Cerebrospinal fluid hydrodynamics in type I Chari malformation

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Purpose: The objective of this study was to review past studies that have used engineering analysis to examine cerebrospinal fluid hydrodynamics in cranial and spinal subarachnoid spaces in both healthy humans and those affected by type I Chiari malformation.
Methods: A PubMed search of literature pertaining to cerebrospinal fluid hydrodynamics was performed with a particular focus on those that utilized methods such as computational fluid dynamics or experimental flow modeling.
Discussion: From the engineer's perspective, type I Chiari malformation is an abnormal geometry of the cerebellum that causes increased resistance to cerebrospinal fluid flow between the intracranial and spinal subarachnoid space. As such, understanding the hydrodynamics of cerebrospinal fluid in the craniospinal subarachnoid space has long been thought to be important in the diagnosis and management of type I Chiari malformation. Hydrodynamic quantification of cerebrospinal fluid motion in the subarachnoid space may better reflect the pathophysiology of the disorder and serve as a prognostic indicator in conjunction with geometric magnetic resonance measurements that are currently used clinically. This review discusses the results of studies that have sought to quantify the hydrodynamics of cerebrospinal fluid motion using computational and experimental modeling and critiques the methods by which the results were obtained.
Conclusion: Researchers have found differences in cerebrospinal fluid velocities and pressures in type I Chiari malformation patients compared to healthy subjects. However, further research is necessary to determine the causal relationship between changes to hydrodynamic parameters such as cerebrospinal fluid velocity, pressure, resistance to flow, and craniospinal compliance and clinical aspects such as neurological symptoms, radiological evidence of severity, and surgical success.

Keywords: Type I Chiari malformation, Cerebrospinal fluid, Hydrodynamics

Introduction

Type I Chiari malformation has historically been described as a change in the morphology of the hindbrain, characterized by herniation of the cerebellar tonsils past the foramen magnum by 3–5 mm, as diagnosed by magnetic resonance imaging[1–3] (Fig. 1). The herniation results in reduced cross-sectional area of the subarachnoid space at the foramen magnum.[2] Thus, at first glance the problem appears to be geometric in nature. However, the problem may be more complex and the herniation may trigger a pathophysiological cascade making cause and effect difficult to decipher. It remains unclear whether the changes in morphology associated with type I Chiari malformation are a consistent result of non-genetic, genetic, and/or epigenetic factors.[1,4,5] The present understanding of the pathophysiological cascade in type I Chiari malformation follows the following logic:

1. morphological changes to the cerebellum crowd the subarachnoid space near the foramen magnum;[6–9]
2. crowding of the local subarachnoid space results in obstruction of cerebrospinal fluid flow pulsations at the foramen magnum;
3. the obstruction of flow pulsations results in abnormal cerebrospinal fluid velocities[10,11] and potentially increased resistance;
4. increased resistance could reduce cerebrospinal fluid flow between the cranial and spinal subarachnoid spaces with each cardiac pulsation. However, the driving pressure (arterial pressure) is much larger than intracranial pressure and, thus, can force the same volume of cerebrospinal fluid out of the cranium even with an obstruction;
5. an increased pressure gradient is required to push the same volume of cerebrospinal fluid from the cranial to the spinal subarachnoid space with the presence of an obstruction;
6. the increased pressure gradient may consequently displace brain tissue, resulting in further alteration to the morphology of the cerebellum, and produce

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DOI 10.1179/016164111X12962202723805

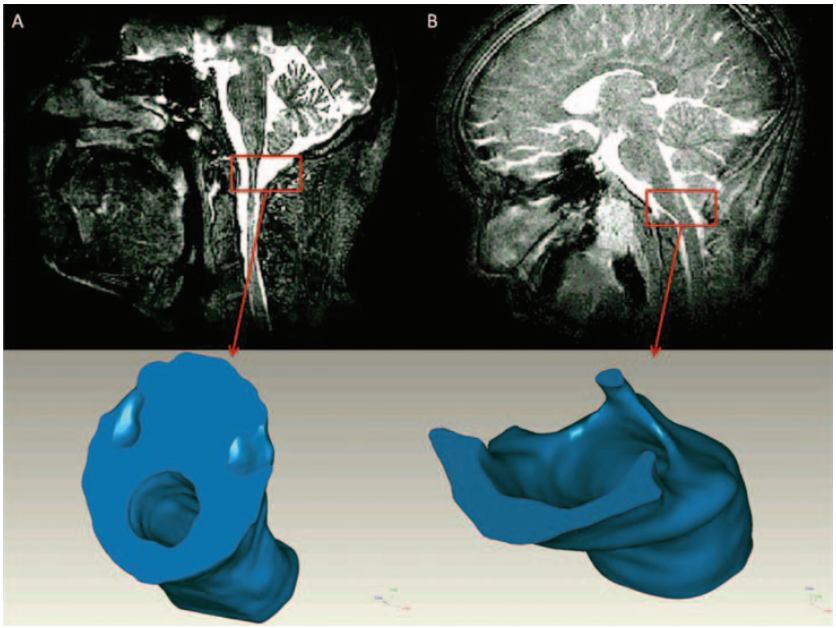

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Figure 1 T2-weighted sagittal magnetic resonance images of the head and cervical spine (above) and three-dimensional reconstruction of the cervical spinal subarachnoid space near the foramen magnum (below). (A) Healthy subject; (B) patient with symptomatic type I Chiari malformation.

abnormal biomechanical forces acting on the neural tissue and vasculature.[12,13]

The abnormal pressures acting on the neural tissue may be at the root of the neurological symptoms associated with type I Chiari malformation.[14] Changes in pressure may also alter the elasticity, permeability, and water content of the neural tissue over time. All these factors in combination produce a flow problem that is more complex than a change in geometry alone. Because some of the etiological factors appear to be hydrodynamic in nature, engineering analysis of cerebrospinal fluid hydrodynamics may be a useful tool to improve understanding of the pathophysiology in type I Chiari malformation.

Existing diagnostic methods: static versus dynamic

While several magnetic resonance imaging 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 function and response to treatment. In particular, the widespread adoption of static anatomic magnetic resonance imaging in diagnosis has called into question the relevance of the classical definition of type I Chiari malformation. For example, Milhorat *et al.*[1] found no correlation between cerebellar herniation depth and the level of disability in patients with the type I malformation. Further studies have shown that patients can exhibit type I Chiari-like neurological symptoms with minimal herniation and be asymptomatic with large herniations.[7,15–18]

Part of the difficulty in establishing useful diagnostic criteria for symptomatic type I Chiari malformation, and perhaps why many different diagnostic methods are being explored, is that its etiology is not well understood. Cerebellar tonsil herniation may result from multiple anatomical factors including genetic disorders,[4,5] 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 type I Chiari malformation have a smaller posterior cranial fossa volume than normal subjects,[19] and thus insufficient space for a normally developed hindbrain, in addition to dimensional abnormalities in other bony landmarks. However, these dimensional abnormalities are not universally present in patients with the type I malformation.[1,9,20] Similarly, studies have demonstrated high incidence of type I Chiari malformation concomitant with lipomyelomeningocele[21] and an acquired version resulting from a fatty terminal filum.[22] However, a study[23] 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 in this context.

Perhaps the discrepancies between the classical definition of type I Chiari malformation and contradictory clinical findings can be attributed to the disorder being more dynamic than previously thought, particularly in terms of cerebrospinal fluid hydrodynamics. At present, it is unclear if the symptomatology and tissue damage resulting from the type I malformation are more the result of

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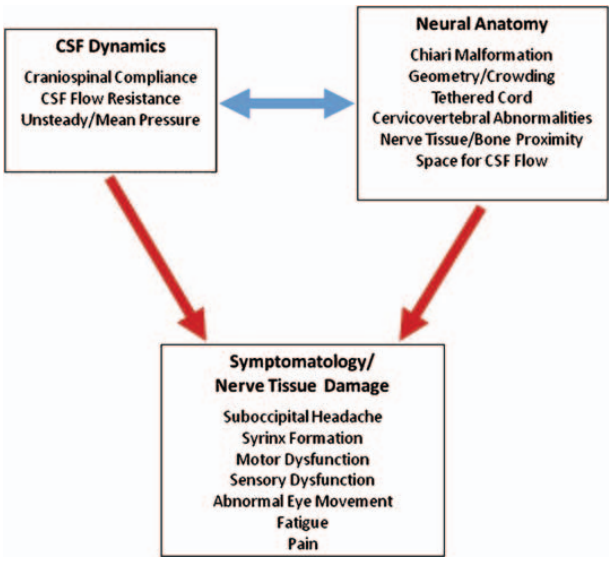

Figure 2 Type I Chiari malformation is characterized by both the altered neural anatomy and cerebrospinal fluid (CSF) dynamics. Presently, it is unclear which of these directly cause the symptoms and/or neural tissue damage that patients experience.

altered neural anatomy or of altered cerebrospinal fluid hydrodynamics (Fig. 2). 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 existing static evaluation techniques. Hydrodynamic measurements could provide doctors 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 with normalization of these parameters.

A number of different magnetic resonance-based dynamic diagnostic tools are available for evaluating type I Chiari malformation, though none of these have yet translated to standard clinical use. These tools include one-dimensional through-plane phase contrast magnetic resonance imaging for measurement of cerebrospinal fluid flow,[10,24,25] high temporal resolution in-plane cerebrospinal fluid pulse wave velocity measurement,[26] measurement of cerebellar tonsil movement,[13,27] and quantification of an index of craniospinal compliance.[28,29] Recent advancements have also opened entirely new magnetic resonance measurement modalities to quantify craniospinal disorders. These modalities include techniques to measure cerebrospinal fluid velocity in 7D,[30] magnetic resonance diffusion tensor imaging to measure neural fiber tract direction and alignment[31] and brain cerebrospinal fluid content and diffusion properties[32], magnetic resonance elastography to measure brain elasticity,[33,34] and magnetic resonance spectroscopy to measure levels of different metabolites in the brain.[35]

In vivo cerebrospinal fluid velocity measurements

Of the dynamic magnetic resonance imaging techniques mentioned above, phase-contrast imaging has been the most widely explored, as it provides *in vivo* measurement of velocity that can be valuable to understanding the flow environment. Though increasingly popular, phase-contrast imaging has yet to translate to standard clinical use due to its need for specific scanning protocols that are often only available at research hospitals. In addition, interpretation of the results is more complicated than the cerebellar tonsil herniation depth measurements obtained from static anatomic imaging. A number of groups have conducted studies to determine the utility of phase-contrast imaging-based measurements. Menick[36] reviewed many early articles describing methods for obtaining and interpreting qualitative and quantitative cerebrospinal fluid velocity and cerebellar tonsil motion data during the cardiac cycle.

More recently, Haughton *et al.*[25] compared systolic and diastolic cerebrospinal fluid velocities in type I Chiari malformation patients and volunteers using phase-contrast magnetic resonance imaging. They found pre-surgical mean peak systolic velocity in patients to be significantly higher than healthy volunteers (3.1 cm/s versus 2.4 cm/s). Inhomogeneity of flow patterns in patients compared to healthy volunteers was also noted as a significant finding and perhaps a characteristic feature of the type I malformation. Similar phenomena were observed in a study conducted by Quigley *et al.*[10] that examined spatial and temporal variation in cerebrospinal fluid velocity at the foramen magnum between healthy volunteers and type I Chiari malformation patients. In healthy volunteers, the highest velocities were found in the paramedial locations of the anterior spinal subarachnoid space. In patients, fluid jets and synchronous bidirectional flow were observed in the anterior subarachnoid space with large cephalad velocities in the anterior subarachnoid space and lower caudad velocities in adjacent regions (Fig. 3). The authors also noted that cerebrospinal fluid flow through the foramen magnum appeared plug-like in healthy volunteers, but not in patients, which reinforced the theory that inhomogeneous flow patterns are characteristic of type I Chiari malformation.

Several studies have sought to characterize type I Chiari malformation severity by examining differences in cerebrospinal fluid velocities in patients before and after decompression surgery. Dolar *et al.*[37] examined differences in systolic and diastolic velocity in patients and found that mean peak caudad velocities (3.4–2.4 cm/s) and mean peak cephalad

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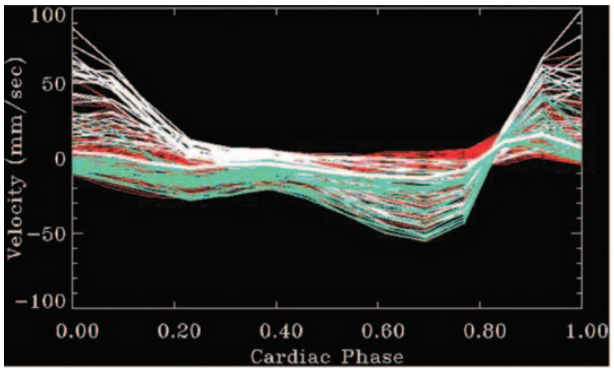

Figure 3 Velocity traces are shown for each voxel of an axial plane phase-contrast magnetic resonance image sequence taken from a patient with type I Chiari malformation over the cardiac cycle by Quigley *et al.*[10] White traces represent voxels that exhibited cephalad velocities in excess of 40 mm/s (velocity jets). Green traces represent voxels that exhibited caudad velocities during most of the cardiac cycle. Red traces represent voxels with low-magnitude (<30 mm/s) cephalad velocities. The spatial mean velocity is shown as a heavy white trace for reference. These traces demonstrate the inhomogeneous distribution of velocities that can occur in the spinal canal of a patient with type I Chiari malformation.

velocities (6.9–3.9 cm/s) decreased as a result of decompression surgery. Peak cephalad velocities varied widely pre-surgery, ranging from 2.5 to 14.6 cm/s, and to a lesser extent post-surgery, ranging from 2.1 to 5.4 cm/s. Overall these results supported the theory that the type I malformation is associated with abnormal cerebrospinal fluid velocities and that peak velocities at the foramen magnum diminish as a result of decompression surgery. However, the studies did not find correlation between change in peak cerebrospinal fluid velocities and the degree of clinical improvement.

In a retrospective study, McGirt *et al.*[38] reviewed pediatric patients undergoing pre-operative pcMRI and decompression for type I Chiari malformation. Unlike Dolar *et al.*,[37] this study's main assessment was a qualitative association of ventral/dorsal cerebrospinal fluid flow abnormalities at the foramen magnum with post-operative symptomatology. Abnormal flow was defined as absent or decreased biphasic flow. Of the patients reviewed, 36% had flow abnormalities dorsal to the cervicomedullary brainstem, 32% had ventral and dorsal flow abnormalities, and the remaining 32% had normal hindbrain flow. Thirty percent experienced some post-surgical symptom recurrence, but instances of recurrence were unrelated to cerebellar tonsil herniation severity or abnormal dorsal flow. However, combined abnormal ventral and dorsal flow was associated with a 2.6-fold reduction in risk of post-operative symptom recurrence, which supported the results obtained by Haughton *et al.*[25] and Quigley *et al.*[10] and added some specificity to what constitutes abnormal or inhomogeneous cerebrospinal fluid flow.

In a study that produced somewhat confounding results to those obtained by Dolar *et al.*[37] and McGirt *et al.*[38], Sakas *et al.*[11] compared cerebrospinal fluid velocities in type I Chiari malformation patients before and after surgery to velocities measured in healthy volunteers using the spatial modulation of magnetization imaging technique. Velocities were measured in the prepontine, anterior cervical, and posterior cervical subarachnoid space. Pre-surgical velocities in patients were 25–79% lower than velocities measured at the same location in healthy volunteers. Post-surgical measurements showed 20–100% increase in velocity over the pre-surgical values. In patients, an increase in the sum of velocities in the anterior and posterior cervical regions by more than 20% over pre-surgical values consistently preceded headache improvement.

Cerebrospinal fluid velocity wave speed in the spinal subarachnoid space of three healthy subjects was calculated to be 4.6 m/s by Kalata *et al.*[26] The study used a novel high-speed sagittal in-plane pcMRI measurement technique. As velocity wave speed is known to relate to the material properties of a flow conduit, it may provide an estimate of tissue stiffness in the craniospinal system when measured in the spinal subarachnoid space. As increased tissue stiffness is known to result from increased pressures, this technique may be useful in quantifying stiffness differences in the spinal subarachnoid space of healthy subjects and patients with type I Chiari malformation. Though only the velocity wave speed in systolic acceleration was found to correlate linearly in the study, mean velocity wave speed during acceleration compared favorably to cerebrospinal fluid pressure wave velocity in the spinal subarachnoid space obtained in several *in vitro* simulations[39,40] and estimated based on *in vivo* measurements.[41–43]

Simulations to Understand Cerebrospinal Fluid Hydrodynamics

Given the inconsistent results of magnetic resonance imaging-based studies, engineers have sought to better understand differences in the craniospinal system of patients with type I Chiari malformation by analyzing the hydrodynamics present in cerebrospinal fluid flow that are not directly measurable by imaging. The ultimate goal of these engineering studies has been to gain insight into the biomechanical nature of the disease. This may be accomplished through the use of computational and experimental tools, which seek to improve diagnostic methods and surgical planning.

Computational fluid dynamics and *in vitro* flow models allow non-invasive analysis of the hydrodynamic environment in the craniospinal system. Computational fluid dynamics simulations have been

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helpful in describing the hemodynamics of blood flow in arteries and veins[44,45] where the shear stresses created by blood flow have been shown to be important in the development of arterial diseases. Both computational and *in vitro* modeling of cerebrospinal fluid flow typically begins with a model of the geometry of interest, either idealized or reconstructed from anatomic magnetic resonance images using solid modeling software, and flow data obtained from one-dimensional phase-contrast imaging measurements. Computational fluid dynamics models approximate hydrodynamic variables, such as pressure and fluid velocity, in the flow field by utilizing the Navier–Stokes equations to numerically simulate cerebrospinal fluid flow. The computational fluid models can be coupled with computational solid models to understand the solid stresses within the neural tissue as a result of the fluid structure interaction.[39,40]

Computer-generated geometries can also be used to create anatomically realistic *in vitro* models. Measurement of velocity at discrete points within the *in vitro* models can be obtained by laser Doppler anemometry or particle image velocimetry, for optically clear models, or the models can be made magnetic resonance imaging-compatible and flow measured by imaging techniques. Pressure transducers can record pressure at discrete points, though not throughout the entire flow field. *In vitro* models have the advantage that no complex mathematical equations need to be solved to resolve features of the flow field, but modeling other system parameters can be difficult, such as matching the viscous, elastic, and porous properties of tissue.

Models of cerebrospinal fluid hydrodynamics — healthy

Characterization of cerebrospinal fluid hydrodynamics in healthy subjects provides an important basis for comparison to pathological subjects. Loth *et al.*[46] conducted computational simulations of cerebrospinal fluid motion in the spinal subarachnoid space based on an annular geometry obtained from the Visible Human Project. This simulation assumed rigid walls and solved a two-dimensional form of the Navier–Stokes equations. Inertial effects were shown to dominate the flow field under normal physiologic flow rates, particularly in the cervical and lower lumbar regions. Instantaneous Reynolds numbers at peak flow rate ranged from 150 to 450 and increased with distance from the foramen magnum. Instantaneous Womersley numbers at peak flow ranged from 5 to 17. Large Dean numbers (>40) in the cervical spine were present due to the small radius of curvature combined with a large hydraulic radius, which suggests the presence of significant secondary velocities. Velocity profiles were blunt at peak systole

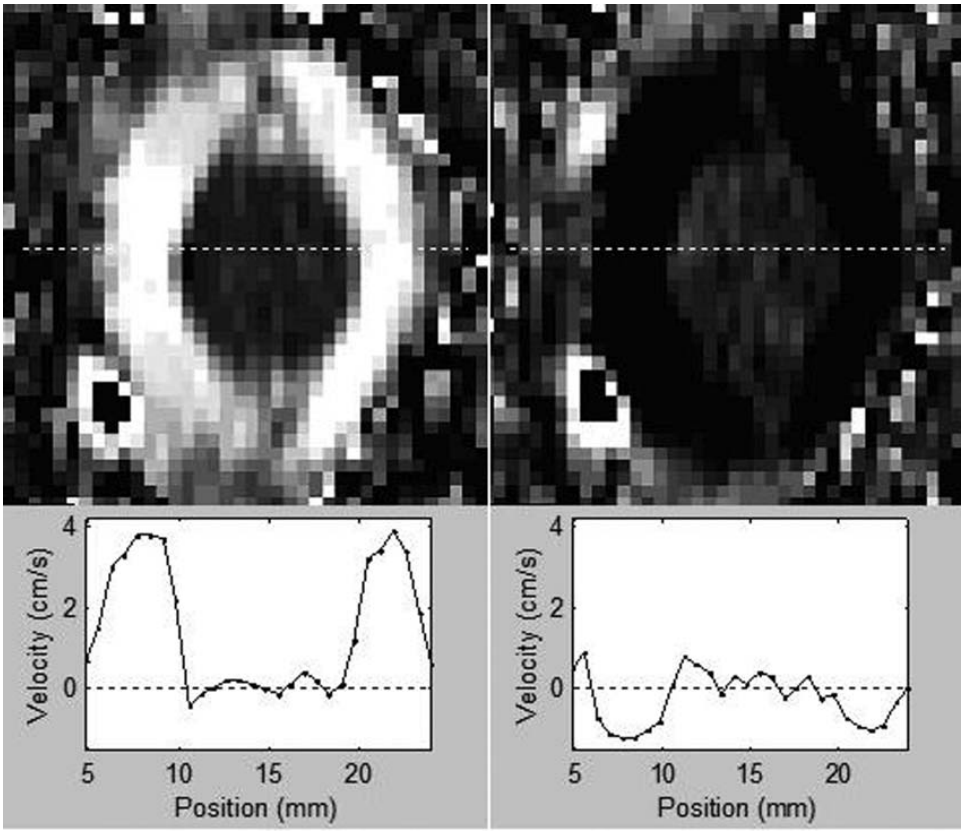

Figure 4 Phase-contrast magnetic resonance images of the pulsatile cerebrospinal fluid velocity observed during systole (left) and diastole (right) and with the corresponding velocity distribution at the location indicated by the white dotted line from Loth *et al.*[46] This demonstrates the blunt velocity profile that would typically be observed in the healthy spinal canal.

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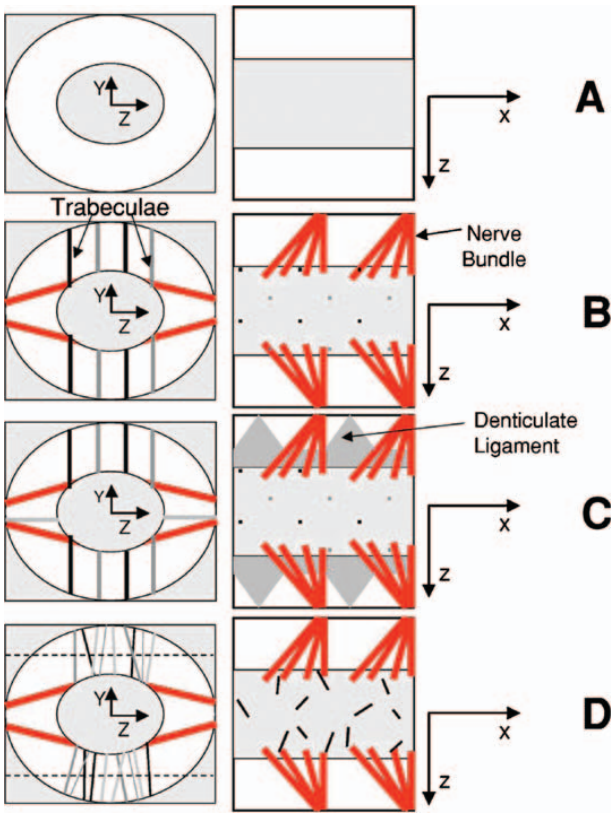

Figure 5 Geometric sketches of the idealized healthy spinal subarachnoid space geometries used for lattice-Boltzmann simulations of cerebrospinal fluid flow by Stockman.[47] Shaded areas represent solid structures. Model A is an open elliptical annular cavity, where the central ellipse represents the spinal cord. Model B adds nerve bundles on the side of the cord (thick lines) and a regularly distributed array of trabeculae on the dorsal and ventral sides of the cord (thin lines). Model C adds a denticulate ligament on the lateral sides of the cord. Model D is like B, but the trabeculae positions are randomized. Though obstructions to flow increase with each model, very little change to the flow field was observed.

and diastole as shown in Fig. 4 *in vivo* for a healthy volunteer using phase-contrast magnetic resonance imaging.

The arachnoid trabeculae, nerve roots, and perivascular vessels of the spinal cord are often neglected in simulations of cerebrospinal fluid motion due to the spatial resolution required to image the fine structures relative to the rest of the subarachnoid space and the computational complexity required to incorporate them into model geometries. Stockman[47] conducted cerebrospinal fluid flow simulations using the lattice Boltzmann method in a rigid annular model that included fine anatomical structures of the spinal subarachnoid space such as trabeculae, nerve bundles, and denticulate ligaments (Fig. 5). The study found that longitudinally averaged flow was not significantly affected by the arachnoid trabeculae when the spacing of trabeculae was regular. Variation in trabeculae width had little effect on the velocity profile for a given pressure distribution, which implied that the pressure environment in the spinal subarachnoid space was not greatly affected by fine structures. However, the arachnoidal trabeculae were found to be important in the superior cranial subarachnoid space in a subject-specific simulation by Gupta *et al.*[48] with the domain modeled as a porous medium. In this simulation, the trabecular microstructure of the superior cranial subarachnoid space was found to offer substantial resistance to cerebrospinal fluid flow. Doubling of the trabecular density from a nominal value corresponding to a subarachnoid space porosity of 0.99 increased the pressure drop across the cranial subarachnoid space by a factor of 2.5. Large spatial variations were found in the velocity distribution in the cranial subarachnoid space, which the authors proposed may influence transport behavior of metabolites, neuroendocrine, and other substances in the cranial cerebrospinal fluid circulation.

Computational fluid dynamics modeling has also been used to characterize flow fields in the ventricles of the brain and the inferior cranial subarachnoid space. A number of studies have focused on the effects of aqueduct of Sylvius stenosis. Jacobson *et al.*[49] examined the effects of both a simple and forked stenosis in an idealized model of the aqueduct. Fin and Grebe[50] constructed a deformable aqueduct of Sylvius based on *in vivo* measurements and found that aqueduct deformation had a large impact on pressure drop for a given flow. Kurtcuoglu *et al.*[51] studied cerebrospinal fluid flow in a simplified model of the brain ventricles and interconnecting pathways using computational fluid dynamics. Flow was driven by sinusoidal wall motion in the third ventricle with and without an aqueduct stenosis present. The results demonstrated complex flow and pressure patterns in the ventricles and a marked pressure increase in the third ventricle in the stenosed case. Another study by Kurtcuoglu *et al.*[52] employed a sophisticated modeling methodology to reconstruct an anatomically accurate third ventricle and aqueduct geometry and obtain subject-specific boundary conditions including caudal motion of the third ventricle wall and cerebrospinal fluid velocity in the aqueduct from magnetic resonance imaging measurements. A subsequent study by Gupta *et al.*[53] simulated subject-specific cerebrospinal fluid flow in the inferior cranial and superior spinal subarachnoid spaces. The study characterized the complex flow patterns present in those regions (Fig. 6) and found the velocity profiles entering the spinal subarachnoid space to be blunt or plug-like, which is consistent with observations made by Loth *et al.*[46] and Quigley *et al.*[10] These studies are useful to understand the boundary conditions that need to be considered at the foramen magnum when

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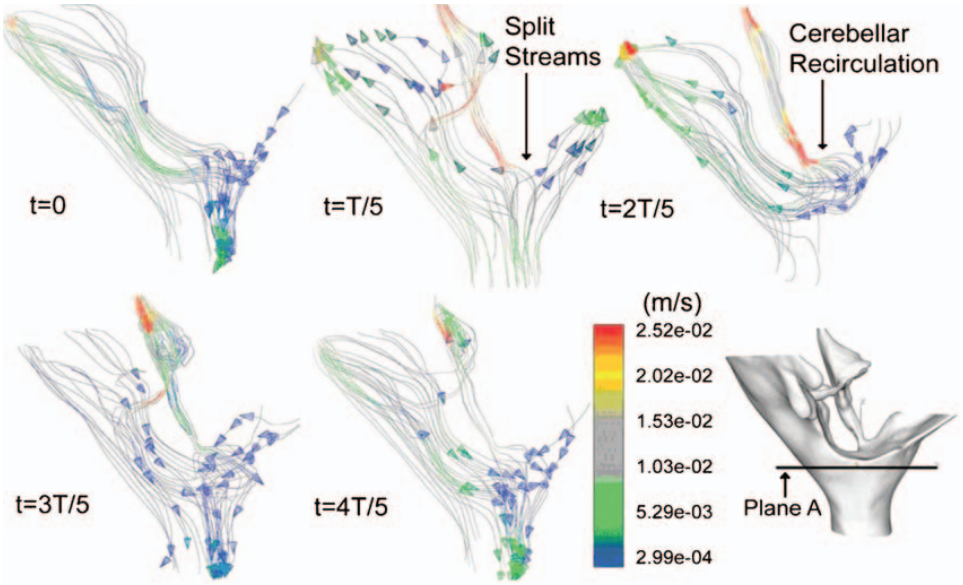

Figure 6 Stream traces colored by velocity magnitude from computational fluid dynamics model of the inferior cranial and superior spinal subarachnoid spaces of a healthy subject geometry by Gupta *et al.*[53] demonstrating the three-dimensional complexity of cerebrospinal fluid motion in that region. Tracer particles were injected at Plane A, which intersected the basal pontine and cerebellomedullary cisterns.

conducting simulations within the spinal subarachnoid space.

Models of cerebrospinal fluid hydrodynamics — type I Chiari malformation

Recently, two numerical simulations have been reported in geometries representative of a patient with type I Chiari malformation. Roldan *et al.*[54] simulated cerebrospinal fluid flow in rigid geometrically realistic spinal subarachnoid space models based on magnetic resonance images from the spinal canal of a patient and a healthy volunteer. The study employed the boundary element method, which neglects inertial effects, to solve the Navier–Stokes equations. Peak systole and peak diastole were modeled separately as steady flow. The pressure gradient between the inlet and outlet was found to be steeper in the patient model than in a healthy model of the same length. Peak pressures in the patient model were 1.5 times higher than the healthy model. Flow fields were heterogeneous with fluid jets observed anterolaterally to the spinal cord in both models. Qualitatively these results were consistent with findings from several phase-contrast imaging studies.[10,25,37] Significant velocity vector components were observed perpendicular to the long axis of the spinal canal (Fig. 7). Linge *et al.*[55] produced similar results using a geometrically idealized model of the posterior cranial fossa and cervical spine. This study examined the effect of anatomic variation on cerebrospinal fluid hydrodynamics. Though the geometry was idealized, spatial variations in flow patterns resembled those observed in *in vivo* phase-contrast imaging studies. The simulated pressure pulse (0.75 mmHg peak-to-peak amplitude) compared favorably with *in vivo* cerebrospinal fluid pulse pressure measurements in healthy subjects (1–4 mmHg[56–58]). Other observations consistent with prior studies were synchronous bidirectional flow and a longitudinal component of velocity that was larger than the lateral or anteroposterior components.

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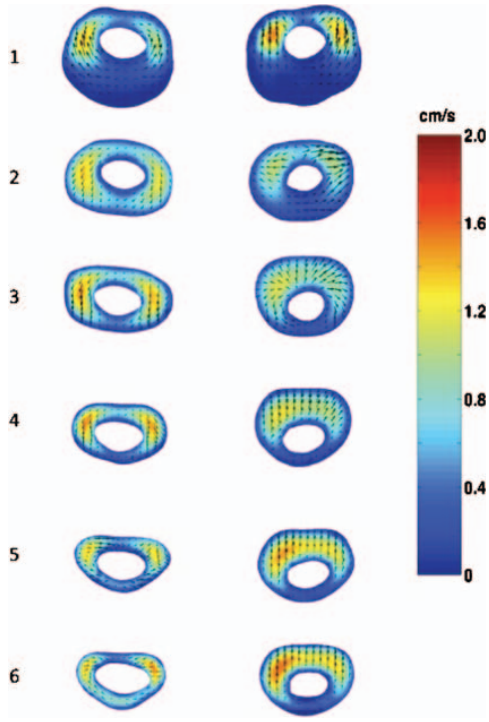

Figure 7 Cerebrospinal fluid velocity patterns obtained from a computational fluid dynamics simulation by Roldan *et al.*[54] of flow at peak systole in six different axial levels in a healthy model (left column) and a type I Chiari malformation-affected model (right column) under steady flow conditions. Colors indicate the magnitude of the axial velocity (caudad direction); arrows indicate the directions and magnitudes of secondary velocities (anterior, medial, or posterior direction).

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Models of cerebrospinal fluid hydrodynamics — syringomyelia

A craniospinal pathology often accompanying type I Chiari malformation that may also significantly impact the hydrodynamic environment of the craniospinal system is syringomyelia. Syringomyelia is characterized by a fluid filled cyst or cysts that form in the spinal cord parenchyma that can expand over time, eventually obstructing cerebrospinal fluid movement in the spinal subarachnoid space. The cyst(s), or syrinx(ges), can form caudal to a flow obstruction, such as the cerebellar tonsil herniation in type I Chiari malformation, and have direct connection to the fourth ventricle or be entirely enclosed as in non-communicating syringomyelia.

From a mechanical perspective, the reason for syrinx formation and progression is unclear because (1) the fluid inside a non-communicating syrinx can be at a considerably higher pressure than the cerebrospinal fluid in the surrounding subarachnoid space;[59–61] and (2) the cerebrospinal fluid has been shown to communicate into the syrinx cavity through the perivascular spaces.[62–64] Thus, a major research question has been how and why fluid moves into and accumulates in the syrinx cavity. A passive mechanism for fluid movement into the syrinx alone is difficult to reconcile mechanically.[59–61]

Considerable interest has been given to using *in silico* and *in vitro* simulations to study the effects of syringomyelia on cerebrospinal fluid hydrodynamics in the spinal subarachnoid space. A review of these simulations is given by Martin *et al.*[65] Bilston *et al.*[66,67] simulated cerebrospinal fluid movement in the perivascular spaces of the spinal cord given different phase delays between cerebrospinal fluid and arterial pulsations. These simulations demonstrated that, given certain phase delays between the cerebrospinal fluid and arterial pulsations, adverse pressure gradients moving perivascular fluid into the syrinx of a few kilopascals could occur.[67] Fluid-filled coaxial elastic tube models of the spinal subarachnoid space with syringomyelia and flow blockage were constructed by Carpenter *et al.*,[43] Berkouk *et al.*,[68] Bertram *et al.*,[39,40] and Cirovic.[69,70] An electrical circuit equivalence model was developed by Chang and Nakagawa.[71] Bilston *et al.*[72] formed a model of syringomyelia with spinal arachnoiditis modeled as a porous obstruction. Martin *et al.*[65,73,74] conducted *in vitro* experiments to examine the importance of spinal stenosis and presence of a non-communicating syrinx on spinal cerebrospinal fluid 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 cerebrospinal fluid flow obstruction and neural tissue. Overall, the *in silico* and *in vitro* syringomyelia experiments 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 cerebrospinal fluid flow blockage at the foramen magnum as in type I Chiari malformation.

Hydrodynamic Parameters Affected by Type I Chiari Malformation

Currently, the state of type I Chiari malformation research is developing magnetic resonance imaging protocols for direct measurement of hydrodynamic parameters by imaging methods or indirect hydrodynamic parameter calculation through computational models. The goal of examining these parameters is to provide clinically useful information to improve care and treatment for patients with type I Chiari malformation. Some challenges to clinical translation of direct or indirect hydrodynamic parameters include:

1. hydrodynamic parameters are not well-established. As with all biological data, each hydrodynamic parameter could vary significantly with age, sex, weight, and other factors. Thus, establishing indices for normal versus pathological hydrodynamic parameters is a difficult task. One possible workaround 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. This type of test would be analogous to diagnostic techniques for assessment of stroke, coronary artery disease, and hypertension by vasodilation;[75]
2. computational models require many assumptions. The assumptions will introduce error to the parameters calculated by the models. Some assumptions are close to reality, such as assuming cerebrospinal fluid behaves like water.[76] 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*;
3. magnetic resonance imaging measurements have resolution limits. It is possible that the current imaging limitations are one of the confounding factors behind seemingly contradictory cerebrospinal fluid hydrodynamic studies. In addition, the accuracy of the simulations can only be as good as the boundary conditions used. Thus, it is important to perform boundary condition sensitivity analysis on the results of computational fluid dynamics simulations before making conclusions on the hydrodynamics;
4. parameter interpretation is complex. While magnetic resonance imaging and simulations have provided many hydrodynamic parameters for assessment of type I Chiari malformation, better

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fundamental understanding of the cerebrospinal fluid system 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, but also most necessary.

At present, the hydrodynamic parameters of interest are geometry, velocity and volume flow, compliance and tissue mechanical properties, resistance, and pressure. The following discussion details each of these parameters in light of the current findings and challenges involved in their determination.

Geometry

While cerebellar tonsil herniation depth has proven to be a poor sole criterion for diagnosis of type I Chiari malformation and has not been satisfactorily correlated with the severity of neurological symptoms, it is clear that cerebrospinal fluid hydrodynamics are altered by the herniation and those geometric changes impact velocity, compliance, resistance, and pressure. However, the sequence in which these system properties become altered is unclear. For example, it is possible that the mechanical properties of neural tissue or craniospinal blood vessels become altered, which can then lead to slight brain settling and consequential cerebellar tonsil herniation. Brain settling may cause increases in fluid velocity and resistance to flow, which in turn creates a larger pressure gradient that may further alter the compliance of the craniospinal system,[14] and the cascade may continue. 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.*[23] 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 is also likely to alter compliance in the cerebrospinal fluid system, leading researchers to question if geometry or compliance is the root cause of the problem.

Obtaining an accurate representation of the cerebrospinal fluid system geometry is difficult with the pre-processing workflow required to perform computational fluid dynamics 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 order of millimeters with varying levels of repeatability and accuracy. The dimensions of the subarachnoid space in a patient with type I Chiari malformation can be small near the herniation 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 (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 (μ) and flow ($dP/dz = 128\mu Q/\pi D^4$). Gap dimensions for collagen meniscus implant (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 coil size 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 be negligible given the importance of gap size. Brain displacements as measured by phase-contrast imaging have been described to be 0.1–0.2 mm with velocities in the range of 1–2 mm/s.[13,77,78] In addition, spinal cord motion has been measured in healthy subjects and velocity values were even greater (12.4 ± 2.9 mm/s[79] and 7.0 ± 1.4 mm/s[80]). Alperin *et al.*[29] reported maximum spinal cord displacement for control volunteers and patients with type I Chiari malformation to be 0.33 and 0.39 mm, respectively.

Velocity

Abnormal velocity distributions in the axial plane have been consistently observed in type I Chiari malformation patients and are thought to be characteristic of the disorder. However, the studies had 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 cerebellar tonsil herniation. However, there may be instances where velocity appears to be uniformly low when crowding is significant. For example, in pre-surgical evaluations of patients, Dolar *et al.*[37] observed velocity jetting in the anterior cervical subarachnoid space 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.

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Additionally, the importance of high cerebrospinal fluid velocities in relation to nerve damage, which is thought to contribute significantly to the symptomatology of type I Chiari malformation, 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.*[29] 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 versus 0.56 ml patient). This implies that while increased resistance due to tonsillar herniation 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.

Phase-contrast imaging-based velocity measurements may also have significant error and could be improved in many ways. Phase-contrast image-based 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. The main sources of error are from noise, breathing artifacts, and difficulty in selection of velocity encoding value since cerebrospinal fluid velocities may vary widely. Difficult regions for fluid velocity measurement are the spinal subarachnoid space and lateral ventricles where cerebrospinal fluid velocities are particularly low and the influence on fluid motion from breathing 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 type I Chiari malformation. 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 type I Chiari malformation, velocity can be the 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.*,[81] Luciano and Dombrowski,[82] and others. Thus, any disruption to the system that alters compliance, such as an obstruction to cerebrospinal fluid flow, could reduce the damping effect on cerebral blood flow pulsations. A reduction in damping of the cerebral blood flow pulsations would 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 cerebrospinal fluid flow at the foramen magnum.[83,84] For example, Sivaramakrishnan *et al.*[85] showed increased intracranial compliance in type I Chiari malformation patients after decompression surgery. Non-invasive methods of measuring compliance and tissue mechanical properties in the spinal subarachnoid space are being developed. These include magnetic resonance imaging techniques that allow calculation of overall compliance in the spinal subarachnoid space from cerebrospinal fluid velocity wave speed in the spinal subarachnoid space[26] and magnetic resonance elastography to measure brain elasticity[33,34] 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 *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;[86–89] and (3) removal and separation of each tissue component is not straight forward, easily repeatable, or always complete.[89] In addition, the time after harvesting, subject age, and preservation methods may influence tissue properties.

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Resistance

Cerebellar tonsil herniation may increase resistance to cerebrospinal fluid flow from the cranial to the spinal subarachnoid space. However, further research is necessary to quantify resistance in order to assess its importance in type I Chiari malformation patients. Such quantification is difficult as the pressure gradient across the blockage requires either invasive pressure measurements or simulations. While resistance can be increased by changes in geometry such as cerebellar tonsil herniation, the impact on cerebrospinal fluid hydrodynamics can follow two different scenarios. First, if the pressure gradient in the subarachnoid space increases greatly, the cerebrospinal fluid flow rate (i.e. the volume of fluid leaving the cranium) can be maintained. However, if the pressure gradient in the subarachnoid space remains unchanged, the flow rate would decrease correspondingly. Phase-contrast imaging 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 cerebellar tonsil herniation 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,[17,18] which has similar symptomatology to the type I malformation but not herniation, is an example of a case in which resistance to cerebrospinal fluid flow might not be the problem.

Pressure

In vivo pressure measurements indicate that pressure magnitude and gradients have an impact in type I Chiari malformation in terms of symptoms and severity. While magnetic resonance 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, cerebrospinal fluid pressure has been quantified in a limited number of invasive studies to be 7–15 mmHg in the supine position and 0–10 mmHg in the vertical position in healthy subjects.[90,91] Pressure in healthy subjects and patients with type I Chiari malformation 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.[56,92] Williams' measurements indicated that pressure differences between the ventricles and spinal subarachnoid space are greater in patients with type I Chiari malformation than in healthy subjects. In another study by Sansur *et al.*,[93] it was found that cerebrospinal fluid pressure measured during coughing was elevated in patients with headache in comparison to patients without headache and healthy volunteers.

Pressure gradients in the cerebrospinal fluid system are the driving forces that cause tissue and cerebrospinal fluid motion and may be the cause for nerve damage in type I Chiari malformation.[14] Local cerebrospinal fluid 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 cerebrospinal fluid, blood, interstitial, and lymphatic fluid would be helpful toward understanding the pathophysiology of type I Chiari malformation and related craniospinal disorders such as syringomyelia.

Many structural and communicating factors influence cerebrospinal fluid system pressure dynamics. Structural factors include the structural layers and neural tissues, such as the vertebrae, skull, brain, spinal cord, dura, pia, and arachnoid membrane, that each have complicated anisotropic, nonlinear, and poroviscoelastic properties. The cerebrospinal fluid system communicates with the cardiovascular system through the veins and arteries supplying blood to the neural tissue.[84,94] In particular, pressure in the venous system likely has a great impact on cerebrospinal fluid pressure since 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.[95] Communication between the cerebrospinal fluid and intrathoracic pressure due to postural changes,[96,97] coughing,[93] valsalva and Queckenstedt's test, and abdominal pressure[98] has been well documented.[56,61,92,93]

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.[51]

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Conclusion

Careful examination of hydrodynamics in type I Chiari malformation 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. Studies of hydrodynamics in type I Chiari malformation are sparse as yet, with the exception of clinical phase-contrast imaging studies of cerebrospinal fluid velocity. Engineering-based models may help identify parameters that could be evaluated to assess clinical significance. This may assist current research efforts that are focused on developing magnetic resonance imaging protocols with an eye toward clinical applications.

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