viscosity of the fluid. For all models, the maximum instantaneous Reynolds number in each distribution was 300 or less. Hence, flow was assumed to be laminar in all models.

The commercial finite volume solver Fluent [Ansys Inc., Canonsburg, PA] was used to carry out fluid flow simulations. The Navier-Stokes equations were discretized using a second-order upwind scheme in space and a second-order implicit scheme in time. SIMPLE was chosen as the pressure-velocity coupling algorithm. PRESTO was chosen as the pressure interpolation scheme.

4.2.8 Longitudinal Impedance

In each simulation, the unsteady pressure drop near the CVJ was computed as the difference in area-weighted average pressure in cross-sectional planes located at the FM, \( P_{FM}(t) \), and at a plane located 25 mm caudal to the FM, \( P_{2.5}(t) \), such that \( \Delta P(t) = P_{2.5}(t) - P_{FM}(t) \). A distance of 25 mm was chosen as clinical studies have reported that CTH > 25 mm has rarely been observed [2]. Hence, it was assumed that 25 mm in the longitudinal direction would encompass the entire region of the SSS where the geometry could be affected by CTH. Impedance modulus, \( Z_L \), was calculated by computing the ratio of Fourier coefficients of the pressure drop, \( \mathcal{F}(\Delta P(t)) \), and flow waveforms, \( \mathcal{F}(Q(t)) \), at each harmonic, where \( Z_L = \left| \frac{\mathcal{F}(\Delta P(t))}{\mathcal{F}(Q(t))} \right| \). The resulting \( Z_L \) (dyn-s/cm⁵) values for each harmonic were integrated from 1-8 Hz to obtain integrated longitudinal impedance (LI) for each subject [131]. The range of 1-8 Hz was chosen because 90-
100% of the signal power for all the flow waveforms used as inlet boundary conditions was contained between those frequencies. Thus, LI in this study was the impedance to the frequency components that displaced most or all of the fluid in a particular waveform (i.e. the dominant carrier frequencies).

4.2.9 Mesh Independence

To ensure mesh-independent solutions, a global mesh-sizing scheme was developed by simulating flow in an SSS model with moderate CTH (6.9 mm). Using an SSS model with a constricted inlet region allowed testing of mesh independence in the presence of high pressure gradients. The working assumption for this approach was that a sizing scheme which yielded a mesh-independent solution for an SSS model with large pressure gradients should also yield a mesh-independent solution for an SSS model with smaller gradients. For the test model, a coarse mesh and a fine mesh with cell counts of 896,172 and 2,298,224, respectively, were generated using maximum element edge sizes of 0.5 and 0.25 mm. Each model was tested with time steps of T/100 and T/1000 and simulated for three periods of the inlet waveform to assess time step and period independence. Solution independence was determined by comparing LI values obtained from each simulation.

The maximum relative change in LI obtained by refining the time step was 2.5%. The maximum relative change obtained by refining grid size was less than 1%. The relative change in LI between periods of the inlet waveform was a maximum of 1% between the second and third cycles of each simulation in all cases. Hence, the remaining CFD simulations were run using the 0.5 mm maximum element edge length sizing scheme with a time step of T/100 for two periods of the waveform.
4.2.10 Sensitivity to Inlet Boundary Conditions

Subject-specific volume flow waveforms were only available for 15 of the 23 cases in this study. To test whether it was feasible to use non-subject-specific flow waveforms for the remaining 8 cases, a preliminary study was conducted to assess the dependence of the LI calculation on the shape of the inlet boundary condition waveform. This was accomplished by varying the waveform in each of nine CFD simulations conducted on the same SSS model. The nine different boundary conditions were as follows: five subject-specific CSF flow waveforms (Q1-Q5 in Figure 3a); four variants of the Q1 waveform altered by doubling (2xA) and halving (A/2) the waveform amplitude and doubling (2xf) and halving (f/2) the waveform fundamental frequency. Sensitivity to the shape of the inlet boundary condition waveform was assessed by computing and comparing LI for each of the nine simulations.

For the nine waveform independence simulations, $Z_L$ values for each harmonic between 1 and 8 Hz were in agreement (Figure 5.3.1). Relative standard deviation for the nine values of LI was 0.3%, which demonstrated that LI was only weakly dependent on the shape, amplitude, and fundamental frequency of the CSF input waveform. Hence, it was assumed that a non-subject-specific CSF flow waveform could be used to analyze impedance in the 15 SSS models for which subject-specific waveforms were unavailable.
Figure 4.2.1: (a) CSF flow waveforms (Q#) from five different subjects and (b) example waveform with modified properties used to demonstrate that LI values (c and d), integrated from the sum of $Z_L$ values on the y-axis, were independent of flow waveform shape over the range of frequencies analyzed (A and f represent waveform amplitude and frequency, respectively).
4.2.11 Modeling Repeatability Assessment

Repeatability of the SSS modeling methodology was assessed by obtaining MRI measurements on the same healthy subject at all three MRI measurement sites. This was important as cerebellar tonsil position may vary with neck orientation. Also, the anatomy imaging parameters were slightly different at each imaging site (e.g. different slice spacing and in-plane resolution) based on the spatial resolution capabilities of each MR system. For the healthy subject, SSS models were reconstructed from the images acquired at each site and CFD simulations were performed. Inter-site variability was assessed by comparing LI for the three models. Values of LI obtained from the three simulations were 246, 251, and 286 dyn/cm$^5$ for SSS models from sites 1, 2, and 3, respectively. This showed that LI computed by the methods of this study may be as much as 16% different if a particular subject were imaged at a different site or on a different day.

4.2.12 Statistical Analysis

Distributions of LI in each group were verified for normality and unequal variances. A one-tailed two-sample t-test was then used to test the null hypothesis that mean LI was equal in the CMI patient and healthy volunteer groups. Assuming a significance level of 0.05 and minimum group size of 8, the power of the statistical comparison was estimated to be approximately 0.9. Measured CTH values for each subject were compared in a similar manner. Outliers in each group were defined as values outside the range (Q1-1.5*IQR, Q3+1.5*IQR), where Q1 and Q3 were the data points at the 25th and 75th percentiles of the distribution of each parameter, respectively,
and IQR, the interquartile range, was Q3-Q1. Finally, linear regression analysis was used to assess the relationship between LI and CTH.

4.3 Results

This section presents analysis of the data obtained using the methods described in the previous section. LI and CTD are discussed separately and then compared to each other.

4.3.1 Study Population

Mean ages in years for the CMI patient and healthy volunteer groups were 38 with a range of 17-58 and 29-47 years, respectively. The gender divisions (female/male) were 15/0 and 3/5 for the CMI patient and healthy volunteer groups, respectively. Due to limited subject availability, only female CMI patients were available to participate in the study. Thus, gender could not be controlled for.

4.3.2 Longitudinal Impedance

Mean values of LI in dyn/cm$^5$ were 551 ± 66 and 220 ± 17 for the CMI patient and healthy volunteer model groups, respectively. Statistical analysis showed that mean LI in the CMI patient model group was significantly higher than in the healthy volunteer model group (p < 0.001). However, there was a large range of values (216-1122 dyn/cm$^5$) in the LI distribution for the CMI patient models (Figure 4a) and no clear stratification of symptomatic and asymptomatic CMI models. The two lowest values in the LI distribution for CMI patients fell within the range of values (157-303 dyn/cm$^5$) for the healthy volunteer group. These data points were from one symptomatic CMI model (290 dyn/cm$^5$) and one asymptomatic CMI model (216 dyn/cm$^5$).
Figure 4.3.1: (a) Distribution and (b) data spread of LI compared with (c) distribution and (d) data spread of CTH for the healthy volunteers (HV) and CMI patients (CMI). Note, ‘+’ indicates a statistical outlier in (a) and (c); the order of data points in (b) and (d) is identical.
4.3.3 *Cerebellar Tonsil Herniation*

Mean values of CTH in mm were 9.0 ± 1.1 and -0.4 ± 0.5 in the CMI patient and healthy volunteer groups, respectively. Statistical analysis showed that mean CTH in the CMI patient group was significantly higher than in the healthy volunteer group (p < 0.001). Similar to LI there was a large range of CTH values (3.7-20.8 mm) in the CMI patient group distribution and no clear stratification of symptomatic and asymptomatic CMI patients. One statistical outlier was identified in each of the CMI patient and healthy volunteer groups. Re-computing the statistical test with the outliers excluded did not affect the results. The ICC for the two sets of CTH measurements was 0.9, indicating good inter-operator agreement.

4.3.4 *Relationship between LI and CTH*

Linear regression analysis revealed that the relationship between LI and CTH was weakly correlated (R²=0.46, p < 0.001). In general, LI was higher in cases with larger CTH as expected (Figure 5), but there was also greater dispersion in LI among cases with larger CTH.
Figure 4.3.2: Relationship between CTH and LI is shown to be weakly correlated. The red line denotes the 3 mm minimum cutoff above which a subject would typically be considered anatomically positive for CMI.

4.4 Discussion

This study presents for the first time LI as a metric for comparing the biomechanical environment in the SSS of symptomatic and asymptomatic CMI patients and healthy volunteers. Our approach was to use CFD methods to assess severity of the partial blockage to CSF motion in terms of the magnitude of the impedance to pulsatile CSF motion and to compare those values with the commonly used clinical morphometric parameter, CTH. The results showed that mean LI was significantly higher in CMI patients compared to controls. Likewise, mean CTH was significantly larger for CMI patients. Thus, CMI patients stratified from healthy volunteers by both parameters. However, the relationship between LI and CTH in both groups was weakly correlated, suggesting that CTH and LI give different information about the pathoanatomy in CMI.
4.4.1 Importance of dynamic parameters to assess CMI

From the regression analysis, it was shown that CTH was a poor predictor of the impedance to the pulsatile component of CSF motion resulting from the stenosis at the CVJ caused by CTH. Thus, it may be that static morphometrics oversimplify the complex partial blockage to CSF motion present in CMI. Because of this, parameters that are based on dynamic analysis, such as LI, may be useful to quantify biomechanical differences between CMI states. Further, utilization of novel parameters that capture the dynamic aspects of the CVJ in CMI could lead to more complete characterization of CMI pathoanatomy and pathophysiology and potentially lead to new treatment options.

Considering CMI from a hydrodynamics perspective, CSF pressure gradients [54], also sometimes referred to as pressure ‘dissociation’ [114, 115], are the driving force from which tissue damage and CMI symptomatology precipitate. Pressure gradients are not easily measured in vivo, but in principle are related to a) impedance to CSF motion, b) CSF velocities, c) neural tissue motion, and d) craniospinal compliance. Further, CMI has a variety of underlying causes (e.g. secondary to hydrocephalus, tethered spinal cord, spina bifida, etc.). Thus, we do not expect better characterization of CMI from a single ‘silver bullet’ parameter, but rather from a combination of biomechanical factors.

4.4.2 CTH Measurement Variability

Though an ICC of 0.9 suggested good inter-operator agreement for the CTH measurements, the maximum inter-operator differences in the CTH measurements were 4.6, 6.7, and 4.8 mm for the symptomatic, asymptomatic, and healthy volunteer groups, respectively. Hence, the same CMI patient could be considered a relatively mild
herniation or much more severe depending on the operator. This difference was likely due to the complexity in making CTH measurement, as described earlier. Each step involved in CTH measurement can introduce error. Thus, it was not surprising that some large disagreements between data points were observed. A study is currently underway by our group to examine CTH measurement accuracy and repeatability.

4.4.3 Symptomatic versus Asymptomatic CMI

From a clinical perspective, the difference between a “symptomatic” and an “asymptomatic” CMI patient is not always distinct. Our group is interested in identifying a biomechanical parameter or set of parameters that could stratify symptomatic from asymptomatic CMI patients in cases that have moderate CTH, or CMI that could be considered anatomically “borderline”. For the CMI patients in this study with CTH in the range 3-9 mm there was a great deal of overlap in LI (Figure 5). Mean LI for the symptomatic (n=10) and asymptomatic (n=5) CMI subgroups was 612 ± 86 and 430 ± 79 dyn/cm$^5$, respectively. Using the same statistical test as the general groups, the difference was not statistically significant (p = 0.073) despite a notable difference in the means. However, the power of this post-hoc test was only 0.3 and the difference between the subgroup means may have been incidental.

Most cases followed the general trend of the regression line in Figure 5. However, four CMI cases highlight differences between LI with similar values of CTH. Two cases that could be considered anatomically borderline (CTH = 6.7 vs. 7.6 mm) are shown in Figure 6. From both the mid-sagittal MRI images (Figure 6a and b) and the reconstructed SSS models (Figure 6c and d), it was apparent that the SSS was more constricted in the symptomatic CMI case in which LI was 4.2 times higher (216 vs. 917
Similarly, two symptomatic CMI cases were measured to have similar CTH (10.3 vs. 10.4 mm), but LI was 3.9 times higher in the second patient (290 vs. 1122 dyn/cm$^5$). In both instances, LI captured a feature of the pathoanatomy that was not obvious from the static morphometric measurement alone.

Figure 4.4.1: (a) Midsagittal MRI image for an (a) asymptomatic CMI patient and (b) symptomatic CMI patient and (c and d) 3D models for each, respectively. CTH was similar for the two cases. However, LI in the symptomatic patient was 4.2 times greater than the asymptomatic patient.
It should be noted that classification of patients as symptomatic or asymptomatic in neurosurgical evaluation was difficult; the reporting of symptom severity by the patients can be highly subjective (e.g., patients have different pain thresholds). Thus, asymptomatic patients may have similar biomechanics to symptomatic patients and could progress to become symptomatic. In future work, it would be helpful to consider the natural history of LI in CMI patients to determine what level of measurement variability exists and if LI may have predictive value for progression to a symptomatic CMI state. In addition, biomechanics is likely not the only factor involved in symptoms.

4.4.4 Limitations

The gender disparity in the CMI patient group may have introduced some bias into both the LI and CTH results. CTH is typically greater in females (Figure 2) that in turn may have resulted in higher mean LI in the symptomatic group. Considering the importance of age and gender on average CTH values, it would be prudent to use stricter gender matching in future work to reduce the effect of any confounding factors, though the feasibility of such restrictions must be considered in the context of the limited patient availability. Likewise, we were unable to control for additional factors that could influence CVJ anatomy, such as height, weight, or body mass index.

Geometric reconstructions of the SSS were performed by a single operator and only one case was analyzed for LI repeatability. Ideally, repeatability of the geometric reconstruction methodology would be assessed for multiple operators and repeatability of the end-to-end model reconstruction and impedance analysis for image sets from different sites would be assessed on multiple pilot subjects to quantify the impact of small differences in the SSS models. Also, the tops of the SSS models could not be perfectly
aligned to the McRae Line and, thus, neck angulation could not be accounted for. However, all patients were imaged using a head coil, so any neck angulation in the SSS models was consistent.

LI was computed using pressure drop over the first 25 mm of the SSS models and integrated from the 1-8 Hz to have a consistent metric by which to compare models. While the pressure drop length was justifiable in the context of a clinical “worst case scenario”, it is not known whether 25mm was the optimal distance over which to analyze LI. That is, some finer details of the spatial distribution of pressure drop may have been missed by only considering the pressures at the two endpoints of the region of interest. Similarly, the frequency range was justifiable as it accounts for most of the signal power in the flow waveforms which drive CSF motion, but it was not parametrically optimized. Though it is outside the scope of this study, both the pressure drop distance and frequency range used to compute LI could be parametrically optimized. For example, pressure drop distance could be optimized by analyzing the spatial distribution of LI near the CVJ or by using a relative length based on CTH, though the latter would be difficult to normalize.

CFD simulations were performed using the assumption that the inner and outer walls of the SSS (i.e. the spinal cord and dura) were rigid. It has been shown that CFD may underestimate the velocity field in rigid-wall SSS models compared to velocities observed in vivo in the SSS using 4D pcMRI [11]. Thus, pressure gradients, and consequently LI, may have been underestimated by this particular CFD methodology. Further, bulk neural tissue displacement in the spinal cord and cerebellar tonsils throughout the cardiac cycle in the rostrocaudal direction ranging from 0 to 0.6 mm has
been documented for CMI patients and healthy subjects [11, 25-27, 30]. This data suggests that elastic elements could be added to the boundary conditions which in turn may impact the pressure and velocity fields. With regard to impedance, the methodology described in this study was concerned with impedance to the main carrier frequencies (1-8 Hz) of the inlet boundary condition waveforms. It is unclear how analyzing impedance in this frequency range would impact the rigid wall assumption. Thus, the assumption of a rigid-walled SSS should be examined in more detail in future studies.

The ICC of 0.9 between the two measurement sets indicated good intra-operator agreement. However, only two sets of measurements were used and repeatability could suffer from the addition of more operators with varying levels of experience in making CTH measurements. For example, different operators may measure CTH on different images from the set, depending on which they perceive to capture the lowest tonsil descent.

4.5 Conclusion

Diagnosis and treatment of CMI patients may benefit from an assessment of their subject-specific biomechanical environment. This work investigates the use of LI as a biomechanical parameter to assess the extent of CVJ stenosis in CMI patients. LI was found to be significantly higher in CMI patients compared to controls. LI and CTH were found to have a weakly linear relationship, suggesting that different morphometric measurements and/or biomechanical parameters may be necessary to characterize the pathoanatomy of CMI. Future work in a larger and age/sex matched study population is planned to fully understand the potential, if any, of LI as a clinical diagnostic tool for CMI.
CHAPTER V

ANALYSIS OF PRESSURE AND IMPEDANCE IN THE SPINAL CANAL OF TYPE I CHIARI MALFORMATION PATIENTS BEFORE AND AFTER DECOMPRESSION SURGERY

This chapter describes a study where subject-specific computational modeling was used to investigate pressure gradient, longitudinal impedance (LI), and quasi-steady resistance to CSF motion in CMI patients before and after decompression surgery to assess the effect of surgery on pressure environment near the craniovertebral junction. LI was also compared cerebellar tonsil descent (CTD) and cross-sectional geometry of the spinal canal. This chapter is written in the format of a paper which is planned for submission.

5.1 Introduction

Type I Chiari malformation (CMI) is a complex disorder of the craniospinal system which has historically been identified radiologically by descent of the cerebellar tonsils more than 3-5 mm below the foramen magnum (FM) into the spinal subarachnoid space (SSS) and compression of the fluid space in the cisterna magna. In hydrodynamic terms, these pathological changes to the anatomy near the craniovertebral junction (CVJ) create a partial blockage to the pulsatile motion of cerebrospinal fluid (CSF) between the cranial and spinal subarachnoid spaces. Although the pulsatile stroke volume of CSF in
each cardiac cycle is only ~1 cc [128, 129], the partial blockage near the CVJ causes elevated CSF pressure gradients [114, 115] which may have damaging potential. Patients with CMI can have a wide variety of neurological symptoms [2] and it is thought that many of these symptoms result from the abnormal pressure acting on cerebellum, brain stem, and spinal cord near the CVJ [54, 124, 125].

For symptomatic CMI patients, the standard treatment method is surgical decompression of the CVJ. Decompression surgery is designed to create more space around the compressed cerebellar tonsils and brain stem, restore the natural flow of CSF, and consequently decrease CSF pressure gradients near the CVJ. The surgical procedure is typically comprised of sub-occipital craniectomy, C1 laminectomy, and opening of the dura mater, which essentially create a larger foramen magnum and cisterna magna. In severe cases, neurosurgeons may also resect portions of the cerebellar tonsils, but this is not as common.

Though decompression surgery is widely accepted as the standard treatment method, surveys of neurosurgeons have shown disagreement regarding when surgery should be recommended and what techniques should be employed. For example, one survey found disagreement regarding the extent of bone removal, whether opening of the dura mater was necessary, and whether brain tissue should be removed [53]. Further, surgical success in published patient series is often not well-defined and subjective in nature, relying on patients’ anecdotal reports of symptom improvement and the surgeon’s judgment as to whether sufficient space was created near the CVJ. For example, two studies reported improved quality of life post-surgery in approximately 80% of patients surveyed and mild-to-moderate symptom recurrence in the remaining 20%. In these
cases, however, it was not clear if surgery was initially successful but then failed over time or if the initial success was overstated due to the subjective nature of the outcome measures and possible influence of a placebo effect.

As such, clinicians and researchers have begun to seek more objective measures to quantify the changes to the CVJ post-decompression surgery. In general, these past studies have focused on analyzing peak CSF velocities [7, 9, 10, 14, 15, 66, 67] and pressure gradients [69, 89, 92, 94]. Pressure gradient may be important, as pressure on the nervous structures near the CVJ is thought to correlate with CMI symptomatology. However, only two recent studies [5, 6] have used impedance analysis to quantify the impact of the blockage caused by CTD on the pressure environment in the SSS near the CVJ. Shaffer et al [6] showed that longitudinal impedance was elevated in CMI patients compared to healthy controls and that the magnitude of the impedance was weakly correlated with CTD. That study, however, did not include any post-decompression surgery patient cases. Martin et al [5] found that impedance decreased by a large amount (>30%) in two post-surgery CMI patients compared to pre-surgery. However, that study lacked the patient sample size to allow any statistical analysis. To the authors’ knowledge, no previous studies have analyzed quasi-steady resistance to CSF motion. The goal of this study was to assess changes to CSF pressure gradients, LI, and quasi-steady resistance as metrics for assessing pre-surgery severity of CMI and post-surgery improvement in the SSS pressure environment. The hypothesis for this study was that all three parameter types would be significantly higher in pre-surgery CMI patients would be significantly higher than healthy volunteers, similar to [6], and that LI would decrease post-surgery.
5.2  Materials and Methods

*Ethics Statement*

MRI data acquisition was performed at the Cleveland Clinic Foundation (CCF), Mayfield Clinic (MC), and Emory University (EU). The study was approved by the institutional review board of each institution. Prior to scanning, written informed consent was obtained for all subjects. All MRI data was anonymized before being transferred for analysis.

5.2.1  *Study Population*

Twenty symptomatic adult CMI patients (age 24 or older) volunteered to participate in the study (9 at CCF, 11 at MC). Consistent with the conventional radiological definition of CMI, the inclusion criterion was CTD greater than 3-5 mm below the FM, crowding of the cisterna magna, and sufficiently severe symptoms to warrant decompression surgery. Patients were excluded that had secondary causes of CTD, such as hydrocephalus, had undergone previous decompression surgery, or had implanted CSF shunts. Each CMI patient was imaged prior to decompression surgery and three to six months post-surgery to assess immediate changes in hydrodynamics near the CVJ. A group of fifteen age-matched healthy volunteers with no history of neurological disorder or spinal trauma volunteered for the control group (5 at CCF, 5 at MC, 5 at EU).
5.2.2 MR Imaging

Subjects were scanned in a supine position on either a 1.5-T Siemens [Siemens Healthcare, Malvern, PA] or a 3.0-T GE [GE Medical Systems, Milwaukee, WI] scanner. Two main imaging sequences were used to obtain the images necessary to construct the SSS models in this study. The first was a T2-weighted 3D balanced steady-state free precession (SSFP) gradient echo sequence which captured the lower cranium and cervical spine of each subject were imaged using. The result of each scan was a set of T2-weighted transverse plane images of the lower cranial and upper cervical SSS. The number of images acquired in each anatomy scan varied based on patient stature. Scanning parameters used at each imaging site are listed in Table 5.1.

Table 5.1: List of imaging parameters for each center used to obtain anatomy images.

<table>
<thead>
<tr>
<th>Imaging Center</th>
<th>MRI System</th>
<th>Image Matrix Size</th>
<th>Image FOV (mm x mm)</th>
<th>Pixel Spacing (mm)</th>
<th>Slice Spacing (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCF</td>
<td>Siemens</td>
<td>240x320</td>
<td>210x280</td>
<td>0.875</td>
<td>1.0</td>
</tr>
<tr>
<td>MC</td>
<td>GE</td>
<td>512x512</td>
<td>240x240</td>
<td>0.469</td>
<td>0.5</td>
</tr>
<tr>
<td>EU</td>
<td>Siemens</td>
<td>256x320</td>
<td>224x280</td>
<td>0.875</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The second scan was a peripheral pulse-gated, retrospective phase contrast MR (pcMR) sequence of through-plane velocity acquired in a transverse plane at the caudal end of the C2 vertebra. The sequence used an encoding velocity of 10 cm/s and acquired 20 images per pulse cycle at uniformly spaced time points. Additional pcMR scanning parameters used by each imaging site are listed in Table 5.2.
Table 5.2: List of imaging parameters for each center used to obtain pcMR images.

<table>
<thead>
<tr>
<th>Imaging Center</th>
<th>MRI System</th>
<th>TE (ms)</th>
<th>TR (ms)</th>
<th>FA (°)</th>
<th>Matrix Size</th>
<th>FOV (mm x mm)</th>
<th>Pixel Spacing (mm)</th>
<th>Slice Thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCF Siemens</td>
<td>5.8</td>
<td>49.3</td>
<td>15</td>
<td>256x192</td>
<td>240x180</td>
<td>0.9375</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>MC GE</td>
<td>5.9</td>
<td>12.9</td>
<td>20</td>
<td>256x256</td>
<td>256x256</td>
<td>0.781</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>EU Siemens</td>
<td>5.9</td>
<td>49.5</td>
<td>20</td>
<td>256x256</td>
<td>320x320</td>
<td>1.25</td>
<td>6.0</td>
<td></td>
</tr>
</tbody>
</table>

5.2.3 CTD Measurement

Measurement of CTD was performed by a single operator using the same high-resolution T2-weighted anatomy image set that was used for 3D modeling of the SSS. The sagittal plane used to measure CTD was pre-set using Osirix [Pixmeo SARL, Switzerland] by the authors to minimize variability. ImageJ [NIH, Bethesda, Maryland] was then used to measure CTD in pre-surgery patients by the following procedure: (1) identify the basion and opisthion within the image, (2) draw the McRae line between the basion and opisthion, and (3) draw a second line perpendicular to the McCrae line that ends at the tip of the cerebellar tonsils, and (4) measure the distance of second line. Because the opisthion was removed during sub-occipital craniectomy, it was necessary to create a reference line for measuring CTD in post-surgery CMI patients. Thus, the Boogaard angle (angle between the McRae line and a line between the basion and sella turcica [132]) was also measured in pre-surgery CMI patients. Then for post-surgery patients, the Boogaard angle and basion-sella turcica line were transposed onto the respective image and used to reconstruct the approximate relative location of the McRae
line. Post-surgery CTD was then measured from the reference McRae line. The reference McRae line was also used to define the top of the 3D anatomy model reconstructions for post-surgery CMI patients.

Figure 5.2.1: Sagittal MR images illustrating the method used for identifying the McRae line and Boogaard angle and measuring CTD in a pre-surgery patient (left) and using the Boogaard angle and basion-sella turcica line to construct a reference McRae line post-surgery (right).
5.2.4 Anatomy Modeling and Meshing

3D geometric models of the SSS were reconstructed for each subject between the upper aspect of the foramen magnum (basion) and the C3-C4 level of the spine by a single operator. The boundary of the SSS was segmented in a semi-automated manner Segment [Medviso, Sweden]. Large blood vessels, such as the vertebral arteries, that were clearly visible in all image sets were not lumped in as part of the SSS. Cross-sectional area ($A_{CS}$) and wetted perimeter ($P_W$) of the SSS were computed from the binary images extracted from each segmentation (Figure 5.2.2) and hydraulic diameter ($D_H$) of the SSS was then computed using the relation $D_H = 4\cdot A_{CS}/P_W$. 
Each 3D segmentation was converted to an STL surface and smoothed to remove pixilation artifacts using a non-eroding smoothing tool (Figure 5.2.3) in Geomagic [Geomagic Inc, Morrisville, NC]. The inlet and outlet faces of each model were extruded 4-5 hydraulic diameters normal to the plane of each face to create entry and exit lengths and minimize the influence of boundary effects in the anatomical section of the geometry.
Figure 5.2.3: Sagittal MR image and 3D reconstruction of the fluid space in the SSS for a pre-surgery CMI patient (top) and an age-matched healthy volunteer (bottom) illustrating the visible but not easily quantifiable differences in SSS anatomy.
5.2.5 **Cross-Sectional Geometry Analysis**

The intent of CMI decompression surgery is to create additional space around the cerebellum and brain stem, which will allow CSF to flow more freely between the cranium and SSS and, ideally, allow the stretched cerebellar tonsils to relax. Thus, the cross-sectional area ($A_{CS}$) and hydraulic diameter ($D_H$) of the SSS would be expected to increase post-surgery. To that end, mean $A_{CS}$ and mean $D_H$ were computed from the segmentation of each model and compared between subject groups. Additionally, $1/A_{CS}$ and $1/D_H$ for each case were compared against impedance and pressure parameters to assess whether the dynamic parameters had predictive value in terms of mean changes to the SSS geometry.

5.2.6 **Volume Flow Rate Waveforms and Boundary Condition Formulation**

Extraction of CSF velocity data from the pcMR images was performed by manually masking the SSS in each sequence using a custom Matlab graphical user interface. Volume flow rate (VFR) waveforms were then computed as the product of the SSS mask area and the average velocity within the mask (Figure 5.2.4). All VFR waveforms were offset to have zero net flow so as to compensate for eddy current artifacts from image acquisition.
Using the VFR waveform from image segmentation, inlet boundary conditions for each CFD model were formulated in three steps. First, the VFR waveform was up-sampled from 20 to 100 time points using piece-wise cubic Hermite interpolation, which preserved fidelity to the original waveform shape in all cases (Figure 5.2.5). Second each waveform was shifted such that the flow cycle began at diastolic deceleration for each case. Finally, each VFR waveform was then scaled by the cross-sectional area of the inlet face of the respective model to create an average velocity waveform. Velocity at the inlet face of each model was then specified as a transient blunt velocity profile based on the respective average velocity waveform.
Figure 5.2.5: Comparison of an example CSF volume flow rate waveform obtained directly from pcMR to an upsampled version the waveform used to formulate the inlet boundary condition for its respective CFD model.
5.2.7 Flow Field Characterization

To characterize the flow field in each model, peak instantaneous Reynolds numbers and Womersley numbers were calculated from image segmentation data. Instantaneous Reynolds number at peak systolic flow was calculated in each model cross-section by the following relation:

\[
Re = \frac{\rho Q_{\text{Peak}} D_H}{\mu A_{CS}}
\]  

(5.1)

Where \( \rho \) was the fluid density, \( \mu \) was the fluid viscosity, \( Q_{\text{Peak}} \) was the peak systolic flow rate, \( D_H \) was the mean hydraulic diameter of the spinal SAS model, and \( A_{CS} \) was the mean cross-sectional area of the spinal SAS model. Similarly, maximum Womersley number in each model was calculated using mean hydraulic diameter by the following relation:

\[
\alpha = \frac{D_H}{4} \sqrt{\frac{2\pi \rho}{\mu}}
\]  

(5.2)

where \( \omega = \frac{2\pi}{T} \) and \( T \) was the period of the flow waveform used to formulate the IBC and other variables were defined similarly to the Reynolds number equation. Maximum Reynolds numbers ranged from 44-214 and maximum Womersley numbers ranged from 3.7-9.9 (Figure 5.2.6). Thus, CSF motion in all cases was assumed to be laminar and moderately-to-strongly pulsatile regardless of subject category.
Figure 5.2.6: Comparison of Womersley number to Reynolds number for all cases, showing that flow was generally laminar and moderately-to-strongly pulsatile regardless of subject category.
5.2.8 *Meshing and Modeling Setup for CFD*

Each SSS model was imported into ICEM CFD [Ansys Inc, Canonsburg, PA] and meshed for CFD analysis using a hybrid prism-tetrahedral cell mesh. The meshing process comprised the following steps: generating an unstructured tetrahedral mesh for the entire volume using the Octree algorithm, smoothing the mesh using the Delaunay algorithm, extruding a layer of prismatic cells near model wall to create a boundary layer, splitting the prismatic layer to create five smaller prismatic layers of linearly increasing aspect ratio, and re-smoothing the tetrahedral core using the Delaunay algorithm. Special care was taken to use additional mesh refinement in “pinched” regions (small gaps between walls) of the SSS models, which allowed for better shape maintenance in more complex geometric regions. The resulting hybrid prism-tetrahedral meshes ranged in size from 0.5-2 million total cells depending on the size of the SSS model and the length of the entry and exit extensions.

Inner and outer walls of the SSS were modeled as rigid and specified with a no-slip (zero-velocity) boundary condition. Because the velocity waveforms used for the inlet boundary conditions were taken from the C2-C3 level of the spine, the model bottom (caudal end) was specified as a velocity inlet and the model top (cranial end) was specified as a zero-pressure outlet for each case. SSS pressure measurements could not be non-invasively measured to obtain a different pressure boundary condition. Thus, this configuration only allowed for computation of pressure gradients.

The commercial finite volume solver Fluent [Ansys Inc., Canonsburg, PA] was used to carry out fluid flow simulations. Based on the estimation of peak instantaneous Reynolds number described previously, a laminar flow model was used for all
simulations. CSF was modeled as water at 37 °C (ρ = 1.0 gm/cm³, μ = 0.01 P) [24]. Using a pressure-based solver, the Navier-Stokes equations were discretized using a second-order upwind scheme in space and a second-order implicit scheme in time. The SIMPLE algorithm was used for pressure-velocity coupling and the Green-Gauss node-based method was used to evaluate the gradient terms in the Navier-Stokes equations. Residuals for continuity and the x-, y-, and z-components of velocity were initially set to 10⁻⁶ as convergence criteria. After grid, time-step, and cycle independence were verified with the baseline settings, it was found that the convergence criteria could be relaxed to 10⁻³ for continuity and 10⁻⁵ for each velocity component without affecting the pressure gradient results. Also, several specialized numerical methods for transient (i.e. PISO) and pulsatile/swirling flows (PRESTO) were also tested and compared to the baseline method. The pressure gradient results produced by the specialized methods were indistinguishable from those produced by the baseline method.

5.2.9 Independence of CFD Solutions

To ensure that CFD solutions were independent of mesh size, time step size, and waveform period, flow was simulated in an SSS model from a randomly selected CMI patient, which had a constricted inlet region. Using an SSS model with a constricted inlet region allowed testing of solution independence in the expected presence of high pressure gradients. The assumption for this approach was that a sizing scheme which yielded a mesh-independent solution for an SSS model where high pressure gradients were expected should also yield a mesh-independent solution for an SSS model where lower gradients were expected. For the test model, a base mesh and a refined mesh were created with cell counts of approximately 480K and 1.5M, respectively. Each model was
tested for time steps of T/100, T/200, and T/400 and simulated for three periods of the inlet waveform to assess time step and period independence. Solution independence was determined by comparing root-mean-square (RMS) error between time course profiles of pressure drop between planes at the FM and 25mm caudal to the FM. 25 mm was chosen as the lower limit for computing pressure drop based on its demonstrated utility in past studies [5, 6]. Plots used to assess independence are given in Appendix A. Results are summarized here.

For the base mesh, the maximum RMS error between pressure drop waveforms was 4.5% between periods 1 and 2 and less than 0.1% between periods 2 and 3 for all time steps analyzed. Similarly, maximum RMS errors of 4.3 % and less than 0.1% were obtained for the refined mesh. Thus, 2 periods of the IBC waveform were sufficient to achieve period independence.

Comparing pressure drop waveforms from the second period of each simulation, the maximum RMS error was 5.8% by refining the time step from T/100 to T/200 and 1.6% by refining the time step from T/200 to T/400. Similar values were obtained for the refined mesh. Thus, it was assumed that a time step of T/200 was sufficient to temporally resolve the pressure drop waveform.

Comparing the time-step and period independent pressure drop waveforms from the base and refined meshes, the maximum RMS error was 1.6%. Thus it was assumed that the meshing scheme used for the base mesh was sufficient to spatially resolve the pressure drop waveform.
Based on these results, the remaining CFD simulations were run using the meshing scheme from the base mesh with a time step of T/200 for two periods of the inlet boundary condition waveform.

5.2.10 Pressure Gradient

Transient pressure gradient in each model was computed as the difference in area-weighted average pressure in cross-sectional planes at the FM and at planes spaced in 5 mm increments perpendicularly caudal to the FM (Figure 5.2.7). Peak systolic pressure gradient, peak diastolic pressure gradient, and peak-to-peak pressure gradient (difference or “swing” between peak systolic and peak diastolic pressure gradient) were recorded for each case and analyzed between groups.

![Figure 5.2.7: Example pressure gradient waveform obtained between the FM and 25 mm caudal to the FM over one flow period in the test model. Peak systolic and peak diastolic pressure gradient are highlighted.](image)
5.2.11 Longitudinal Impedance

LI was computed for this study using the following method. In each simulation, the transient pressure gradient near the CVJ was computed as the difference in area-weighted average pressure in cross-sectional planes located at the FM and at planes spaced in 5 mm increments perpendicularly caudal to the FM as described previously. The impedance moduli, $Z_{Ln}$, were then calculated by computing the ratio of the Fourier coefficients of pressure gradient and volume flow rate at each harmonic such that $Z_{Ln} = \frac{\text{FFT}(\Delta P(t))}{\text{FFT}(Q(t))}$. The resulting impedance curves were then integrated from 1-8 Hz to obtain an integrated LI modulus for each subject, which provided a single metric for comparison. LI computed in this way was the impedance to the frequency components that displaced most or all of the fluid (Figure 5.2.8) in a particular waveform (i.e. the dominant carrier frequencies). The range 1-8 Hz was chosen as it represents 85-100% of the power spectrum density (PSD) for all the flow waveforms used as inlet boundary conditions was contained between those frequencies (Figure 5.2.9).
Figure 5.2.8: Example of a typical frequency spectrum (left) and %PSD (right) for a CSF flow waveform used as a CFD inlet boundary condition.

Figure 5.2.9: Distributions of % PSD contained in the frequency range 1-8 Hz for all inlet boundary condition waveforms used in CFD models.
5.2.12 *Quasi-steady resistance*

Though previous studies [5, 6] have focused on the utility of LI in examining the resistance to the CSF flow pulsation, it has not previously been established whether LI was superior to simpler parameters, such as quasi-steady resistance in systole or diastole, in terms of showing differences in the pressure environment of the SSS pre-surgery and post-surgery. To that end, quasi-steady systolic resistance ($\Delta P_{SYS}/Q_{SYS}$), quasi-steady diastolic resistance ($\Delta P_{DIA}/Q_{DIA}$), and quasi-steady peak-to-peak resistance ($\Delta P_{P-P}/Q_{P-P}$) were computed for each case and analyzed between groups. Because there was no mean VFR component due to eddy current correction, it was necessary to use the quasi-steady approximation of resistance instead of simply analyzing the zero-eth harmonic of LI.

5.2.13 *Parametric Variation of Length Used for Pressure Gradient Calculations*

To understand the impact of the length used to calculate pressure gradient, the distance was parametrically varied in the CMI patient models used for this study to identify a minimum distance, if any, at which there arises a significant difference in pressure gradient or pressure gradient-based parameters between CMI patients pre-surgery and post-surgery. In previous studies [5, 6], pressure gradient in models of the SSS was computed between planes at the level of the foramen magnum and 25 mm caudal to the FM. The justification for this was that cases of CMI where CTD has been measured at greater than 25 mm were extremely rare. Thus, computing pressure gradient between the bounds of a worst-case scenario provided a consistent metric for comparison among SSS models from CMI patients. While this may have been sufficient for comparing CMI patients to healthy volunteers, it is not known whether this criterion is useful for comparing CMI patients pre-surgery and post-surgery.
To assess the utility of the three pressure gradient parameters and four impedance/resistance parameters discussed previously, each was compared in pre-surgery and post-surgery SSS models and the length used to compute the pressure gradient was parametrically varied for distances of 5, 10, 15, 20, 25, and 30 mm perpendicularly caudal to the plane of the FM.

5.2.14 Statistical Analysis

Because decompression surgery is meant to increase space in the SSS, it was hypothesized that geometric parameters would increase post-surgery and impedance and pressure based parameters would decrease. Thus for each parameter examined, a single-tailed paired t-Test was used to test the generic null hypothesis that there was no difference in each parameter between the pre-surgery and post-surgery groups. The generic alternative hypothesis was that parameters in post-surgery patients were significantly different in the direction that change was intuitively expected (e.g. increase in mean cross-sectional area of the SSS). Single-tailed two-sample t-tests assuming unequal variances were used to compare parameters between each CMI patient group and the healthy volunteer group. Assuming a significance level of 0.05, minimum group size of 15 in all groups, and using the impedance data from a prior iteration of the study to make a point estimate, the statistical power was estimated to be 0.9.
5.3 Results

For the 20 CMI patients, the mean age in years was 38 with a range of 24-58. For the 15 healthy volunteers, the mean age in years was 36 with a range of 22-51. Gender divisions (female/male) were 19/1 and 8/7 for the CMI patient and healthy volunteer groups, respectively. Due to limited subject availability, only one male CMI patient was available to participate in the study. Thus, gender could not be controlled for. The preponderance of female patients was not completely surprising, as CMI is known to affect females more often than males [127]. Due to post-surgery complications, three of the CMI patients (all female) withdrew from the study. The number of pre/post-surgery data pairs used for paired statistical analysis was reduced to seventeen. No pre/post-surgery changes to any of the geometric or hydrodynamic parameters analyzed were found to correlate with patient age.

5.3.1 Cerebellar Tonsil Descent

Mean CTD was measured to be 9.5 ± 1.2, 6.9 ± 1.0, and -1.7 ± 1.0 mm for the pre-surgery, post-surgery, and healthy volunteer groups respectively. Statistical analysis showed that mean TD decreased significantly post-surgery for CMI patients (2.6 mm average decrease, p = 0.04), but was still significantly greater than CTD observed in healthy volunteers (p < 0.001). Though CTD decreased post-surgery in CMI patients on average, four cases showed a small increase and one showed approximately no change in TD (Figure 5.3.1). Only three patients of the seventeen analyzed showed TD relax to a level below the 3-5 mm criterion.
Figure 5.3.1: Group distributions (left) and changes in TD between pre-surgery and post-surgery measurements (right). Statistical outliers are denoted by ‘+’.

5.3.2 Parametric Variation of Length Used for Pressure Gradient Calculations

By parametrically varying the length used to compute the pressure gradient for comparative analysis, it was shown that $\Delta P_{SYS}$, $\Delta P_{DIA}$, and $\Delta P_{P-P}$ decreased post-surgery on average, but the mean pre/post-surgery differences were not statistically significant for any of the lengths tested (Table 5.3). Hence, pressure gradient parameters may have some utility in qualitatively describing changes to the SSS pressure environment, but were not useful as metrics to statistically differentiate pre-surgery subjects from post-surgery subjects.

Significant mean pre/post-surgery differences in LI were found when the pressure gradient used to make the LI calculation was measured between the FM and 15-25 mm perpendicularly caudal to the FM (Table 5.4). This range corresponded to the region in the SSS where pre/post-surgery differences in mean $A_{CS}$ and, especially, mean $D_{H}$ were the most consistent (Table 5.5). It should also be noted that the 15-25 mm range was, on average, past the tip of CTD. Thus for computing pressure gradient for LI analysis in this
study, a good rule of thumb was to choose a location for the caudal plane past the
cerebellar tonsil tip where the cross-section of the SSS was consistently expanded, but
not so far caudal to the FM that the geometric differences caused by CTD were washed
out by averaging. As the most severe instance of CTD in this study was 20 mm, the 25
mm plane was determined to be the most appropriate reference plane to provide a
consistent comparison between both CMI patient groups.

All three quasi-steady resistance parameters decreased post-surgery on average.
However, the mean changes were weakly non-significant for $\Delta P_{SYS}/Q_{SYS}$ and not
statistically significant for normalized $\Delta P_{DIA}/Q_{DIA}$ or normalized $\Delta P_{P-P}/Q_{P-P}$. Hence,
quasi-steady resistance parameters may also have some utility in qualitatively describing
changes to the SSS pressure environment, but were not useful as metrics to statistically
differentiate pre-surgery subjects from post-surgery subjects.

Because significant mean pre/post-surgery differences were only found for LI and
cross-sectional geometry, only those parameters are discussed in greater detail here.
Table 5.3: Tabulated values for $\Delta P_{\text{SYS}}$, $\Delta P_{\text{DIA}}$, and $\Delta P_{\text{P-P}}$ (mean $\pm$ SE) for the pre-surgery and post-surgery CMI patient groups and alpha levels for the paired t-test between groups obtained by varying the length of pressure gradient computation.

<table>
<thead>
<tr>
<th>Gradient Length</th>
<th>$\Delta P_{\text{SYS}}$ (dyn/cm$^2$)</th>
<th>$\Delta P_{\text{DIA}}$ (dyn/cm$^2$)</th>
<th>$\Delta P_{\text{P-P}}$ (dyn/cm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Pst</td>
<td>$p$</td>
</tr>
<tr>
<td>5 mm</td>
<td>61.7 ± 10.2</td>
<td>55.4 ± 14.2</td>
<td>0.27</td>
</tr>
<tr>
<td>10 mm</td>
<td>99.0 ± 20.2</td>
<td>90.6 ± 24.5</td>
<td>0.32</td>
</tr>
<tr>
<td>15 mm</td>
<td>121.6 ± 23.8</td>
<td>110.9 ± 27.2</td>
<td>0.31</td>
</tr>
<tr>
<td>20 mm</td>
<td>138.8 ± 25.3</td>
<td>129.0 ± 28.5</td>
<td>0.34</td>
</tr>
<tr>
<td>25 mm</td>
<td>156.9 ± 26.3</td>
<td>148.8 ± 30.3</td>
<td>0.38</td>
</tr>
<tr>
<td>30 mm</td>
<td>176.3 ± 28.5</td>
<td>172.3 ± 32.8</td>
<td>0.44</td>
</tr>
</tbody>
</table>
Table 5.4: Tabulated values for normalized DP_{SYS}, normalized DP_{DIA}, normalized DP_{P-P}, and LI values (mean ± SE) for the pre-surgery and post-surgery CMF patient groups and alplα levels for the paired t-test between groups obtained by varying the length of pressure gradient computation.

<table>
<thead>
<tr>
<th>Gradient Length</th>
<th>LI (dyn/cm²)</th>
<th>ΔP_{SYS}/Q_{SYS} (dyn-s/cm²)</th>
<th>ΔP_{DIA}/Q_{DIA} (dyn-s/cm²)</th>
<th>ΔP_{P-P}/Q_{P-P} (dyn-s/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Pst</td>
<td>p</td>
<td>Pre</td>
</tr>
<tr>
<td>5 mm</td>
<td>176 ± 22</td>
<td>140 ± 34</td>
<td>0.06</td>
<td>25.0 ± 3.2</td>
</tr>
<tr>
<td>10 mm</td>
<td>282 ± 50</td>
<td>223 ± 49</td>
<td>0.09</td>
<td>40.1 ± 6.7</td>
</tr>
<tr>
<td>15 mm</td>
<td>353 ± 62</td>
<td>275 ± 52</td>
<td>0.013</td>
<td>49.7 ± 8.2</td>
</tr>
<tr>
<td>20 mm</td>
<td>403 ± 64</td>
<td>323 ± 53</td>
<td>0.018</td>
<td>56.8 ± 8.4</td>
</tr>
<tr>
<td>25 mm</td>
<td>458 ± 62</td>
<td>376 ± 56</td>
<td>0.016</td>
<td>64.5 ± 8.5</td>
</tr>
<tr>
<td>30 mm</td>
<td>509 ± 65</td>
<td>437 ± 59</td>
<td>0.048</td>
<td>72.6 ± 9.2</td>
</tr>
</tbody>
</table>
Table 5.5: Tabulated values of mean $A_{CS}$ and mean $D_H$ (mean ± SE) for the pre-surgery and post-surgery CMI patient groups and alpha levels for the paired t-test between groups obtained by computing the mean between the reference planes used for the corresponding LI comparisons.

<table>
<thead>
<tr>
<th>Gradient Length</th>
<th>Mean $A_{CS}$ (cm²)</th>
<th>Mean $D_H$ (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Pst</td>
</tr>
<tr>
<td>5 mm</td>
<td>1.82 ± 0.20</td>
<td>2.38 ± 0.26</td>
</tr>
<tr>
<td>10 mm</td>
<td>1.94 ± 0.18</td>
<td>2.36 ± 0.22</td>
</tr>
<tr>
<td>15 mm</td>
<td>2.01 ± 0.15</td>
<td>2.33 ± 0.16</td>
</tr>
<tr>
<td>20 mm</td>
<td>2.07 ± 0.12</td>
<td>2.29 ± 0.14</td>
</tr>
<tr>
<td>25 mm</td>
<td>2.08 ± 0.11</td>
<td>2.22 ± 0.10</td>
</tr>
<tr>
<td>30 mm</td>
<td>2.04 ± 0.11</td>
<td>2.14 ± 0.12</td>
</tr>
</tbody>
</table>
5.3.3 Longitudinal Impedance to CSF Motion

Using the FM and 25 mm caudal to the FM as common reference planes, mean values of LI were 458 ± 62, 376 ± 56, and 237 ± 11 dyn/cm$^5$ for the pre-surgery, post-surgery, and healthy volunteer groups, respectively. Statistical analysis showed a significant difference in LI between CMI patients pre-surgery and post-surgery (65.1 dyn/cm$^5$ average decrease, p = 0.016). As expected, mean LI in pre-surgery CMI patients was significantly higher than in healthy volunteers (p = 0.002). Interestingly, mean LI in post-surgery CMI patients was still significantly higher than in healthy volunteers (p = 0.004) despite overlapping ranges (207-904 dyn/cm$^5$ vs. 155-308 dyn/cm$^5$, respectively).

Though LI decreased post-surgery in CMI patients on average, four of the seventeen cases showed an increase in LI (Figure 5.3.2) and four showed only small changes.

Figure 5.3.2: Distributions of longitudinal impedance near the CVJ for each subject group (left) and changes in longitudinal impedance between pre-surgery and post-surgery measurements (right).
Similar to the results in previous studies [6], CTD was only weakly correlated with LI magnitude (Figure 5.3.3) and the dispersion of LI data was much greater for subjects with CTD greater than 3mm.

Figure 5.3.3: Relationship between CTD and LI for all pre-surgery, post-surgery and healthy volunteer cases. The line denoting the minimum 3mm CTD criterion (red dash) also denotes where dispersion of LI relative to CTD increases.
5.3.4 SSS Cross-Sectional Geometry

Using the FM and 25 mm caudal to the FM as common reference planes, mean
\( A_{CS} \) for the pre-surgery, post-surgery, and healthy volunteer groups was 2.08 ± 0.11, 2.22
± 0.10, 2.77 ± 0.14 cm², respectively. Statistical analysis showed that mean \( A_{CS} \)
increased significantly post-surgery for CMI patients (0.1 cm² average increase, \( p = 0.009 \)), but was still significantly smaller than mean \( A_{CS} \) measured in healthy volunteers
(\( p = 0.008 \)). Though \( A_{CS} \) increased post-surgery in CMI patients on average, four of the
seventeen cases showed a small decrease in mean \( A_{CS} \) (Figure 5.3.4). Further, mean \( A_{CS} \)
in the SSS was only weakly related to the extent of CTD in each subject (Figure 5.3.5),
but \( 1/A_{CS} \) was strongly related to the magnitude of LI in the SSS (Figure 5.3.6).

Figure 5.3.4: Distributions of Mean \( A_{CS} \) for each subject group (left) and relative change
in Mean \( A_{CS} \) between pre-surgery and post-surgery measurements (right).
Figure 5.3.5: Relationship between CTD and $1/A_{CS}$ for all pre-surgery, post-surgery and healthy volunteer cases showing only weakly linear correlation. Data dispersion was high irrespective of the CTD criterion for determining CMI patients.

Figure 5.3.6: Relationship between $1/A_{CS}$ and LI for all pre-surgery, post-surgery and healthy volunteer cases, showing a strong increasing linear correlation.
Similarly mean $D_H$ for the pre-surgery, post-surgery, and healthy volunteer groups was at 0.62 ± 0.03, 0.65 ± 0.03, and 0.83 ± 0.03 cm, respectively. Statistical analysis showed that mean $D_H$ increased significantly post-surgery for CMI patients (0.03 cm average increase, $p = 0.024$) despite only a small difference in group means. Further, mean post-surgery $D_H$ was still significantly smaller than mean $D_H$ in healthy volunteers ($p<0.001$). Though $D_H$ increased post-surgery in CMI patients on average, five of the seventeen cases showed a small decrease in mean $D_H$ (Figure 5.3.7). Further, mean $1/D_H$ in the SSS was only weakly related to the extent of CTD in each subject (Figure 5.3.8), but $1/D_H$ was strongly related to the magnitude of LI in the SSS (Figure 5.3.9).

Figure 5.3.7: Distributions of Mean $D_H$ for each subject group (left) and relative change in Mean $D_H$ between pre-surgery and post-surgery measurements (right).
Figure 5.3.8: Relationship between CTD and $1/D_H$ for all pre-surgery, post-surgery and healthy volunteer cases showing only weakly linear correlation. Data were slightly less scattered than $1/A_{CS}$ vs. CTD.

Figure 5.3.9: Relationship between $1/D_H$ and LI for all pre-surgery, post-surgery and healthy volunteer cases, showing a strong increasing linear correlation.
Thus, the changes to the cross-sectional geometry of the SSS created by decompression surgery were favorable but somewhat mixed. Further, changes to the cross-sectional geometry did not increase space in the SSS to the level observed in healthy controls.

5.3.5 Natural Variation in SSS Geometry and Impedance

In order to assess whether changes observed in geometric or hydrodynamic variables were the result of decompression surgery or natural variation, the first five healthy volunteer subjects were scanned a second time and compared for LI, mean A_{CS}, and mean D_{H}. Based on the tabulated results (Table 5.5), as much as 6% of the difference in geometry parameters between two SSS models of the same subject may be accounted for by natural variation caused by imaging the subject at different time points.

Table 5.6: Mean values of LI, mean A_{CS}, and mean D_{H} (mean ± standard error) computed from healthy volunteer SSS models at primary and secondary scans.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Primary</th>
<th>Secondary</th>
<th>Mean % Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LI (dyn/cm^5)</td>
<td>233 ± 20</td>
<td>239 ± 20</td>
<td>2.7</td>
</tr>
<tr>
<td>A_{CS} (cm^2)</td>
<td>2.90 ± 0.32</td>
<td>2.91 ± 0.28</td>
<td>1.0</td>
</tr>
<tr>
<td>D_{H} (cm)</td>
<td>0.80 ± 0.05</td>
<td>0.80 ± 0.04</td>
<td>0.3</td>
</tr>
</tbody>
</table>
5.4 Discussion

This study presented analysis of impedance to CSF motion in the SSS near the CVJ as a metric to quantify differences between CMI-affected spinal canals before and after decompression surgery. Subject-specific CFD modeling was used to simulate CSF motion around the partial blockage caused by CTD and LI was calculated using the pressure gradient between the FM and 25 mm caudal to the FM to give a consistent means of comparison between pre-surgery CMI patients, post-surgery CMI patients, and healthy volunteers. LI was also compared against CTD, the commonly used clinical morphometric, more conventional geometric parameters, $A_{CS}$ and $D_H$, and more commonly reported pressure parameters, gradients at peak systole, peak diastole, and peak-to-peak pressure gradient.

Results showed that the difference in LI between pre-surgery and post-surgery CMI patients was greatest when the pressure gradient used to compute LI was measured between the FM and a plane 15-25 mm perpendicularly caudal to the FM, where a sustained area expansion past the tip of the cerebellar tonsils was observed on average in the SSS. The worst case of CTD in the CMI patient group of this study was ~20 mm, so the 25 mm criterion was used in general analysis to provide a common, consistent reference plane for all patient and healthy volunteer cases.

In this patient group, LI was found to be significantly lower post-surgery compared to pre-surgery. However, LI in post-surgery CMI patients was still significantly higher than in healthy volunteers. A mean decrease in LI of 65.1 dyn/cm$^5$ was observed between pre-surgery and post-surgery cases, which corresponded to a mean decrease in CTD of 2.6 mm. The relationship between change in CTD and change in LI
did not follow a discernable pattern. Likewise, there was only weak correlation between CTD and the SSS cross-sectional geometry parameters, mean $A_{CS}$ and mean $D_H$.

Decreases in LI did, however, correspond with small increases in mean $A_{CS}$ and mean $D_H$ in the SSS. This suggested that the pressure environment in the SSS was highly sensitive to small mean changes in cross-sectional geometry.

5.4.1 Importance of capturing three-dimensionality and dynamic aspects of CMI.

CTD only correlated weakly with LI, similar to previous work [6]. This was likely the result of CTD being static 1D information about a dynamic 3D environment. To better capture the three-dimensionality of the blockage, mean cross-sectional geometry parameters in the SSS (effectively the volume of fluid space near the CVJ) were analyzed. The correlation between LI and mean $A_{CS}$ ($R^2 = 0.73$) and mean $D_H$ ($R^2 = 0.79$) was much stronger than CTD. Thus, a better estimate of the effect of blockage three-dimensionality on LI was obtained by estimating the cross-sectional constriction the in SSS. However, the correlation between LI and both geometric parameters was not perfect. For example, the cluster of data points in the low-to-moderate LI range (150-600 dyn/cm$^5$) corresponds to the mean $D_H$ range of 0.6-1.1 cm. While LI in healthy volunteer SSS models increased linearly with $1/D_H$, LI in CMI patient SSS models showed more dispersion. This suggested that there was small but likely important non-linear effect caused the complexity of the blockage that couldn’t be captured by considering average cross-sectional geometry. For example, LI in one pre-surgery CMI patient model was nearly twice as high as in a healthy volunteer model (567 vs 308 dyn/cm$^5$) despite only a small difference in mean $D_H$ (0.7 vs. 0.6 cm).
5.4.2 Limitations

The gender disparity in the CMI patient group may have introduced some bias into both the impedance and geometry data. In addition to CMI being more prevalent in females, CTD is also typically naturally greater in females [4]. However, though females generally have smaller stature than males, females in the healthy volunteer sample of this study had, on average, slightly larger mean $A_{CS}$ ($2.93 \pm 0.25$ vs. $2.59 \pm 0.02$ cm) and larger mean $D_H$ ($0.87 \pm 0.05$ cm vs. $0.78 \pm 0.03$ cm) than males. This translated to LI in female volunteers being 13% lower on average ($224 \pm 20$ vs. $257 \pm 5$ dyn/cm$^2$). While it is unclear what impact this difference would have on the CMI-affected SSS, it may explain the occurrence of so many low-impedance pre-surgery CMI patients. Thus, geometry-based hydrodynamic parameters may have been biased large in the CMI patient groups due to the gender disparity. In future work, it would be prudent to use more balanced gender matching or perhaps even conduct separate studies of male and female CMI patients. However, the feasibility imposing such restrictions must be considered in the context of the limited patient availability.
Geometric reconstructions of the SSS were performed by a single operator and only one healthy volunteer subject was imaged at all three sites such that a measurement repeatability analysis could be conducted. Ideally, end-to-end model reconstruction and analysis would be assessed for multiple pilot subjects. However, inter-operator variability analysis using similar modeling methods was conducted in another image-based modeling study [133] and found that the impact of different operators was small when a consistent modeling methodology was employed. Thus, we suspect that the geometry of the SSS models would not be significantly different had the reconstructions been performed by a different operator using a similar methodology.

Cross-sectional geometry parameters were not computed orthogonal to the centerline of the SSS because of the shape complexity of the 3D models. Thus, it was necessary to compute cross-sectional geometry parameters in planes along the longitudinal axis (Cartesian z-axis) of the coordinate system in each MR image stack. While this method was useful to obtain average values of $A_{CS}$ and $D_H$, it could not directly account for angulation of the head and neck which may be an important consideration near the CVJ. For example, if the angle of the FM plane to horizontal were large, a small segment of the cerebellomedullary cistern immediately above the FM would have been captured in the averaging. Thus, the average value of either $A_{CS}$ or $D_H$ may have been slightly biased smaller or larger depending on the crowdedness of the fluid space in the cerebellomedullary cistern for all cases and the extent of decompression surgery in post-surgery CMI patients.

CFD simulations in this study used the assumption of rigid inner and outer walls of the SSS (i.e. the spinal cord and dura). In actuality, these tissues are compliant and the
spinal cord and cerebellar tonsils have some component of motion. Thus, pressure in the SSS may be somewhat underestimated. Bulk tissue displacement in the cerebellar tonsils in the rostrocaudal direction may range from 0 to 0.6 mm in CMI patients and healthy subjects [11, 25-27, 30]. As the width of the fluid space between tissue and dura may be as small as 1mm, it may be important to account for cerebellar tonsil motion in future studies. However, it was shown by Cheng et al. [96] that spinal cord motion has a negligible impact on pressure in the SSS.

It is also known that pulsatile flow models which employ moving or flexible walls are computationally expensive and difficult to interpret. Thus, the need for a fully detailed fluid-structure interaction model must also be weighed against the potential impact of such detail.

5.5 Conclusion

Diagnosis and treatment of CMI patients may benefit from an assessment of their subject-specific biomechanical environment. This work investigates the use of pressure and impedance parameters as biomechanical metrics to compare CMI patients before and after decompression surgery. Of all the parameters investigated, only LI was found to decrease significantly post-surgery in this patient sample on average. Changes were not always large, however, and post-surgery LI remained significantly higher than LI observed in healthy volunteers. LI was found to be sensitive to small average changes in the cross-sectional geometry of the SSS, but only correlated weakly with changes to CTD. Because of the preponderance of female patients in the study, pre-surgery and post-surgery LI data may have been biased low. Future work in a study population with
better age-gender matching is planned to fully understand the potential, if any, of LI as a clinical diagnostic tool for CMI patients of both genders.

5.6 Acknowledgements

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CHAPTER VI

QUANTITATIVE AND QUALITATIVE ANALYSIS OF VELOCITY IN THE SPINAL CANAL OF TYPE I CHIARI MALFORMATION PATIENTS BEFORE AND AFTER DECOMPRESSION SURGERY

This chapter describes a study which analyzes velocity data obtained from the CFD models described in previous work (Chapter V) and compares computational CSF velocities against physical velocity measurements obtained with 2D phase-contrast MR imaging. The goals were 1) to assess whether peak velocities show the same mean pre/post-surgery differences as LI and cross-sectional geometry and 2) to assess whether physical measurements of velocity match those observed in the computational models and, thus, validate the computational models. This section was written in the form of a supplementary paper to the results in Chapter V.
6.1 Introduction

Since the advent of phase-contrast magnetic resonance imaging (pcMRI), cerebrospinal fluid (CSF) motion has been studied at great length. The intent of early CSF motion studies was to further understanding of the origin and mechanism of the CSF pulsation [27, 29-33]. More recently, researchers have been interested in the augmentation of CSF motion caused by craniospinal disorders, such as Type I Chiari Malformation (CMI) [7-10, 12, 66, 67]. The reason for this interest is two-fold. First, cranial morphometric measurements taken from static anatomy MR images have been insufficient to explain patient symptoms or quantify outcomes of corrective surgery [2, 47]. Second, it is thought that hydraulic pressure on nervous structures is likely at the root of CMI symptomatology, and characterization of CSF velocity and flow in CMI-affected spinal canals may provide a non-invasive means to assess severity. Though the unidirectional velocity encoding of 2D through-plane pcMRI only allows for analysis of the axial velocity component, its potential utility in showing qualitative [8, 13] and quantitative [7, 9, 10] velocity field differences between the healthy spinal canal and the CMI-affected spinal canal has been demonstrated in the past.

More recently, computational fluid dynamics (CFD) modeling has also been used to study CSF motion in the spinal canal and craniovertebral junction. Though most of these studies have used either idealized spinal canal geometry [68, 89, 90, 92, 94] or idealized boundary conditions [69, 91], several have employed both [5, 6, 88, 96, 97, 128, 134]. However, studies with idealized model inputs have claimed good agreement with velocity data from pcMR imaging, whereas studies with subject-specific models have reported mixed results in terms of velocity agreement. Specifically, velocity data from
subject-specific CFD has been shown to agree somewhat with individual pixel velocity profiles obtained from 2D pcMRI [134] but not with planar velocity fields obtained from 4D (time-resolved 3D) pcMRI [97, 128]. To the author’s knowledge, the agreement between both peak velocities and in-plane velocity field profiles from CFD and 2D pcMRI has not yet been reported for a large sample of subject-specific models of the spinal canal.

Hence, the goal of this study was to use the CFD data from the previous Chapter to quantitatively compare peak and mean CSF velocities and qualitatively compare through-plane velocity fields from the C2 level of the CFD models and from 2D pcMR images taken at the C2 level of the physical spinal canal. The hypothesis for quantitative comparison was that peak CSF velocities would be higher in pre-surgery CMI patients than in healthy volunteers and that velocity would decrease post-surgery.
6.2 Materials and Methods

Study population

Sixteen symptomatic adult CMI patients (age 24 or older) from the previous study (7 from CCF, 9 from MC) were included in this iteration. Eleven of the healthy volunteers from the previous study were also included in the control group for this iteration (5 at CCF, 5 at MC, 1 at EU).

6.2.1 MR imaging and computational modeling

Details of the MR imaging sequences used to obtain data are described in the previous Chapter. The CFD models used for comparison are the same as those used for the pressure and LI analysis in the previous Chapter.

6.2.2 Quantitative and qualitative velocity analysis

For each subject, pcMR images obtained from both the FM and C2 levels of the spine were processed for velocity data by manually masking the cervical spinal subarachnoid space in each image set using a custom Matlab graphical user interface. Special care was taken to exclude areas of the SSS that appeared to have abnormally high velocities due to the presence of blood vessels. Likewise, the SSS had to be truncated in some cases due to lack of signal or presence of noise. Once masked, velocity profiles for each pixel in the SSS were exported for analysis.

For each CFD model, velocity data planes were specified at the FM and at a level in line with the C2-C3 intervertebral disc. Each plane surface in the computational model was approximately collocated with the plane used to obtain pcMR image data. For each data set, the peak through-plane (z-component) velocity at peak systole (caudal-directed) and peak diastole (cranial-directed) were captured and used for the quantitative analysis.
comparison between groups and between measurement methods. Two comparisons were then made to assess how well CFD results matched pcMRI measurements. First, peak through-plane (z-component) velocity at peak systole (caudal-directed) and peak diastole (cranial-directed) at both the FM and C2 planes were compared between subject groups and then between measurement techniques. Second, mean velocities at peak systole and peak diastole at the C2 level were then compared between measurement techniques to assess the impact of the different imaging protocols and segmentation methods on the velocity fields (Figure 6.2.1).

Figure 6.2.1: Example C2 plane velocity distributions obtained from pcMRI and CFD.
6.2.3 Statistical Analysis

Because decompression surgery is meant to increase space in the SSS, it was hypothesized that peak CSF velocities at both the FM and C2 levels and peak WSS near the CVJ would decrease post-surgery. Thus for each parameter examined, a single-tailed paired t-Test was used to test the generic null hypothesis that there was no difference in each parameter between the pre-surgery and post-surgery groups. The generic alternative hypothesis was that parameters in post-surgery patients were significantly different in the direction that change was intuitively expected (e.g. increase in mean cross-sectional area of the SSS). Single-tailed two-sample t-tests assuming unequal variances were used to compare parameters between each CMI patient group and the healthy volunteer group. Assuming a significance level of 0.05 and minimum group size of 11 in all groups, the power of each statistical test was estimated to be 0.9.
6.3 Results

For the 16 CMI patients, the mean age in years was 40 with a range of 24-58. For the 11 healthy volunteers, the mean age in years was 38 with a range of 22-51. Gender divisions (female/male) were 15/1 and 7/4 for the CMI patient and healthy volunteer groups, respectively. Due to limited subject availability, only one male CMI patient was available to participate in the study. Thus, gender could not be controlled for. The preponderance of female patients was not completely surprising, as CMI is known to affect females more often than males [127].

6.3.1 Peak velocities at the FM

For the pre-surgery, post-surgery, and healthy volunteer groups, mean values of $V_{SYS}$ at the FM plane measured with 2D pcMRI were $-5.2 \pm 0.6$, $-5.5 \pm 0.5$, and $-3.3 \pm 0.2$ cm/s, respectively. Statistical analysis showed that mean $V_{SYS}$ from pcMRI was significantly higher in pre-surgery and post-surgery CMI patients compared to healthy volunteers ($p<0.01$ both), but the difference between CMI patients groups was not significant ($0.3$ cm/s mean increase, $p=0.30$). Though $V_{SYS}$ was expected to decrease in magnitude post-surgery for each case, the observed results were mixed with eight cases showing decreases, six cases showing increases, and two cases showing approximately no change (Figure 6.3.1).
For the pre-surgery, post-surgery, and healthy volunteer groups, mean values of $V_{SYS}$ at the FM plane computed from CFD were $-5.3 \pm 0.9$, $-4.0 \pm 0.8$, and $-1.6 \pm 0.2$ cm/s, respectively. Statistical analysis showed that mean $V_{SYS}$ from CFD was significantly higher in pre-surgery and post-surgery CMI patients compared to healthy volunteers ($p<0.01$ both), but the difference between CMI patients groups was not significant (1.2 cm/s mean decrease, $p=0.30$). The observed changes were mixed with seven cases showing decreases, three cases showing increases, and six cases showing only very small changes (Figure 6.3.2). Thus, the small mean velocity decrease may have been an incidental finding.
Figure 6.3.2: Distributions of $V_{SYS}$ from CFD at the FM plane for each subject group (left) and changes in $V_{SYS}$ between pre-surgery and post-surgery measurements (right).
Comparison of $V_{SYS}$ measured from pcMRI and CFD generally showed poor agreement. At the FM level, there was no linear agreement between $V_{SYS}$ from pcMRI and CFD (Figure 6.3.3). $V_{SYS}$ from CFD misestimated the corresponding pcMRI measurement by anywhere from 83% underestimation to 364% overestimation.

Figure 6.3.3: Relationship between $V_{SYS}$ from pcMRI and CFD at the FM level of the SSS.
For the pre-surgery, post-surgery, and healthy volunteer groups, mean values of $V_{\text{DIA}}$ at the FM plane measured with 2D pcMRI were 4.3 ± 0.3, 3.9 ± 0.3, and 3.0 ± 0.2 cm/s, respectively. Statistical analysis showed that mean $V_{\text{DIA}}$ from pcMRI was significantly higher in pre-surgery and post-surgery CMI patients compared to healthy volunteers (p<0.01 both), but the difference between CMI patients groups was not significant (0.4 cm/s mean increase, p=0.11) However, individual observed changes were mixed with five cases showing decreases, six cases showing increases, and five cases only very small changes (Figure 6.3.4). Thus, the mean velocity increase may have been an incidental finding.

Figure 6.3.4: Distributions of $V_{\text{DIA}}$ from 2D pcMRI at the FM plane for each subject group (left) and changes in $V_{\text{SYS}}$ between pre-surgery and post-surgery measurements (right).
For the pre-surgery, post-surgery, and healthy volunteer groups, mean values of $V_{DIA}$ at the FM plane computed from CFD were $3.6 \pm 0.5$, $2.4 \pm 0.4$, and $3.0 \pm 0.2$ cm/s, respectively. Statistical analysis showed that mean $V_{DIA}$ from CFD was significantly lower post-surgery compared to pre-surgery ($p < 0.01$), but $V_{DIA}$ in both patient groups was significantly higher than in healthy volunteers ($p<0.01$, both). Though $V_{DIA}$ in CMI patients showed a mean decrease of $1.2$ cm/s, the individual observed differences in $V_{DIA}$ showed a wide range of values, with two cases showing a small increase in $V_{DIA}$ and three cases showing approximately no change (Figure 6.3.5).

Figure 6.3.5: Distributions of $V_{DIA}$ from CFD at the FM plane for each subject group (left) and changes in $V_{SYS}$ between pre-surgery and post-surgery measurements (right).
Similar to $V_{SYS}$, comparison of $V_{DIA}$ measurements from pcMRI and CFD showed poor agreement between the two methods despite a more linear relationship (Figure 6.3.6). $V_{DIA}$ derived from CFD underestimated the corresponding pcMRI measurement by an average of approximately 51%.

Figure 6.3.6: Relationship between $V_{DIA}$ from pcMRI and CFD at the FM level of the SSS.
6.3.2 *Peak velocities at C2*

For the pre-surgery, post-surgery, and healthy volunteer groups, mean values of $V_{\text{SYS}}$ at the C2 plane measured with 2D pcMRI were $-3.9 \pm 0.2$, $-4.2 \pm 0.4$, and $-4.5 \pm 0.3$ cm/s, respectively. Statistical analysis showed that mean $V_{\text{SYS}}$ from pcMRI was not significantly different in any of the three groups. Though $V_{\text{SYS}}$ was expected to decrease in magnitude post-surgery for each case, the observed results were mixed with eight cases showing decreases, six cases showing increases, and two cases showing approximately no change (Figure 6.3.7).

![Graph showing distributions of $V_{\text{SYS}}$ and changes in $V_{\text{SYS}}$ between pre-surgery and post-surgery measurements.](image)

**Figure 6.3.7:** Distributions of $V_{\text{SYS}}$ from 2D pcMRI at the C2 plane for each subject group (left) and changes in $V_{\text{SYS}}$ between pre-surgery and post-surgery measurements (right).
For the pre-surgery, post-surgery, and healthy volunteer groups, mean values of $V_{SYS}$ at the C2 plane measured with CFD were $-2.4 \pm 0.2$, $-2.7 \pm 0.2$, and $-3.2 \pm 0.3$ cm/s, respectively. Statistical analysis showed that mean $V_{SYS}$ from CFD was also not significantly different in any of the three groups. Though $V_{SYS}$ was expected to decrease in magnitude post-surgery for each case, most cases showed only a small change (Figure 6.3.8) despite an overall mean increase of 0.3 cm/s.

Figure 6.3.8: Distributions of $V_{SYS}$ from 2D CFD at the C2 plane for each subject group (left) and changes in $V_{SYS}$ between pre-surgery and post-surgery measurements (right).
At the C2 level, there was also poor agreement between $V_{sys}$ from pcMRI and CFD (Figure 6.3.9), though the agreement was slightly better than at the FM level. On average, $V_{sys}$ from CFD underestimated the corresponding pcMRI velocity measurement by 33%.

Figure 6.3.9: Relationship between $V_{sys}$ from pcMRI and CFD at the C2 level of the SSS.
For the pre-surgery, post-surgery, and healthy volunteer groups, mean values of $V_{DIA}$ at the C2 plane measured pcMRI were $3.4 \pm 0.2$, $3.7 \pm 0.4$, and $4.0 \pm 0.4$ cm/s, respectively. Statistical analysis showed that mean $V_{DIA}$ from pcMRI was not significantly different in any of the three groups. Though $V_{SYS}$ was expected to decrease in magnitude post-surgery for each case, most cases showed only a small change (Figure 6.3.8) despite an overall mean increase of 0.3 cm/s.

Figure 6.3.10: Distributions of $V_{DIA}$ from 2D pcMRI at the C2 plane for each subject group (left) and changes in $V_{DIA}$ between pre-surgery and post-surgery measurements (right).
For the pre-surgery, post-surgery, and healthy volunteer groups, mean values of $V_{DIA}$ at the C2 plane measured with CFD were 1.6 ± 0.1, 1.8 ± 0.2, and 2.0 ± 0.2 cm/s, respectively. Statistical analysis showed that mean $V_{DIA}$ from CFD was also not significantly different in any of the three groups. Though $V_{SYS}$ was expected to decrease in magnitude post-surgery for each case, most cases showed only a small change (Figure 6.3.11) and the mean post-surgery increase in $V_{DIA}$ was only 0.1 cm/s.

![Graph](image)

Figure 6.3.11: Distributions of $V_{DIA}$ from 2D CFD at the C2 plane for each subject group (left) and changes in $V_{DIA}$ between pre-surgery and post-surgery measurements (right).
Comparison of $V_{DIA}$ measurements from pcMRI and CFD also showed poor agreement between the two methods despite a more linear relationship (Figure 6.3.12). $V_{DIA}$ derived from CFD underestimated the corresponding pcMRI measurement by an average of approximately 51%.

Figure 6.3.12: Relationship between $V_{DIA}$ in pcMRI and in CFD at the C2 level of the SSS.
6.3.4 *Quantitative and qualitative comparison of C2 velocity fields.*

Similar to peak velocity comparisons, the comparison between mean $V_{SYS}$ obtained from pcMRI and CFD showed poor agreement (Figure 6.3.13). On average, mean $V_{SYS}$ derived from CFD underestimated the corresponding pcMRI measurement by approximately 20%.

![Relationship between mean $V_{SYS}$ in pcMRI and in CFD at the C2 level of the SSS.](image)

Figure 6.3.13: Relationship between mean $V_{SYS}$ in pcMRI and in CFD at the C2 level of the SSS.
Likewise, the comparison between mean $V_{\text{DIA}}$ obtained from pcMRI and CFD showed poor agreement (Figure 6.3.14). On average mean $V_{\text{DIA}}$ derived from CFD underestimated the corresponding pcMRI measurement by approximately 52%.

Figure 6.3.14: Relationship between mean $V_{\text{DIA}}$ in pcMRI and in CFD at the C2 level of the SSS.
However, the comparison of volume flow rate at peak systole ($Q_{SYS}$) at C2 obtained from pcMRI and calculated from CFD was nearly perfect (Figure 6.3.15). A similarly strong agreement was observed for volume flow rate at peak diastole ($Q_{DIA}$) at C2 (Figure 6.3.16). It should be noted that while translation of peak flow rates should theoretically be perfect (conservation of mass), there were some small discrepancies between the flow rates in 2D pcMRI and CFD resulting from interpolation when up-sampling the volume flow waveform.

![Graph showing the relationship between $Q_{SYS}$ in pcMRI and CFD at the C2 level of the SSS.](image)

Figure 6.3.15: Relationship between mean $Q_{SYS}$ in pcMRI and in CFD at the C2 level of the SSS.
Thus, the most likely reason for the disagreement between mean velocities from CFD data and pcMRI measurements was disagreement in cross-sectional area of the SSS between the two different methods. Some cases (Figure 6.3.17) compared relatively well between pcMRI and CFD in terms of both mean velocities, velocity distribution throughout the SSS, and the SSS shape in both pre-surgery and post-surgery cases for the respective measurement methods. This suggested two ends. The first was that pcMRI velocity measurements at the C2 level may have good repeatability if the peak flow rates are similar. Likewise a repeated measurement on the same subject should yield the same SSS shape. Thus, if signal quality is similar in both scans, the C2 level would be a reliable location to obtain CSF velocity data.

The second was that, despite the anatomy of the craniovertebral junction being augmented by CMI decompression surgery, the impact of the surgery on the CSF velocity
field may not extend all the way to C2. Thus, if a future study were interested in identifying changes to the CSF velocity field created by CMI decompression surgery, the investigation likely need not extend lower than the C2-C3 intervertebral disc.

Figure 6.3.17: Comparison of C2 velocity fields from a CMI patient case (p04) pre-surgery (top) and post-surgery (bottom) at peak systole (left) and peak diastole (right) from pcMR and CFD showing good agreement.
Other cases (Figure 6.3.18) compare well in terms of velocity distribution, but with the exception of a truncated annulus in the pcMR images due to low signal or noise in the posterior SSS, which caused disagreement between SSS area in the two methods. This truncation was not surprising considering the pinched gap between the spinal cord and dura in the posterior SSS, which was visible in the CFD velocity profile. Likewise, considering the difference in pixel resolution between the pcMRI and anatomy MRI scans (0.781-1.25 mm for pcMRI vs. 0.469-0.875 mm for anatomy MRI), it was not surprising that the gap in the posterior SSS was visible in the anatomy images, which had finer spatial resolution, but only appeared as a low/no signal region in the pcMR images. This suggested the occurrence of a phenomenon known as voxel averaging. In voxel averaging, the SSS gap distance would be below the in-plane resolution of the MR scanner and the signal from moving fluid may have been averaged together with that from static tissue, giving the appearance of low/no flow.
Figure 6.3.18: Comparison of C2 velocity fields from a CMI patient case (p03) pre-surgery (top) and post-surgery (bottom) at peak systole (left) and peak diastole (right) showing good anterior agreement and poor posterior agreement between pcMR and CFD.
The poorest comparisons between CFD and pcMRI resulted from a significantly truncated annulus (Figure 6.3.19). In cases of a significantly truncated annulus, the posterior gap in the SSS was clearly pinched in the CFD velocity profile. However, the region appeared to be low/no flow in the profile from pcMR imaging. Hence, with flow concentrated in the spatially smaller anterior SSS in the pcMR profile but not in the CFD profile, there was a large disagreement in cross-sectional area and velocity distributions between the two methods and approximately a two-fold difference in the magnitude of peak velocities. However, there was relatively good agreement in velocity distributions and peak magnitudes between the pre-surgery and post-surgery profiles of each method. This reinforced the observation that pre-surgery and post-surgery velocity distributions at the C2 level should be comparable for each method if the peak flow rates are similar.
Figure 6.3.19: Comparison of C2 velocity fields from a CMI patient case (p01) pre-surgery (top) and post-surgery (bottom) at peak systole (left) and peak diastole (right) showing poor agreement between pcMRI and CFD.
Similar to the results in CMI patients, comparison of velocity fields from pcMRI and CFD at the C2 level of the spine in healthy volunteers yielded mixed results. Again, flow and peak velocities in pcMR images were concentrated in the anterior and lateral SSS. In contrast, velocities in the corresponding CFD models were uniformly distributed, with peak velocities skewed toward pinched spaces between spinal cord and dura. Cases where the full annulus of the SSS was visible in pcMR images compared relatively well with the corresponding CFD model (Figure 6.3.20). However, most cases were again truncated, with a low/no flow region in the posterior SSS (Figure 6.3.21) and, in some cases, flow void in the lateral SSS due to the influence of small structures, such as nerve roots (Figure 6.3.22).

Figure 6.3.20: Comparison of C2 velocity fields from a healthy volunteer case (v03) at peak systole (left) and peak diastole (right) from pcMRI and CFD showing good agreement.
Figure 6.3.21: Comparison of C2 velocity fields from a healthy volunteer case (v04) at peak systole (left) and peak diastole (right) from pcMRI and CFD showing fair agreement in the anterior SSS and a truncated posterior.

Figure 6.3.22: Comparison of C2 velocity fields from a healthy volunteer case (v12) at peak systole (left) and peak diastole (right) from pcMRI and CFD showing cross-sectional area disagreement caused by a good agreement.
6.4 Discussion

This study presented analysis of CSF velocities at the FM and C2 planes using both 2D pcMRI and CFD to quantify differences between CMI-affected spinal canals before and after decompression surgery and to assess differences between the two methods. Velocities from 2D pcMRI were obtained by direct measurement from each subject. Subject-specific CFD modeling was used to simulate CSF motion in the SSS and velocity data was obtained from planes at the FM and C2 levels that were approximately collocated with the respective 2D pcMR imaging planes.

Results showed that, for both 2D pcMRI and CFD, $V_{SYS}$ magnitude at the FM level was significantly higher in CMI patients than in volunteers, but was not significantly different between pre-surgery and post-surgery CMI patients. Similarly, $V_{DIA}$ magnitude at the FM level was significantly higher in CMI patients than in volunteers. However, $V_{DIA}$ magnitude decreased significantly post-surgery in both 2D pcMRI and CFD. No significant differences were found between any of the three groups at the C2 level for either 2D pcMRI or CFD.

Comparison of peak velocity magnitudes measured from pcMRI to those computed from subject-specific CFD showed significant disagreement at both the FM and C2 levels. Assuming that the 2D pcMRI measurement was the more accurate, CFD badly mis-estimated peak velocities at the FM plane (range 83% underestimation to 364% overestimation). Agreement between pcMRI and CFD at the C2 level was slightly better than at the FM, underestimating $V_{SYS}$ and $V_{DIA}$ by an average of 33% and 51%, respectively.
Disagreement between 2D pcMRI and subject-specific CFD may have been the result of several issues. The most obvious issue was the over-estimation of the SSS cross-sectional area in the CFD models, which was demonstrated by comparing mean $V_{SYS}$ and mean $V_{DIA}$ to $Q_{SYS}$ and $Q_{DIA}$. Whereas the relationship between volume flow rates from 2D pcMRI and CFD was linear at each peak, the relationship between mean velocities was comparably poor to the relationship between peak velocities. The 3D anatomy models used for computational simulation were obtained using a different MRI sequence with different spatial resolution than the pcMRI measurements. Thus, it is possible that cross-sectional geometry in the CFD anatomy models was larger than the actual in vivo area. This would result in lower peak and mean velocities for an incompressible fluid flowing in a rigid conduit. However, it was estimated that CFD-derived velocities underestimated pcMRI velocities by as much as 2x in some case. This would imply that the cross-sectional area in the model was double that of the in vivo anatomy, which was unlikely.

Similar to area over-estimation, underestimation of the volume flow waveform used for the inlet boundary condition of the CFD models would also result lower peak velocities in the CFD models. The inlet boundary condition for each model was specified as a blunt, transient velocity based on average velocity at the C2 level of the SSS. Due to poor signal in the posterior SSS, which was shown in several examples, some volume flow may not have been included in constructing the waveform. Additionally, because an average velocity was used as the boundary condition, higher peak velocities may have been smoothed out. However, velocity patterns in some cases were qualitatively similar.
between pcMRI and CFD, which suggests that using average velocity as an inlet boundary condition was a reasonable approach.

The SSS was modeled as an open conduit, yielding smooth velocity profiles and high velocity regions due mainly to pinched gaps between the spinal cord and dura. In contrast, pcMRI data showed higher velocities in the open anterior SSS and a more inhomogeneous velocity distribution. This disagreement in distribution may be due to the fact that arachnoidal trabeculae and other small structures in the SSS actually create a flow field that would be better represented by a porous media model. A past study using a single SSS model showed that considering the SSS as a porous medium had an impact on CSF pressure gradients, which could impact CSF velocities in turn [88]. Inhomogeneous distribution of the arachnoidal trabeculae could then explain inhomogeneities in the velocity field. Likewise, animal models have shown that arachnoidal trabeculae may be more densely packed in the posterior SSS [135], which, in addition to voxel averaging, could explain the low/no flow region seen in the posterior SSS.

Though there were inherent limitations on how accurately the CFD model could replicate the in vivo SSS, some of the disagreement between methods could also be attributed to limitations in the pcMRI sequence. For example, the imaging sequence requires a maximum measurable encoding velocity to be set a priori. In this study, 2D pcMR images were acquired using an encoding velocity of 10 cm/s. Thus, in vivo velocities significantly lower than this (e.g. less than 1 cm/s) may either not have been detectable or appeared as noise.
6.5 Conclusion

In summary, analysis of peak velocities was useful for showing that systolic CSF velocities are elevated at the FM compared to healthy volunteers. However, systolic velocities at the FM were not found to decrease significantly post-surgery in CMI patients. In contrast, peak diastolic velocities did decrease significantly post-surgery. Both peak and mean velocities compared poorly between CFD and 2D pcMRI. CFD showed a trend of smaller peak velocities compared 2D pcMRI at both the FM and C2 levels of the spinal canal. Examples comparing CFD velocity profiles lacked the anterior flow dominance and heterogeneous velocity distributions typically seen in 2D pcMRI measurements. Thus, while the velocity data presented here was useful for analyzing difference between velocities in CMI-affected spinal canals and healthy spinal canals, CFD velocity fields could not be validated using 2D pcMRI. However, as mentioned at the beginning of the Chapter, this study was only meant to be a supplement to the study described in Chapter V. Accurate representation of the velocity fields was not the primary goal of using this particular CFD methodology.

6.6 Acknowledgements

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CHAPTER VII

CONCLUSIONS

7.1 Summary of main findings

The research studies that have contributed to the present body of work have helped to understand how CSF dynamics near the craniovertebral junction are affected by CMI and how they change with decompression surgery using subject-specific CFD modeling. To the author’s knowledge, this collection is the first of such to conduct subject-specific modeling of CSF dynamics in CMI patients using large subject sample sizes.

In Chapter IV, subject-specific CFD modeling was used to compare the biomechanical environment in the SSS of symptomatic and asymptomatic CMI patients and healthy volunteers. Subject-specific CFD models were used to assess severity of the partial blockage to CSF motion in terms of the longitudinal impedance pulsatile CSF motion and to compare those values with the commonly used clinical morphometric parameter, CTD. Results showed that mean LI was significantly higher in CMI patients compared to controls, which corresponded with CTD being significantly larger for CMI patients. CMI patients stratified from healthy volunteers by both parameters, however the relationship between LI and CTD was only weakly linear. This suggested that LI captured a different aspect of the CMI pathoanatomy than did CTD. An important side
finding of this study was that LI could be reliably computed in models of the SSS using a non-specific CSF flow waveform.

Chapter V expanded on the result of Chapter IV by analyzing longitudinal impedance to CSF motion in the SSS near the CVJ to quantify differences between CMI-affected spinal canals before and after decompression surgery. Subject-specific CFD modeling was again used to simulate CSF motion around the partial blockage caused by CTD. LI was compared against CTD, the commonly used clinical morphometric, more conventional geometric parameters, $A_{CS}$ and $D_H$, and more commonly reported pressure parameters, gradients at peak systole, peak diastole, and peak-to-peak pressure gradient. The distance used to compute pressure gradients was parametrically varied to show that the largest differences between pre-surgery and post-surgery CMI patients were found when the caudal reference plane was positioned 15-25 mm perpendicularly caudal to the FM, where there was a sustained area expansion past the tip of the cerebellar tonsils for all cases.

LI in CMI patients was found to be significantly lower post-surgery compared to pre-surgery. However, LI in post-surgery CMI patients was still significantly higher than in healthy volunteers. Though CTD also decreased post-surgery, the relationship between change in CTD and change in LI did not follow a discernable pattern. Decreases in LI were found to correspond with small increases in mean $A_{CS}$ and mean $D_H$ in the SSS, which suggested that the pressure environment in the SSS was highly sensitive to small mean changes in cross-sectional geometry.

Chapter VI showed that peak velocities at the FM were significantly higher in CMI patients than healthy volunteers, but only showed significant post-surgery decrease
at peak diastole. In general, CSF velocity magnitudes compared poorly between CFD and 2D pcMRI. CFD was found to underestimate peak velocities at both the FM and C2 levels of the spinal canal compared 2D pcMRI. Qualitative analysis of through-plane CFD velocity profiles showed that CFD models lacked the anterior flow dominance and heterogeneous velocity distributions typically seen in 2D pcMRI measurements.

7.2 Future research directions

Subject-specific modeling of CSF dynamics in patients with poorly understood craniospinal disorders such as CMI offers potential for better understanding of the pathophysiology of the disorder using non-invasive analysis methods. However, a number of potentially critical assumptions were used in order to make the present studies workable with a large number of models to be analyzed. For instance, fine structures in the SSS anatomy, such as nerve roots and small blood vessels were necessarily not included in the 3D anatomy models due to MRI spatial resolution limits. However, it was observed from 2D pcMRI that the presence of nerve roots in the SSS may create low/no flow regions. In a recent study, fine structures were successfully incorporated into a model of the SSS [97] and were found to have an impact on local CSF velocity fields. However, that study found that pressure gradients were only slightly altered. Likewise, velocity parameters near the FM were also not greatly affected due to lack of fine structures in that region. Thus, if the primary objective of a subject-specific CFD model study was to assess the impact of CMI on the biomechanical environment local to the CVJ, incorporation of fine structures into model geometry may not be important. However, if the goal of the study was to validate the numerical method used to simulate
CSF flow against physical measurements, incorporation of fine structures could be critically important.

Another potentially critical assumption that should be addressed in future work was modeling the SSS as an open conduit and not as a porous medium, which may more accurately represent the presence of arachnoidal trabeculae. Inclusion of a porous media model has been accomplished in the past and shown to have an impact on the pressure gradient in the cranial subarachnoid space [136]. Considering the sensitivity of LI to small changes in cross-sectional anatomy of the SSS shown in Chapter V of this collection of work, another factor that augments pressure in the subarachnoid space could be important to consider.

Finally, it may be important to account for motion of the cerebellar tonsils and spinal cord in future subject-specific modeling studies. The spinal cord and cerebellar tonsils are known to move a small but detectable amount through the CSF pulse cycle [27, 30, 137]. It has been shown in one fluid-structure interaction study that spinal cord motion had a negligible impact on pressure in the SSS [96]. However, that study was conducted for a healthy subject and the impact of cord motion could be different in the more constricted spaces of the CMI-affected CVJ.

In summary, any additional model complexity that could more accurately represent pressure dynamics near the CVJ would likely be a good addition to future subject-specific modeling work. However, model complexity must also be considered in the context of potential for clinical translatability of the modeling method. In fact, more complex models could lead to poorer clinical translatability. A simplified approach, such
as using directly measurable CSF velocities to estimate impedance, could hypothetically be just as valuable as a fully-detailed computational model.

The simplified models used in the present collection of work were able to establish longitudinal impedance as a subject-specific model-derived parameter which showed quantifiable differences between CMI patients before and after decompression surgery and represent a first step toward the use of subject-specific modeling as a tool to quantify the impact of CMI decompression surgery.
REFERENCES


APPENDIX A
SUMMARY OF INDEPENDENCE STUDIES

To ensure that CFD solutions were independent of mesh resolution, time step resolution, and waveform period, flow was simulated in an SSS model from a randomly selected CMI patient (Figure A.1.1). The details that follow are the results of independence testing.

Figure A.1.1: SSS geometry model (CMI patient) used for independence studies.
A.1 Independence using transient pressure gradient profiles

Because the LI calculation was a key element of this study, it was necessary to understand whether grid resolution, time step resolution, or number of periods simulated would have an impact on the transient pressure gradient waveform input to the calculation. For the test geometry model, two mesh densities (base, refined) and three time steps (T/100, T/200, T/400) were tested for three periods of the inlet boundary condition waveform. Differences between each combination of inputs were assessed by computing the root-mean-square (RMS) error between waveforms. The results of these tests are described in Chapter VI.

Figure A.1.2: SSS geometry model (left) used for independence studies and example of resulting transient pressure gradient profile obtained from the indicated planes (right).
Figure A.1.3: $\Delta P$ waveforms for the first, second, and third cycles of the simulation using the base mesh and time step $T/200$.

Figure A.1.4: $\Delta P$ waveforms from the second period for simulations using the base mesh and time steps of $T/100$, $T/200$, and $T/400$. 
Figure A.1.5: $\Delta P$ waveforms from the second period for simulations using time step $T/200$ for the base and refined meshes.
A.2 Mesh independence using in-plane pressure profiles

Because the RMS error between waveforms obtained from the base and refined meshes for time step T/200 was sufficiently small to achieve mesh independence without having to introduce a third mesh resolution, normalized in-plane pressure profiles from the FM, C1, C2, and C3 levels were also examined (Figure A.1.6). The goal of introducing this extra test was to assure that the independence obtained from the waveform test was not the result of waveform RMS error being insensitive to mesh resolution. This methodology is similar to that used in previous studies [88, 138].

Results show that the profiles for normalized pressure in all four planes at both peak systolic pressure (Figure A.1.7) and peak diastolic pressure (Figure A.1.8) are indistinguishable. Therefore, it was concluded that the flow field was sufficiently resolved by the base mesh.
Figure A.1.6: Isometric view of the test geometry showing the locations of the line surfaces used to obtain in-plane pressure profiles at the FM, C1, C2, and C3.

Figure A.1.7: Normalized pressure profiles at peak systolic pressure from the FM, C1, C2, and C3 levels of the SSS model.
Figure A.1.8: Normalized pressure profiles at peak diastolic pressure from the FM, C1, C2, and C3 levels of the SSS model.
APPENDIX B
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Shaffer, N, Martin, BA, Dombrowski, S, Luciano, M, Tew, J, and Loth, F. “Investigation of Post-Surgical Changes to Cerebrospinal Fluid Flow Impedance in Type I Chiari Malformation” *Proceedings of the World Congress of Biomechanics* (Boston, MA, 7/6-11, 2014)


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