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Inter-Operator Dependence of Magnetic Resonance Image-Based Computational Fluid Dynamics Prediction of Cerebrospinal Fluid Motion in the Cervical Spine

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Abstract

For the first time, inter-operator dependence of MRI based computational fluid dynamics (CFD) modeling of cerebrospinal fluid (CSF) in the cervical spinal subarachnoid space (SSS) is evaluated. *In vivo* MRI flow measurements and anatomy MRI images were obtained at the cervico-medullary junction of a healthy subject and a Chiari I malformation patient. 3D anatomies of the SSS were reconstructed by manual segmentation by four independent operators for both cases. CFD results were compared at nine axial locations along the SSS in terms of hydrodynamic and geometric parameters. Intraclass correlation (ICC) assessed the inter-operator agreement for each parameter over the axial locations and coefficient of variance (CV) compared the percentage of variance for each parameter between the operators. Greater operator dependence was found for the patient ($0.19 < \text{ICC} < 0.99$) near the craniovertebral junction compared to the healthy subject ($\text{ICC} > 0.78$). For the healthy subject, hydraulic diameter and Womersley number had the least variance ($\text{CV} = \sim 2\%$). For the patient, peak diastolic velocity and Reynolds number had the smallest variance ($\text{CV} = \sim 3\%$). These results show a high degree of inter-operator reliability for MRI-based CFD simulations of CSF flow in the cervical spine for healthy subjects and a lower degree of reliability for patients with Type I Chiari malformation.

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CONFLICT OF INTEREST

None.

Keywords

cerebrospinal fluid (CSF); computational fluid dynamics (CFD); magnetic resonance imaging (MRI); Chiari malformation; neurohydrodynamics; subarachnoid space

INTRODUCTION

Abnormal cerebrospinal fluid (CSF) dynamics can result in devastating neurologic disorders such as hydrocephalus (1 in 2000 births ⁵³), Chiari I malformation (CMI) (1 in 3000 ⁴⁸) and syringomyelia (1 in 8000 ⁴⁸). Investigators have begun to research the link of CSF dynamics and disease states in terms of objective parameters such as CSF velocities ⁶, flow ^{2,20}, and flow features, such as velocity jets ^{17,41}. A powerful way to help understand the possible link of CSF dynamics and disease is the usage of computational fluid dynamics (CFD) based on subject-specific medical imaging of *in vivo* geometry and flow ³⁹.

Although CSF dynamics have been investigated invasively for more than a century ⁹, usage of MRI has enabled significant advances in recent years. Approximately 25 ml of CSF is contained within the spinal subarachnoid space (SSS) ¹⁶ where it moves in an oscillatory manner ^{15,32}, with zero mean flow, synchronous with each cardiac cycle around the spinal cord. SSS CSF flow has been characterized to have a peak Reynolds number, based on internal flow in a tube, ranging from 300 to 400 ¹⁸ and Womersley number ranging from 5 to 17 ³². Phase-contrast MRI (PCMRI) measurements have quantified the total volumetric CSF pulsation, moving in and out of the intracranial space at the neck level, to be ~0.25 to 1 milliliter ^{3,37}. Peak systolic CSF flow velocities within the SSS range from ~1 to 10 cm/s in healthy subjects ⁷.

While the CSF pulsation within the SSS is small, many craniospinal pathologies have been associated with abnormalities in CSF flow dynamics ^{17,23,29,41,44}. 2D PCMRI has been the mainstay for *in vivo* analysis of CSF flow dynamics. Recent studies have also used time-resolved 3D velocity encoded phase-contrast MRI (4D PCMRI) to assess 3D CSF flow field complexities, such as bisynchronous flow jets and vortices ^{6,7}.

To further understand the importance of CSF flow, CFD ^{4,14,19,21,26,30,32} and *in vitro* bench-top experiments ^{33,35,36} have been used to investigate CSF flow and quantify parameters that can be difficult to measure or that lack detail when acquired by MRI, such as pressure ³⁸. These experimental and computational methods also enable variational analysis and application of reductionism that cannot be applied *in vivo*, for example reductionism to determine impact of anatomical features on CSF flow, such as spinal cord nerve roots and denticulate ligaments ¹⁸. In addition, they can be used to identify new quantitative parameters to assess disease states; for example, application of CFD in the cervical spine for CMI patients showed elevated impedance to CSF flow compared to controls ^{34,46}.

Uncertainty in model geometry impacts the reliability of CFD-based prediction of CSF flow. To date, CFD studies of CSF flow have relied on a single operator segmentation of the CSF space. Analysis of inter-operator dependence of CFD results has been an important part of CFD investigation of vascular hemodynamics ^{1,11,12,31,39}. However, analysis of inter-

operator dependence of MRI-based CFD results for CSF flow in the SSS has not yet been completed. To analyze this dependence, our approach was to conduct four CFD simulations based on MRI-based geometries that were manually segmented by four independent operators for a healthy subject and a representative disease case with CMI. Inter-operator agreement of the CFD results was assessed in terms of eight geometric and hydrodynamic parameters quantified at nine axial planes along the SSS.

MATERIALS AND METHODS

Ethics statement

MRI data was acquired at the Department of Radiology of the University of Münster. The study was approved by the institutional review board of the University of Münster. Before the MRI exams were conducted, written informed consent was obtained from the healthy subject and CMI patient. MRI data were anonymized prior to post-processing.

4D PCMRI data acquisition

The CFD models were based on subject-specific T2-weighted MRI and 4D PCMRI measurements in the cervical spine of a healthy subject (22-years-old) with no history of neurological disorder or spinal trauma and a male CMI patient (5 years old). The healthy subject and the CMI patient are referred to as HV3 and CM4 patient, respectively in a previous study by our group⁵⁴. All images were acquired on a 1.5 T MRI scanner (Achieva 2.6 scanner, Philips, Best, The Netherlands). In order to define the flow boundary conditions for the CFD models, 4D PCMRI measurements were acquired with a standard 16-channel head and neck coil using the sequence parameters as described in the protocol by Bunck et al.⁷. In brief, a retrospective ECG-triggered, T1-weighted, segmented gradient echo sequence (T1-TFE) was used. MRI sequence parameters were as follows: TR and TE was set to “shortest” resulting in a TR of 8.6–9.5 ms and a TE of 5.4–6.3 ms slightly varying with encoding velocity, flip angle: 5°, acquired isotropic resolution: 1.5 mm (reconstructed voxel resolution: 1 mm). Flow velocities were encoded in anterior–posterior, in feet–head and in right–left direction. The encoding velocity was set to 10 cm/s for the healthy subject and 20cm/s for the CMI patient. To define the cervical spine geometry for the CFD simulations, a high-resolution T2-weighted 3D, turbo spin-echo sequence (VISTA) with an isotropic spatial resolution of 0.8 was obtained.

3D Reconstruction and mesh generation

The 3D anatomies of the cervical SSS and craniocervical junction, including the dura mater, spinal cord and cerebellar tonsils, was reconstructed by four operators (Op.1–4) based on the same set of T2-weighted MRI images for the healthy and patient case. All four operators had the same degree of expertise in manual segmentation. Manual segmentation, in three orthogonal planes, was completed using ITK Snap software (Version 2.2.0, PA, U.S.A.). The boundaries of the SSS were outlined manually on the voxels of the individual axial slices. No automated threshold-based segmentation was used and all operators used the same image contrast and display interpolation settings in the segmentation software. Vertebral arteries were included in the models near the foramen magnum. Other fine structures such as spinal cord nerve roots, blood vessels, and denticulate ligaments were not included in the

segmentations. The caudal end of each model was segmented approximately 5 cm below C7 to prohibit entrance length effects within the region analyzed. See Figure 1 for a segmentation example of the CMI patient.

After segmentation, each 3D geometry (Figure 2) was smoothed with the Laplacian smoothing algorithm within MeshLab software (Version 1.3.0, Italy, Rome). The 3D geometries were then imported into ANSYS ICEM CFD software (Version 13.0, Canonsburg, PA) and rigid wall unstructured computational grids were generated by a single operator consisting of approximately 2 million tetrahedral elements.

CFD simulations

For the CFD simulation inlet flow boundary condition, we selected the CSF flow waveform from the axial location with the greatest peak CSF flow rate measured by 4D PCMRI (see Yiallourou et al.⁵⁵). This was located at C3 for the healthy subject and C2M for the CMI patient. The flow waveform was imposed as a blunt CSF velocity profile at the caudal end of the geometries. A no-slip boundary condition was specified at the walls with a zero pressure boundary condition imposed at the model outlet (Figure 3, cranial end)^{25,42}. The CFD simulations were completed using ANSYS CFX (Version 13.0, Canonsburg, PA) with CSF modeled as an incompressible Newtonian fluid with fluid properties of water at body temperature (density of $\rho=1000\text{kg/m}^3$ and dynamic viscosity of $\mu=0.001\text{ Pa}\cdot\text{s}$)^{13,24}. Flow was assumed to be laminar. Within the CFX solver settings, second order accuracy advection scheme was implemented to solve the Navier-Stokes equations by the use of Gauss's Divergence Theorem. The time-step size was chosen to be $T/100$, where T represents the period of the CSF flow cycle. The utilized transient time-stepping scheme was second order implicit backward Euler. The root-mean square residual (RMS) was set to 10^{-4} as a convergence criterion. The total duration time for the completion of each CFD simulation to reach convergence was approximately 5 hours while running in parallel on a computer with 8 cores and 12 GB of RAM. Grid and time independence were demonstrated for the above methods in an earlier study by our group for the same geometry and CFD settings⁵⁴. Results were analyzed for the third CSF flow cycle after convergence was reached.

Data processing

CFD results were analysed using ANSYS CFD-post (Version 13.0, Canonsburg, PA). Nine axial planes (located between the foramen magnum (FM) to C7 vertebral level) were placed along the CFD models orthogonal to the primary CSF flow direction (Figure 3). For each location, through-plane peak systolic velocity profiles were visualized for each of the healthy and patient CFD models. The following geometric and hydrodynamic parameters were quantified for each axial location:

a) Geometric parameters—Cross-sectional area, A_{CS} , and hydraulic diameter D_h , based on the wetted perimeter, P_{WET} and A_{CS} was calculated according to equation (1):

$$D_h = \frac{4A_{CS}}{P_{WET}} \quad (1)$$

In addition, a qualitative assessment of segmentation differences among the four operators for the healthy and patient geometry was completed by the following methodology. The 3D segmentations completed by the four operators were overlaid, using the original MRI coordinate system as a reference, and assessed at the nine axial planes. The geometric variation in the nine axial cross-sections was visualized by outlining the greatest difference in the location of the spinal cord and dura surface.

b) Peak through-plane CSF velocities—The maximum through-plane velocity value within each of the nine axial cross-sections was determined at two time points resulting in the calculation of peak CSF flow in the caudal (peak systolic, V_{sys}) and cranial (peak diastolic, V_{dia}) directions.

c) Reynolds number—Reynolds number, Re , based on hydraulic diameter, D_h , and V_{sys} was quantified by equation (2) to help validate the assumption of laminar flow for the CFD model.

$$Re = \frac{\rho D_h V_{sys}}{\mu} \quad (2)$$

Where ρ is the density of CSF and μ refers to the dynamic viscosity of CSF.

d) Womersley number—Womersley number, a , was computed by equation (3) in order to define the importance of transient inertia on the flow field.

$$a = \frac{D_h}{4} * \sqrt{\frac{\omega}{\nu}} \quad (3)$$

where ω is the angular velocity ($\omega = 2\pi/T$) of the volume flow waveform and ν is the kinematic viscosity of CSF ($\nu = \mu/\rho$).

e) Pressure gradient—The unsteady pressure gradient, $P(t)$, was calculated across each spine segment (e.g. FM-C1). In addition, the pressure gradient over the entire CFD models from FM to C7 was obtained. Peak pressure gradient magnitude across each spine segment was also quantified.

f) Integrated longitudinal impedance—Longitudinal impedance, or the unsteady flow resistance, was calculated as the ratio of Fourier coefficients of the pressure gradient, $F(P(t))$ and the input flow waveform, $F(Q(t))$ at each harmonic³⁴. The impedance modulus Z_L was calculated for each frequency according to equation (4) :

$$Z_L = \left| \frac{\Im(\Delta P(t))}{\Im(Q(t))} \right| \quad (4)$$

The resulting curves for Z_L (in dyn-s/cm⁵) for each harmonic were integrated from 1–8 Hz to obtain the integrated longitudinal impedance (ILI), for each of the spine segments (e.g. FM-C1) for all CFD simulations.

Statistical analysis

Mean±standard deviation (SD) of each parameter for the four operators was calculated for both the healthy and CMI patient simulations. Statistical analysis was conducted with Minitab 16 (State College, PA) and Excel (Microsoft Office 2007, Redmond, WA). Analysis of variances (ANOVA) was used to estimate the level of inter-operator agreement for each parameter over all locations analyzed by computing the intraclass correlation coefficient (ICC) with a confidence interval of 95%. Coefficient of variation (CV) was used to quantify the parameter variability between the four operators at each of the measurement locations for both the healthy and CMI patient simulations.

RESULTS

Geometric parameters

Comparison of geometric parameters, D_h and A_{cs} , among the operators showed agreement over the cervical spine (Figure 4 and Table 1). Qualitative inspection of the cross-sectional geometry variations among the four operators showed that the detected dura surface location was less consistent than the spinal cord (Figure 5). Discrepancies in the dura surface location were greatest in the lateral SSS and in the Chiari patient near the foramen magnum. The spinal cord and dura surface locations had a maximum difference among the operators of approximately 1.0 and 2.5 mm, respectively. Agreement for D_h and A_{cs} was best near C2M for the healthy subject. In the CMI patient, agreement was best in the lower cervical spine (Table 2). ICC for D_h and A_{cs} was greater than 0.98 for the healthy subject; whereas for the CMI patient ICC was 0.35 and 0.83 for D_h and A_{cs} , respectively.

Hydrodynamic parameters

Agreement of hydrodynamic parameters was better for the healthy subject geometries than the patient geometries. V_{sys} , V_{dia} , a , and P and ILI , showed a strong agreement among the four operators for the healthy subject geometry, with an ICC greater than 0.92, excluding Reynolds number, Re , with an ICC of 0.78 (Figure 6 and Table 2). V_{sys} , V_{dia} , a and Re showed greater variability for the CMI patient, with ICC in the patient ranging from 0.19 to 0.61 for these parameters. Hydrodynamic parameters had the lowest CV near C2M for the healthy subject and within the C4 to C6 levels for the CMI patient (Figure 7). These alterations coincided with visual alterations in the SSS cross-sectional geometry (Figure 5). Similar to geometric parameters, the agreement of V_{sys} and V_{dia} between the operators decreased along the spine towards the feet for the healthy subject with a maximum CV of ~17% at C6 (Figure 6 and 7, Table 2). For the CMI patient, agreement of V_{sys} and V_{dia} between the operators decreased along the spine towards the head with a maximum CV of ~27% at C2M. This location coincided with the maximum V_{sys} and V_{dia} (Table 1). Maximum CV of Reynolds number occurred at C6 for the healthy subject (CV=12.6%) and at the FM for the patient (CV=12.6%). A maximum CV for Womersley number, a , occurred at C6 for the healthy subject (9%) and at C2M for the patient (CV=11.5%).

Peak pressure gradient, P , over the cardiac cycle increased along the spine (Table 3). The maximum CV of the P and ILI was calculated within the C6–C7 segment for the healthy subject, while at the C1–C2M and C5–C6 segments the smallest CV occurred (Figure 8, Table 2). The opposite behavior was observed for the CMI patient, with the maximum and minimum CV of both P and ILI occurring at C1–C2M and C5–C6 spine segments, respectively. Unsteady pressure gradient measured between the FM to C7 showed similar trends in waveform shape and magnitude for each of the operators (Figure 8 and 9).

Based on qualitative inspection, CFD-computed velocity profiles for the four operators had similar trends in terms of velocity distribution around the spinal cord (anterior versus posterior) and location of peak velocities (Figure 10) for both the healthy and patient case. Differences in velocity profiles were most noticeable from C3 to C7 for the healthy case and from C1 to C3 and C7 for the Chiari patient case. For the healthy subject, velocity profiles from FM to C2M were nearly identical. Velocity profiles showed elevated velocities within the narrower, posterior and anterolateral, SSS of the healthy subject in all operators in a number of planes (C2P–C7). The same trend was observed in the patient case in a number of planes (e.g. C1–C4).

DISCUSSION

CFD has been used to investigate CSF dynamics in the upper cervical spine^{8,14,15,18,19,27,32,34,40,44,45,54}. In all of these studies, a single operator segmented the anatomic MR images that were used to create the CFD geometry. The present study is the first to quantify how much CFD results vary due to different operators making the anatomic segmentations of the MR images. Our approach was to compare CFD results from manually segmented models of the cervical spine of both a healthy subject and a CMI patient that were each created by the same group of four independent operators. The same subject-specific CSF inlet flow boundary condition was used for the four healthy CFD models and the four CMI patient CFD models. Thus, the differences in CFD results were only due to geometric variations between the operators.

The analyzed geometric and hydrodynamic parameters varied substantially among the operators. However, these variations must be interpreted in context of their potential clinical application. At present, CSF dynamics have been investigated using PCMRI in healthy controls versus CMI patients and alterations in patients that occur pre- and post-craniospinal decompression surgery. Thus, the discussion in this section focuses on parameter variability in the present study compared to variability of the same parameters previously reported in CMI patients and controls. Also, when possible, parameter variability is considered for CMI patients pre- and post-spinal decompression surgery. Ideally, a parameter's variability due to different operators should be significantly less than the sensitivity required for diagnosis/detection of the disease state and analysis of surgical treatment.

Dura surface segmentation is the major source of variability

Inconsistent detection of the dura surface location was the most important factor leading to CFD-based parameter variability. Inter-operator agreement of the geometric and hydrodynamic parameters was better for the healthy subject geometry compared to the

patient geometry. For the healthy subject, ICC agreement of all parameters was greater than 0.92 excluding Reynolds number ($ICC=0.78$). These alterations coincided with visual inspection of cross-sectional area differences in the location of the dura (Figure 5). In general, the spinal cord surface location was detected more consistently than the dura surface among the operators. A greater inconsistency in dura surface location may be attributed to the lack of T2-weighted MR image contrast due to close proximity of epidural fat and intra-voxel averaging of CSF and fine anatomical structures such as the spinal cord nerve roots. In addition, patients with craniospinal disorders, such as CMI, can have restricted CSF flow spaces with greater geometric complexity that can make geometric segmentation of the dura difficult. Our results show that inter-operator inconsistency was greatest within the region of greatest anatomical complexity (located at the craniovertebral junction in the CMI patient). High-resolution MRI sequences⁴⁷ that can more accurately quantify these anatomical structures and sequences that are better sensitized to differentiate the tissue and fluid types (CSF versus epidural fat) are needed to produce a more consistent geometry.

Inter-operator impact on geometric parameters

Geometric assessment of the cervico-medullary junction has been a mainstay for morphometric analysis studies of Chiari malformation and syringomyelia⁵⁰. At present, these studies have focused on 1D assessment of features in the mid-sagittal plane and thus provide a limited view of the 3D geometry presented by the spinal cord, medulla, cerebellar tonsils and dura mater. It is expected that future work will increasingly include 3D analysis of the SSS and thus, quantification of the inter-operator geometric variability of manual segmentation of the SSS is crucial.

The four operators provided fairly consistent geometric reconstruction of the CSF space for both the healthy subject and the CMI patient (Figure 5). ICC was greater than 0.95 and maximum CV was ~11% (Table 2) for D_h and A_{cs} (Figure 4 and 6, Table 1) for the healthy subject, while for the CMI case ICC was smaller than 0.83 with a maximum CV of ~13% for D_h and A_{cs} (Table 2). The C2M axial location had the lowest CV in both parameters for the healthy subject, indicating that this region is more consistently segmented. CV increased further down the cervical spine showing that this region was more difficult to be segmented consistently. In contrast, CV increased further upper the cervical spine in the case of the Chiari patient, showing that this region was the most difficult to be segmented consistently.

The present study results show that operator dependence of D_h and A_{cs} is likely not an important factor when differentiating patients from controls. A study by Bunck et al.⁶ documented that A_{cs} in healthy controls ($n=10$) was ~400 and ~200% greater than Chiari malformation patients ($n=20$) at the foramen magnum and C1, respectively ($p<0.001$). Similar magnitude of differences between the Chiari patient population and controls was quantified by others⁵⁴. In another study by Martin et al., average D_h and A_{cs} near the cervico-medullary junction were more than 200% greater in a healthy subject compared to two Chiari patients pre-spinal decompression surgery³⁴. For that study, average D_h and A_{cs} was found to increase by 10 to 50% post spinal decompression surgery ($n=2$). These changes are similar in magnitude as those seen in the present study due to the operator. Albeit, the

differences observed by Martin et al. were computed for the average D_h and A_{cs} over a 2.5 cm region below the FM, thus any particular axial slice location could have a much greater difference. Also, these considerations are based on *in vivo* studies with few subjects and should be examined in a larger population. More detailed study of geometric alterations in D_h and A_{cs} due to CMI decompression surgery is needed.

Inter-operator impact on CSF velocities

Elevated peak CSF velocities have often been found near the FM in Chiari malformation^{6,17,23,34,54}. Researchers have hypothesized that the elevated CSF velocities are due to FM obstruction (stenosis) by the cerebellar tonsils⁴⁴. However, the current *in vivo* PCMRI measurements lack detail about the complexity of the CSF flow field. Subject-specific CFD has been applied as a tool to understand CSF dynamics in greater detail and as a potential means for disease assessment. As such, it is necessary to understand the variability of peak CSF velocities due to geometric reconstruction from different operators.

Similar to geometry, the present study results show that operator dependence of CFD-based values of V_{sys} and V_{dia} is likely not an important factor to differentiate patients from controls, but may be important to detect changes in velocity due to surgery. V_{sys} and V_{dia} showed a strong level of agreement (ICC = 0.92, Figure 7 and Table 2) between the operators for the healthy subject. Peak velocities had small variance for the axial locations analyzed and had a maximum difference in the lower cervical spine (CV at C6 was <17%). The greater variance of velocity lower in the spine can be attributed to an increase in D_h and A_{cs} variance within that region and vice versa. Analysis of the peak CSF flow velocities among the four CMI patient geometries showed poor agreement (ICC = 0.25, with a maximum CV of 27.4% at the C2M level). However, several *in vivo* studies have shown peak CSF velocities to be ~200 to 300% greater in Chiari patients than controls^{6,17,23,54}. Thus, while the alterations due to the operator in the CMI patient are substantial, they would not wash out the expected differences seen between patients and controls.

Qualitative comparison of the through-plane CSF velocity profiles at peak systole showed similar CSF velocity patterns (Figure 10). All simulations showed profile skewing at some axial locations to the posterior and anterior-lateral SSS. As expected, peak velocities were inversely related with A_{cs} and D_h and locations with greater variance in A_{cs} and D_h had greater differences in velocity profiles (e.g. at C6 for the healthy subject and C2M for the Chiari subject). Greater differences in velocity profiles were located where the dura surface varied to a greater degree among the operators (compare Figure 5 and 10).

Inter-operator impact on pressure-related parameters

A great deal of evidence points towards the role of abnormal pressure gradients in CSF system pathologies. Pressure differences (dissociation) within the CSF system, caused by the pulsatile intracranial blood flow and CSF motion, are complex in terms of magnitude and distribution¹⁵ and, when abnormal, may damage tissue and result in pathologic conditions⁴⁴. *In vivo* measurements have found craniospinal pressure dissociation to be elevated in CMI patients compared to controls, to decrease after surgery and to be associated with symptom improvement^{43,51,52}.

The results showed that P reliability between the operators is likely sufficient to help detect CMI patients versus controls, but not alterations in P post-surgery. Unsteady pressure gradient, $P(t)$, between the FM and C7 showed strong agreement in terms of waveform magnitude and shape (Figure 9) and axial distribution for both the healthy (ICC=0.99, Tables 2 and 3) and CMI patient cases (ICC=0.98, Tables 2 and 3). P variance showed a similar trend as D_h and A_{cs} with the greatest CV values lower in the cervical spine (C6–C7) and the smallest CV near the cervico-medullary junction (FM–C1). The opposite occurred in the CMI patient, with the maximum CV at the upper cervical spine at C1–C2M and the smallest at C5–C6 (Figure 8, Tables 2 and 3). Peak P in the CMI patient was ~30% greater than the healthy subject. In comparison, CFD studies in the literature found peak P in CMI patients to be up to 200% greater in patients than controls^{8,34}. Post surgery (n=2), P ranged from an increase of ~10% to a decrease of ~20%³⁴.

The presented methodology required solving the full 3D Navier-Stokes equations to obtain pressure gradients in the flow field. It should be noted that viscous effects were insignificant with Womersley number ranging from 4 to 12 (Table 1). Thus, it is expected that P waveforms can be predicted by A_{cs} spatial integration of the linearized Navier-Stokes equations³².

Unsteady resistance to CSF flow, ILI, was computed based on the inlet volume flow, $Q(t)$, measured from MRI, and the pressure gradient, $P(t)$, calculated from CFD for the axial sections of each model (e.g. pressure gradient between FM to C1)³⁴. ILI is a hydrodynamic parameter that has been used to help objectively quantify CSF flow blockage inside the SSS for CMI patients. Similar to P , ILI agreement was strong for both the healthy and patient case (ICC=0.99). ILI followed the same trend as the peak pressure gradient, with the greatest CV at C6–C7 segment for the healthy subject and at C1–C2M for the patient case. In addition, CV presented the least variation at C1–C2M in the healthy subject and at C5–C6 for the CMI patient (Figure 8). ILI for the healthy and CMI subjects in this study ranged from 86 to 320 and from 83–160 dyn/cm⁵, respectively (Table 3) a value similar to other studies in healthy subjects^{18,34,45}. Shaffer et al. found that ILI was more than 200% greater in CMI patients than controls ($P<0.001$). In addition, Shaffer found ILI to vary by 16% for CFD studies based on geometries that were reconstructed for the same person scanned on three different MRI machines.

Inter-operator impact on dimensionless parameters

The analysis of Reynolds and Womersley number is presented to help understand the hydrodynamics. These parameters are not expected to relate directly with disease states but rather are helpful to compare the present study results with the literature and validate the CFD methodology assumptions, such as laminar flow. For the healthy subject, maximum Reynolds number for all simulations was ~225 and located at C6, the location where maximum V_{sys} and minimum D_h occurred. For the patient case, the maximum Reynolds number for all simulations was ~400 and located at the levels C2M and C2P. Reynolds number was lower than the critical value of transition to turbulence and agreed with studies in the literature^{18,34}. Albeit, one study in the literature has noted possible transitional CSF

flow features in the cervical spine¹⁹. For all four CFD models, Reynolds number was shown to increase with distance from the skull (Table 1).

Womersley number, a , had a similar trend as D_h (Table 1) with the maximum and minimum value at the FM and C5/C6 for the healthy subject, respectively. In addition, a was found to have the maximum and minimum values at the FM and C4/C5, respectively. Values of a found in this study are in the range reported in the literature^{32,34} with inertial effects dominating the flow field, particularly in the upper cervical spine.

Comparison of CSF velocities measured by 4D PCMRI and predicted by CFD

Studies have shown that the CSF velocities measured by 4D PCMRI and predicted by CFD modeling have poor agreement^{40,54}. The CFD results for all of the operators in the present study also show poor agreement with in vivo 4D PCMRI measurements (Figure 11). Thus, while the CFD-based parameters were fairly consistent among the operators in the present study, the difference in operators did not explain why CFD modeling lacked agreement with in vivo measurements. In particular, the CFD-predicted CSF velocities by all operators were much smaller than those observed in vivo (compare peak velocity values in Figure 10 and 11). Also, anterior dominance of CSF flow and CSF flow jets were observed in vivo and not observed in the CFD results. The exact reason for these discrepancies remains unclear. The present study supports that these discrepancies are not due to operator segmentation error.

Limitations

Each operator segmented the geometry of one healthy subject and one patient with CMI that was scanned once on a single MRI machine. If the same subject was scanned in different MRI machines it is expected that different imaging parameters could have an impact on the reconstructed geometries. Thus, further studies are needed to understand the possible importance of inter-operator segmentation, magnetic field strength (1.5 versus 3.0 and 7.0 T), MR signal-to-noise-ratio, T2 MRI sequence parameters used, and post-processing for motion compensation. Also, scanning multiple times on different machines could introduce error due to alterations in neck angulation. These factors may have an important impact on geometry and should be analyzed, but were not the subject of the present study. It should also be noted that patients with craniospinal disorders, such as CMI, often have restricted CSF spaces, with smaller areas, that can make geometry segmentation more difficult. However, the smallest A_{cs} in the present study (1.2 cm² at C6, Table 1) was similar to that measured in CMI patients *in vivo* (1.2–2.4 cm² at the FM³⁴). Thus, we expect the variance in geometric and hydrodynamic parameters observed in the present study to be of similar magnitude for CMI patients at the FM.

Another limitation of the presented work was that the “gold standard” geometry was not available as a basis for assessment of geometric reconstruction accuracy. This could be assessed by conducting an *in vitro* study where the model geometry is known as in previous hemodynamics studies³⁹. However, an *in vitro* model is still limited because it does not have identical properties as human tissue. Another approach could be to utilize high resolution 7T MRI⁴⁷ to better define the geometric boundaries *in vivo*, however in this case the “gold standard” geometry would still not be known.

While CFD-based simulations can provide insights into CSF hydrodynamic, they require many simplifications to the complex *in vivo* anatomy. CFD studies of CSF flow in the cervical spine have been conducted under geometrically simplified^{5,28,32}, subject-specific 3D models without fine anatomical structures^{18,19,22,42,49,54} and with idealized spinal cord nerve rootlets and denticulate ligaments¹⁸. Spinal cord nerve rootlets and denticulate ligaments were not included in the modeling approach of the present study as these were not possible to quantify based on the MR images¹⁸. Thus, some of the *in vivo* flow features observed by MRI, such as increased CSF flow velocities (jets) near nerve rootlets^{10,41,54} were not present in the models of this study.

Our approach was to utilize the most commonly used CFD method for CSF flow modeling in order to determine the importance of segmentations done by different operators on the results. This approach included a geometry with rigid spinal cord and dura mater and subject-specific CSF flow boundary condition. However, this common CFD modeling approach should be compared with *in vivo* 4D PCMRI measurements in greater detail to assure that it accurately reflects the *in vivo* CSF flow phenomenon.

CONCLUSION

This study represents the first analysis of inter-operator dependence of MRI-based CFD modeling of CSF dynamics in the cervical spine. The findings show that the variation in geometries segmented by different operators had little impact on the CFD-based geometric and hydrodynamic parameters for a healthy subject and had greater impact on those parameters for a CMI patient. The maximum coefficient of variance for the healthy subject and CMI patient was 17% and 51%, respectively for all parameters analysed. Variability was greater in the lower cervical spine compared to the upper (CV at FM ~ 2–5%) for the healthy subject, while the opposite phenomenon occurred in the CMI patient. When considered with respect to disease, the operator variability in the CFD-based parameters analysed was smaller in comparison to the differences observed for the same parameters quantified by *in vivo* MRI on CMI patients compared to controls. These results support the use of subject-specific MR-based CFD modelling of CSF flow within the cervical spine to quantify geometric and hydrodynamic parameters for potential clinical diagnostic and assessment purposes.

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Figure 1.

a) T2-weighted MR image of the cervical spine for the healthy subject. b) Example of manual segmentation of the SSS from the T2-weighted MRI completed by one of the operators.

Figure 2. Three-dimensional CFD model of the healthy cervical SSS built from manual segmentation (left). Zoom of the upper cervical spine (right) showing the cervical subarachnoid space where the CSF flows (blue).

Figure 3.

Axial locations of the nine planes shown on a representative segmented geometry based on the healthy subject (top). Zero pressure boundary condition was set at the cranial end. The CSF flow rate, based on *in vivo* PCMRI measurement at C3, was used to obtain the velocity inlet boundary condition at the caudal end for all simulations.

Figure 4. Mean values and standard deviations of the cross-sectional areas, A_{cs} (top) and hydraulic diameters, D_h , (bottom) computed at each axial plane of the cervical SSS of the healthy and Chiari subject for the four operators (FM = foramen magnum, C2M = middle of 2nd cervical vertebra, C2P = junction of C2/C3 vertebra).

Figure 5.

Visualization of the segmentation differences among the four operators for the spinal cord and dura surface locations in the healthy and CMI patient geometries. Thicker outlines correspond to greater difference between operators.

Figure 6.

Mean values and standard deviations of the peak systolic, V_{sys} , and diastolic, V_{dia} , velocities obtained from the four CFD simulations based on each operator (Op.1 to Op.4) for both healthy and CMI patient. Positive (diastolic) and negative (systolic) velocities reflect head and foot directed flow, respectively.

Figure 7.

(top) Coefficient of variance for the hydraulic diameters, D_h , and cross-sectional areas, A_{cs} , and (bottom) peak systolic, V_{sys} , and diastolic, V_{dia} , velocities obtained from the four CFD simulations based on each operator (Op.1 to Op.4).

Figure 8.

(left) Coefficient of variance for the maximum pressure gradient and ILI obtained within each axial segment (e.g. FM-C1) from the four CFD simulations based on each operator (Op.1 to Op.4).

Figure 9. Unsteady pressure gradient waveform for the healthy subject (a) and CMI patient (b) computed between the FM and C7 for each CFD simulation for the four operators (Op.1 to Op.4).

Figure 10.

Through-plane peak systolic velocity profiles at nine axial locations along the cervical spine for the geometries segmented by the four operators (Op.1 to Op.4) for the healthy subject (left) and CMI patient (right). Note, velocity scale is 0–1.94 cm/s for healthy case and 0–4.85 cm/s for CMI patient.

Figure 11.

In vivo 4D PCMRI measurement of through-plane peak systolic velocity profiles at nine axial locations along the cervical spine for the healthy subject (left) and CMI patient in the present study (right). The nine axial locations are placed identical to those shown in Figure 10. Note, the large difference in velocity profiles shown in Figure 10 compared to Figure 11.

TABLE 1

SUMMARY OF CALCULATED GEOMETRIC AND HYDRODYNAMIC PARAMETERS FOR THE CMI PATIENT AND HEALTHY SUBJECT CFD SIMULATIONS (VALUES ARE GIVEN AS MEAN $\pm$ SD FOR THE FOUR OPERATORS).

Axial level	D_h (cm)		A_{cs} (cm ²)		V_{sys} (cm/s)		V_{dia} (cm/s)		Reynolds number		Womersley number	
	Patient	Healthy	Patient	Healthy	Patient	Healthy	Patient	Healthy	Patient	Healthy	Patient	Healthy
FM	0.92 $\pm$ 0.05	1.7 $\pm$ 0.06	2.7 $\pm$ 0.2	6.1 $\pm$ 1.7	-3.7 $\pm$ 0.6	-0.9 $\pm$ 0.04	2.5 $\pm$ 0.3	0.6 $\pm$ 0.05	341 $\pm$ 43	146 $\pm$ 8	17 $\pm$ 1.0	12 $\pm$ 0.4
C1	0.80 $\pm$ 0.07	1.2 $\pm$ 0.03	1.6 $\pm$ 0.2	2.6 $\pm$ 0.7	-4.7 $\pm$ 0.8	-1.8 $\pm$ 0.07	3.2 $\pm$ 0.6	1.3 $\pm$ 0.05	374 $\pm$ 32	202 $\pm$ 8	15 $\pm$ 1.4	8 $\pm$ 0.2
C2M	0.82 $\pm$ 0.09	1.0 $\pm$ 0.01	1.5 $\pm$ 0.2	2.1 $\pm$ 0.5	-4.8 $\pm$ 0.9	-1.8 $\pm$ 0.04	3.3 $\pm$ 0.9	1.2 $\pm$ 0.04	382 $\pm$ 39	171 $\pm$ 3	15 $\pm$ 1.7	7 $\pm$ 0.1
C2P	0.92 $\pm$ 0.05	0.8 $\pm$ 0.04	1.8 $\pm$ 0.1	1.8 $\pm$ 1.0	-4.4 $\pm$ 0.3	-2.5 $\pm$ 0.1	2.9 $\pm$ 0.3	1.7 $\pm$ 0.06	399 $\pm$ 20	212 $\pm$ 5	16 $\pm$ 1.0	6 $\pm$ 0.3
C3	0.81 $\pm$ 0.06	0.7 $\pm$ 0.05	1.6 $\pm$ 0.1	1.5 $\pm$ 1.0	-4.4 $\pm$ 0.3	-2.7 $\pm$ 0.2	3.0 $\pm$ 0.2	1.9 $\pm$ 0.2	358 $\pm$ 9	185 $\pm$ 5	15 $\pm$ 1.2	5 $\pm$ 0.3
C4	0.79 $\pm$ 0.05	0.6 $\pm$ 0.05	1.6 $\pm$ 0.1	1.4 $\pm$ 1.0	-4.0 $\pm$ 0.3	-2.8 $\pm$ 0.2	2.8 $\pm$ 0.1	1.9 $\pm$ 0.1	316 $\pm$ 7	171 $\pm$ 5	14 $\pm$ 1.0	4 $\pm$ 0.3
C5	0.81 $\pm$ 0.04	0.6 $\pm$ 0.03	1.7 $\pm$ 0.1	1.2 $\pm$ 0.7	-3.8 $\pm$ 0.3	-3.2 $\pm$ 0.2	2.5 $\pm$ 0.3	2.2 $\pm$ 0.1	305 $\pm$ 3	179 $\pm$ 3	14 $\pm$ 0.9	4 $\pm$ 0.2
C6	0.82 $\pm$ 0.07	0.6 $\pm$ 0.05	1.6 $\pm$ 0.1	1.2 $\pm$ 1.5	-4.0 $\pm$ 0.3	-4.0 $\pm$ 0.7	2.7 $\pm$ 0.1	2.8 $\pm$ 0.3	328 $\pm$ 7	225 $\pm$ 28	15 $\pm$ 1.3	4 $\pm$ 0.4
C7	0.91 $\pm$ 0.09	0.7 $\pm$ 0.04	1.6 $\pm$ 0.2	1.4 $\pm$ 0.5	-4.0 $\pm$ 0.5	-2.8 $\pm$ 0.2	2.7 $\pm$ 0.3	2.0 $\pm$ 0.08	367 $\pm$ 9	189 $\pm$ 17	16 $\pm$ 1.8	5 $\pm$ 0.3

Abbreviations: CMI= Chiari I malformation, D_h = hydraulic diameter, A_{cs} = cross-sectional area, V_{sys} = peak systolic velocity, V_{dia} = peak diastolic velocity, SD = standard deviation

TABLE 2
ICC VALUES FOR THE GEOMETRIC AND HYDRODYNAMIC PARAMETERS.

Parameter	Min CV (axial location)		Max CV (axial location)		ICC (95% CL)	
	Patient	Healthy	Patient	Healthy	Patient	Healthy
D_h	5.9% (FM)	1.6% (C2M)	11.4% (C2M)	8.8% (C6)	0.35 (0.001–0.718)	0.98 (0.98–1.00)
A_{cs}	5.9% (C2P)	2.2% (C2M)	13.1% (C5)	12.2% (C6)	0.83 (0.57–0.96)	0.99 (0.99–1.00)
V_{sys}	6.4% (C3)	2.1% (C2M)	20.4% (C2M)	16.8% (C6)	0.25 (–0.07–0.54)	0.92(0.73–0.98)
V_{dia}	3.15% (C4)	3.1% (C2M)	27.4% (C2M)	12.2% (C6)	0.19 (–0.09–0.39)	0.95 (0.79–0.98)
Re	0.83% (C5)	2.0% (C2M)	12.6% (FM)	12.6% (C6)	0.61 (0.11–0.84)	0.78 (0.45–0.93)
a	5.8 % (C2P)	1.6% (C2M)	11.5% (C2M)	8.8% (C6)	0.35 (0.001–0.72)	0.98 (0.97–1.00)
P	6.15%(C5–C6)	2.7%(C1–C2M)	51.2%(C1–C2M)	12.2%(C6–C7)	0.98 (0.93–0.99)	0.99 (0.97–1.00)
ILI	5.2%(C5–C6)	6.6%(C5–C6)	24.3%(C1–C2M)	22.2%(C6–C7)	0.99 (0.98–0.99)	0.99 (0.98–1.00)

Abbreviations: ICC=intra-class operator variability, CI=confidence interval, CV=coefficient of variation, D_h = hydraulic diameter, A_{cs} = cross-sectional area, V_{sys} = peak systolic velocity, V_{dia} = peak diastolic velocity, Re= Reynolds number, a=Womersley number, P = pressure gradient, ILI = integrated longitudinal impedance

TABLE 3

MEAN VALUES OF PEAK PRESSURE GRADIENT AND INTEGRATED LONGITUDINAL IMPEDANCE FOR THE CFD SIMULATIONS (MEAN $\pm$ SD).

Location	Peak P (Pa)		ILI (dyn/cm ⁵)	
	Patient	Healthy	Patient	Healthy
FM-C1	4.0 $\pm$ 0.3	1.9 $\pm$ 0.04	111 $\pm$ 15	86 $\pm$ 10
C1-C2M	4.2 $\pm$ 2.2	3.0 $\pm$ 0.08	94 $\pm$ 23	137 $\pm$ 13
C2M-C2P	3.1 $\pm$ 0.3	3.4 $\pm$ 1.0	83 $\pm$ 9	156 $\pm$ 17
C2P-C3	6.1 $\pm$ 0.5	5.2 $\pm$ 0.2	162 $\pm$ 13	229 $\pm$ 18
C3-C4	5.2 $\pm$ 0.4	7.8 $\pm$ 0.6	131 $\pm$ 8	313 $\pm$ 28
C4-C5	4.9 $\pm$ 0.3	7.0 $\pm$ 0.5	124 $\pm$ 8	264 $\pm$ 29
C5-C6	3.9 $\pm$ 0.2	8.1 $\pm$ 0.6	101 $\pm$ 5	319 $\pm$ 21
C6-C7	6.1 $\pm$ 0.6	7.4 $\pm$ 0.9	158 $\pm$ 13	321 $\pm$ 71
Total	37.7 $\pm$ 4.7	43.3 $\pm$ 2.7	963 $\pm$ 73	1826 $\pm$ 127

Abbreviations: P = pressure gradient, ILI = integrated longitudinal impedance, SD = standard deviation