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Impact of Neurapheresis System on Intrathecal Cerebrospinal Fluid Dynamics: A Computational Fluid Dynamics Study

It has been hypothesized that early and rapid filtration of blood from cerebrospinal fluid (CSF) in postsubarachnoid hemorrhage patients may reduce hospital stay and related adverse events. In this study, we formulated a subject-specific computational fluid dynamics (CFD) model to parametrically investigate the impact of a novel dual-lumen catheter-based CSF filtration system, the NeurapheresisTM system (Minnetronix Neuro, Inc., St. Paul, MN), on intrathecal CSF dynamics. The operating principle of this system is to remove CSF from one location along the spine (aspiration port), externally filter the CSF routing the retentate to a waste bag, and return permeate (uncontaminated CSF) to another location along the spine (return port). The CFD model allowed parametric simulation of how the Neurapheresis system impacts intrathecal CSF velocities and steady–steady streaming under various Neurapheresis flow settings ranging from 0.5 to 2.0 ml/min and with a constant retentate removal rate of 0.2 ml/min simulation of the Neurapheresis system were compared to a lumbar drain simulation with a typical CSF removal rate setting of 0.2 ml/min. Results showed that the Neurapheresis system at a maximum flow of 2.0 ml/min increased average steady streaming CSF velocity 2× in comparison to lumbar drain (0.190 ± 0.133 versus 0.093 ± 0.107 mm/s, respectively). This affect was localized to the region within the Neurapheresis flow loop. The mean velocities introduced by the flow loop were relatively small in comparison to normal cardiac-induced CSF velocities. [DOI: 10.1115/1.4044308]

1 Introduction

Subarachnoid hemorrhage (SAH) is a severe and often-fatal incident [1], in which blood is released into the cerebrospinal fluid (CSF) due to intracranial insult, ruptured intracranial aneurysm, and/or other head trauma. Permanent disability, stroke, hydrocephalus, and even death can occur if the blood flow is not re-established. Standard of care for SAH patients typically involves: (a) securement of the aneurysm, (b) pharmacologic therapies targeted at neural protection (such as calcium-channel blockers, e.g., nimodipine), (c) attempt to control the relationship between cerebral perfusion (via hypertension, hypervolemia, and hemodilution therapy, collectively termed “triple-H” [2]), and (d) relief of high intracranial pressure via pharmacologic and interventional approaches. After securement of a ruptured aneurysm, the body is susceptible to inflammation related complications as it breaks down and reabsorbs any remaining blood from the subarachnoid space. As such, patients are closely observed in the hospital for 10–14 days to monitor for high intracranial pressure, cerebral vasospasm, edema, and hydrocephalus.

It has been hypothesized that early and rapid filtration of blood and blood breakdown byproducts (e.g., hemoglobin and other inflammatory mediators) post-SAH may reduce the incidence of stroke, cerebral vasospasm [3], hydrocephalus/permanent shunting, and/or shorten hospital course [4–7]. Table 1 summarizes clinical studies involving removal of blood from the CSF in terms of clearance modalities, population, and observed outcomes. Reduction in the incidence of these complications would, in principle, reduce length of stay, decrease utilization of hospital resources, improve clinical functional outcomes, and have an overall reduction of healthcare economic burden. This hypothesis has been studied utilizing various blood removal techniques such as intracranial cisternal drainage [8,9], cisternal lavages [10,11], external-ventricular drains, lumbar drains [12–19], or a combination of drainage scenarios [20,21]. Cisternal lavages involve irrigation of the cranial cisterns and ventricles with artificial CSF intended to flush out blood. Cisternal lavage may be combined with administration of thrombolytic agents directly to the site of clot formation [22–25]. Vibratory motion of the head coupled with cisternal lavage has been investigated a potential method to improve blood clearance rates [26,27]. Another study developed a simplified in vitro model of the basal cistern from medical images, and demonstrated that head “shaking” can accelerate clearance due to increased mixing [28]. At present, there is no consensus on

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Table 1 Summary of clinical studies focused on clearance of blood from the CSF postsubarachnoid hemorrhage

Author	Study inhabitants	Primary outcome measure	Primary outcome (%)
Maeda et al. [17]	LD = 34 versus EVD = 17	Favorable outcome	LD = 64.7, EVD = 23.5
Klimo et al. [15]	LD = 81 versus control = 86	Vasospasm risk reduction	LD FG3 = 68, LD FG3 + 4 = 49
Al-Tamimi et al. [12]	LD = 105 versus control = 105	Prevalence of DIND	LD = 21, control = 35
Park et al. [19]	LD = 126 versus control = 8	Vasospasm	LD = 19, control = 42
Kwon et al. [16]	LD = 47 versus control = 60	Vasospasm	LD = 23, EVD = 63
Kawamoto et al. [27]	CI + shake = 114 versus CI = 116	Vasospasm	CI + shake = 14, CI = 26
Mizoi et al. [24]	CI + IT tPA = 30 versus CI = 75	Vasospasm	CI + IT tPA = 13, CI = 15

Note: CI, cisternal infusion; DIND, delayed ischemic neurological deficits; EVD, external-ventricular drain; IT tPA, intrathecal injection of tissue-type plasminogen activator; LD, lumbar drain; shake, head shake during procedure; fixed, head held in fixed position during procedure.

the best protocol for blood clearance to mitigate postaneurysm securement complications.

A computational model of CSF filtration could help understand and optimize blood clearance from the CSF system. At present, only one published computational model of CSF filtration using an anatomically idealized geometry has been brought forth by Tangen et al. [29]. This novel study provided information about the potential of CSF filtration to assist with blood removal. Empirical models limit our ability to investigate CSF filtration technologies, highlighting the need for a computational tool. Human clinical trials have been conducted (PILLAR trial [30,31]), but these studies lack real-time visualization of blood distribution and are only able to sample CSF from select locations. A rabbit model for filtration of cryptococcal meningitis from CSF has been brought forth, but requires modifications to the system and approach due to a small subarachnoid space [32]. Also, in principle, a nonhuman primate experimental model of SAH could be developed, but such primate studies are expensive, only available at limited research centers, and have different CSF dynamics than humans [33–36].

Thus, the present study objective was to formulate a computational model of CSF filtration incorporating a novel dual-lumen CSF flow looping catheter, also termed “Neurapheresis” therapy (Fig. 1) [32]. In brief, Neurapheresis therapy involves aspiration of CSF from the lumbar spinal subarachnoid space (SSS), filtration of CSF pathogens specific to the disease, removing it to a waste bag, and then return of the CSF to the SSS at the thoracic spine. The different location of the aspiration and return port results in an induced CSF flow between the ports. We sought to first investigate the impact of the Neurapheresis system on CSF flow velocities and steady streaming, as it is not yet known what impact Neurapheresis therapy has on these parameters under different operating conditions and how it compares to lumbar drain devices for SAH blood removal.

2 Materials and Methods

To study the impact of the CSF filtration system (Fig. 1), a CFD model was built to represent SSS anatomy with the Neurapheresis dual-lumen catheter located at the midline of the dorsal subarachnoid space (Fig. 2). In summary, the CFD model involved: (1) specification of the SSS geometry based on anatomic magnetic resonance (MR) imaging and dual-lumen catheter shape, (2) specification of flow boundary conditions, (3) analysis of CSF velocities with Neurapheresis therapy applied and, for comparison, with lumbar drain alone.

2.1 Specification of Model Geometry. For the model geometry, we utilized a previously developed anatomically realistic open-source three-dimensional intrathecal space model with spinal cord nerve rootlets [34]. In brief, the magnetic resonance imaging (MRI) protocol and image segmentation methods used to form the anatomic boundaries for the model are described in detail by Khani et al. [33,35] and Sass et al. [34]. In brief, T2-weighted anatomic MRI was acquired for a 23-yr-old female volunteer using a 3T MRI system (Fig. 1). The MR images were manually segmented by an expert trained operator to define the spinal cord and dura geometry along the spinal axis. Thirty-one pairs of idealized dorsal and ventral spinal cord nerve roots were added to the model based on the MR imaging and review of the literature related to cadaveric measurements of nerve root radicular line, descending angle, and other geometric features [34].

A dual-lumen catheter geometry was added to the posterior SSS at the L3–L4 level and positioned at the midline (Fig. 2). The posterior SSS was chosen for catheter placement since the catheter would be inserted posteriorly via a lumbar puncture needle. Also, the dorsal subarachnoid space posterior to the cord is wider than the ventral subarachnoid space. Thus, the catheter is most likely to naturally position within that region of the SSS. The catheter termination was located at the T2 vertebral level. The catheter has a five French outer diameter that tapers to approximately three French near the distal (thoracic placed) end. The catheter had two series of holes located 300 mm apart, designed for redundancy to avoid the case of blockage or clogging. The holes located near the catheter termination (T2) allowed fluid to return from the filtration

Fig. 1 Schematic of the Neurapheresis filtration system. CSF is removed from the lumbar spine at the aspiration port of a dual lumen intrathecal catheter. Blood is then removed from the CSF by the external filtration system. The filtered fluid is then returned to the CSF system in the upper thoracic spine via the dual lumen catheter. Note: the flow rate of fluid returned to the system is slightly less than that aspirated due to the loss of volume removed by the filtration system. The loss in fluid is compensated for by production of CSF within the ventricles.

Fig. 2 (a) Overview of three-dimensional CFD model of the subarachnoid space with inserted Neurapheresis catheter. (a1)–(a4) Details of computational meshes for the Neurapheresis catheter: (a1) magnified view of the return port with arrows indicating flow direction. (a2) Magnified view of the surface mesh near the return port catheter tip. (a3) Magnified view of the aspiration port with arrows indicating flow direction. (a4) Magnified view of the surface mesh near the aspiration port. (b) Volumetric and surface mesh visualization with zoom of the upper cervical spine. (c) Subject-specific CSF flow rates imposed by the computational model based on in vivo phase-contrast MRI measurements obtained at C2–C3, C7–T1, and T10–T11 vertebral levels.

system and enter the SSS (return, Figs. 2(a1) and 2(a2)). The proximal holes located near L2 allowed aspiration of fluid from the SSS to the filtration system (Figs. 2(a3) and 2(a4)).

An unstructured tetrahedral computational mesh of the SSS and dual lumen catheter was generated using the ANSYS ICEM software (version 19.1, ANSYS, Inc., Canonsburg, PA) (Fig. 2(b)). The computational mesh was refined near the catheter return and aspiration ports to have a final mesh of 14.8×10^6 cells.

2.2 Specification of Computational Fluid Dynamics Model Flow Boundary Conditions. Flow boundary conditions were specified to reproduce subject-specific nonuniform CSF flow along the spine (Fig. 2(c)) and the catheter system aspiration and return flow rates. Thus, we applied our previously developed method for nonuniform dura deformation to reproduce subject-specific CSF flow along the spine [33,35]. In brief, this method involved a user-defined function that introduces spring-based mesh deformation of cells near the dura to reproduce the local

CSF flow waveforms that are measured by MRI. Stroke volume was 0.76 mL per cardiac cycle at the C2–C3 level with a nonuniform decline in amplitude caudally along the spine (Fig. 2(c)).

Boundary conditions were applied to represent the catheter flow at the aspiration and return port under varying flow rates while maintaining a fixed difference between the two, called the waste rate, of 0.2 mL/min (Table 2). “Maximum flow” represented Neurapheresis flow with an aspiration and return flow rate of -2.0 and $+1.8$ mL/min, respectively. The net direction of the induced flow was craniocaudal ($\downarrow$), where negative values represent fluid removal from the system and vice versa. The return rate was not identical to aspiration, as blood is filtered out of the CSF and diverted to waste (Fig. 1) and therefore, return flow rate is equal to the aspiration flow rate minus the waste rate. Also, it is expected that for safety reasons, the magnitude of CSF volume removal should not exceed CSF production rate that is estimated to be ~ 500 mL/day or 0.35 mL/min [37]; in practice, this is often translated to a lumbar drainage rate of ~ 10 mL/h to remain below

Table 2 Specification of flow rates at the Neurapheresis catheter aspiration and return port

Name	Type	Flow direction	Aspiration (ml/min)	Return (ml/min)
Maximum flow	Neurapheresis flow at maximum rate	$\downarrow$	-2.0	$+1.8$
Low flow	Neurapheresis flow at low rate	$\downarrow$	-0.5	$+0.3$
No flow	Neurapheresis therapy off	N/A	0.0	0.0
Lumbar drain	Lumbar drain	$\downarrow$	-0.2	0.0
Dynamic mesh off	Neurapheresis flow at maximum rate with No CSF pulsation	$\downarrow$	-2.0	$+1.8$
Reverse flow	Neurapheresis flow with reverse loop	$\uparrow$	$+1.8$	-2.0

Note: + represents flow into the control volume, – represents flow out of the control volume, $\downarrow$ indicates flow loop applied in the craniocaudal direction, $\uparrow$ indicates flow loop applied in the caudocranial direction.

this production rate. “Low flow” was similar to Maximum Flow except with a 4× reduced aspiration rate of −0.5 ml/min and a corresponding 6× reduced return rate (0.3 ml/min) to maintain a waste rate of 0.2 ml/min. To help understand the impact of induced flow direction, aspiration and return locations were inverted in “reverse flow.” In “dynamic mesh off,” we turned off the dynamic mesh motion to help understand the individual impact of CSF pulsation compared to Neurapheresis therapy on its own. “No flow” was conducted with the induced flow turned off to show the effect of the presence of the catheter alone. “Lumbar drain” was applied to represent a lumbar drain with a typical aspiration rate of 0.2 ml/min. For that case, the catheter geometry remained within the SSS, but the return port was turned off, thus only allowing CSF to be drained from the port at the lumbar region. This case provides a baseline for the cases with non-zero return flow.

The simulated transient flows resulted in a net flow into the SSS of 0.2 ml/min from the cranial opening due to the difference in aspiration and return flow rates (for all cases except no flow). This flow rate of 0.2 ml/min is approximately equivalent to the assumed CSF production rate. The model outlet was specified as a zero pressure outlet with fluid free to enter/exit at the outlet. We did not simulate how decreasing SSS volume would affect intracranial pressure. The focus of this study was on the flow loop’s effect on transient CSF velocities and steady streaming within the spine.

Cerebrospinal fluid was modeled as an incompressible fluid with a density of 993.8 kg/m³ and viscosity of 0.693 mpa s (equivalent to water at body temperature) [38,39]. Unsteady CSF velocity field was computed using ANSYS FLUENT 19.1 (ANSYS, Inc., version 19.1, Canonsburg, PA) by solving the continuity equation (Eq. (1)), and Navier–Stokes equation (Eq. (2)) where ρ is the density, μ is the viscosity, $\vec{u}(\vec{x}, t)$ is the velocity vector, and p is the pressure field

$$\vec{\nabla} \cdot [\rho \vec{u}(\vec{x}, t)] = 0 \quad (1)$$

$$\rho \frac{\partial \vec{u}}{\partial t} + \rho \vec{u} \cdot \vec{\nabla} \vec{u} = -\vec{\nabla} p + \vec{\nabla} \cdot \mu \vec{\nabla} \vec{u} \quad (2)$$

Details on mesh, cycle, and time-step independence studies for this model with nonuniform dura deformation and anatomically realistic nerve roots are provided in our previous research [35]. Results were obtained for the second flow cycle with a time-step size of 0.01 s (total cardiac cycle = 0.85 s), second-order momentum and pressure gradient solver, and convergence criteria of 1×10^{-6} for velocity, continuity, and momentum.

2.3 Analysis of Cerebrospinal Fluid Velocities. Cerebrospinal fluid flow was quantified in terms of axial distribution of Reynolds number, $Re(z)$, and velocity contours around the catheter aspiration and return ports. $Re(z)$ was calculated as $Re(z) = \frac{|Q_{\max}(z)|D_H(z)}{\nu A_{cs}(z)}$, where $D_H(z)$ is hydraulic diameter, $|Q_{\max}(z)|$ is the absolute value of the peak flow rate, $A_{cs}(z)$ is the cross-sectional area at each 1 mm slice along the z -axis and ν is kinematic viscosity. Velocity streamlines were visualized based on line sources located within the catheter lumen proximal to the return and aspiration holes.

As detailed in our previous study [35] and by others [40], oscillatory flow within an eccentric annulus can result in steady-streaming CSF velocities due to convective acceleration. To visualize steady streaming along the spinal axis, the cyclic mean z -velocity, $U_{z-\text{mean}}$, at each node was calculated. The cross-sectional steady-streaming velocity magnitude was also calculated as

$$U_{ss}(z) = \frac{\sum_{\text{cell}} |U_{z-\text{mean}}(z)| V(z)}{\sum_{\text{cell}} V(z)} \quad (3)$$

Table 3 Average steady-streaming velocity magnitude, $U_{ss}(z)$, and nondimensional fraction of flow rate amplitude, $Q_{ss}(z)$, for the simulations analyzed

Name	Mean $\pm$ standard deviation (mm/s)	Mean $\pm$ standard deviation
Maximum flow	0.190 $\pm$ 0.133	0.154 $\pm$ 0.138
Low flow	0.105 $\pm$ 0.103	0.063 $\pm$ 0.030
No flow	0.088 $\pm$ 0.108	0.041 $\pm$ 0.026
Lumbar drain	0.093 $\pm$ 0.107	0.048 $\pm$ 0.023
Dynamic mesh off	0.130 $\pm$ 0.135	0.129 $\pm$ 0.155
Reverse flow	0.174 $\pm$ 0.115	0.143 $\pm$ 0.139

where $|U_{z-\text{mean}}(z)|$ is the absolute value of $U_{z-\text{mean}}$ in the z -direction and $V(z)$ is the cell volume at each axial location along the z -axis. To see the effect of different Neurapheresis scenarios, $U_{ss}(z)$ and $U_{z-\text{mean}}$ were compared for all cases (Table 3). $U_{ss}(z)$ is impacted by the cross-sectional area. Thus, as described in our previous study, a nondimensional fraction of flow rate amplitude, $Q_{ss}(z)$, was computed as

$$Q_{ss}(z) = \frac{U_{ss}(z)A_{cs}}{2Q_{\max}(z)} \quad (4)$$

3 Results

3.1 Cerebrospinal Fluid Flow Velocities. For Maximum flow, maximum Re was 180 and located within the cervical spine (Fig. 3(a)). Visualization of unsteady CSF velocity contours in the sagittal plane (Fig. 3(b)) showed that peak CSF velocities occurred in the cervical spine. Unsteady CSF velocity magnitudes were nearly identical across all cases (not shown). CSF velocity profiles near the aspiration and return ports showed that most of the flow into and out of the domain originated from the first four holes at the return port and the first two holes at the aspiration port, respectively (Figs. 3(b1)–3(b4)).

3.2 Steady-Streaming Cerebrospinal Fluid Velocity Quantification. The Neurapheresis flow loop altered $U_{z-\text{mean}}$ velocity profiles within the catheter flow loop region, depending on rate and direction (Fig. 4). $U_{z-\text{mean}}$ velocity profiles were affected little outside of the flow loop region (above the return port and below the aspiration port) for all cases analyzed. Lumbar drain had a lower impact on steady streaming in comparison to maximum flow, low flow, and reverse flow. No flow was most similar to lumbar drain. Neurapheresis flow reversal (reverse flow) drastically altered the direction of $U_{z-\text{mean}}$. The sagittal $U_{z-\text{mean}}$ velocity profiles for maximum flow, low flow, no flow, and lumbar drain (Fig. 4) showed a region of caudally directed ($\downarrow$) $U_{z-\text{mean}}$ in the posterior SSS in the middle thoracic spine and in the anterior SSS in the cervical spine. Reverse flow showed a similar trend, but with an opposite cranial direction ($\uparrow$) within the catheter region. Dynamic mesh off showed similar $U_{z-\text{mean}}$ values within the catheter region, but $U_{z-\text{mean}}$ was decreased in the region cranial to the return port compared to maximum flow.

In comparison to lumbar drain, the cases for maximum flow, low flow, and reverse flow resulted in greater $U_{ss}(z)$ and $Q_{ss}(z)$ (Fig. 5). For all cases with Neurapheresis flow applied, the increase in steady streaming had little impact outside of the catheter region. Greater Neurapheresis flow rate increased $U_{ss}(z)$ within the flow-loop region (Fig. 5(a)). Average value for $U_{ss}(z)$ was 0.19 ± 0.13 and 0.09 ± 0.11 mm/s (mean $\pm$ stdev) for maximum flow versus no flow (Table 3). The region of greatest difference in $U_{ss}(z)$ values was located between the return and the aspiration ports in the thoracic and lumbar spine (T2–L2) that had up to 3× larger value of $U_{ss}(z)$ in maximum flow compared to no flow.

Fig. 3 (a) Reynolds number distribution computed along the spine for the maximum flow simulation. (b) Visualization of sagittal velocity magnitude profiles simulated by CFD at 0.06 s time-point (Fig. 2(c)). (b1) Magnified coronal view of the return port. (b2) Magnified transverse view of the CSF flow field near the return port showing diffusivity of the returned flow near the first hole. (b3) Magnified view of the aspiration port. (b4) Magnified transverse view of the CSF flow field near the aspiration port. Note: To help visualize the entire spine, z-scaling of the geometry is set at 0.5 with respect to x and y-dimensions. Thus, spine curvature appears greater than without scaling.

Fig. 4 Visualization of midsagittal steady-streaming CSF velocity profiles for all cases analyzed (Table 2). Steady-streaming CSF velocities, $U_{z-\text{mean}}$, increase with Neurapheresis therapy (maximum flow, low flow, reverse flow, and dynamic mesh off) compared to lumbar drain (lumbar drain) and with Neurapheresis therapy off (no flow). Placement of return and the aspiration ports shown with dotted lines for reference. Note: To help visualize the entire spine, z-scaling of the geometry is set at 0.5 with respect to x and y-dimensions. Thus, spine curvature appears greater than without scaling.

Fig. 5 (a) Steady-streaming velocity magnitude, U_{ss} , and (b) nondimensional fraction of flow rate amplitude, Q_{ss} , increases with Neurapheresis therapy compared to lumbar drain only between the return and the aspiration ports. Dotted lines indicate that maximum U_{ss} occurs close to the aspiration and the return ports and at the cervical spine near the intersection of spinal cord nerve roots into the dura.

$Q_{ss}(z)$ (Fig. 5(b)) showed a trend similar to $U_{ss}(z)$ for lumbar drain compared to low flow. The average value for $Q_{ss}(z)$ was 0.154 ± 0.138 and 0.041 ± 0.026 for maximum flow and no flow (Table 3).

4 Discussion

The objective of this study was to apply CFD modeling to investigate the impact of a dual-lumen CSF filtration catheter system, Neurapheresis therapy (Fig. 1) [32], on intrathecal CSF velocities. The operating principle of this system is to introduce an intrathecal flow loop by a dual lumen catheter that removes CSF in the lumbar spine at an aspiration port, filters the CSF externally, and returns CSF to the upper thoracic spine via the same catheter. The return flow rate is not identical to the aspirated flow because some material is filtered out; in the case of SAH, that material is blood. We sought to parametrically quantify how the catheter system, operating under varying flow rates and flow directions, impacts intrathecal CSF velocities and steady-streaming flow dynamics [35] and compared results to a lumbar drain operating under a typical drain rate. The lumbar drain was

selected for comparison because it is used in select centers for CSF blood removal post-SAH (Table 1). CFD modeling was utilized to predict the catheter impact on CSF dynamics because invasive parametric studies are not feasible to conduct on SAH patients. Also, noninvasive measurement of CSF flow velocities by phase contrast MRI [41] is not accurate enough to quantify the relatively small alterations in net CSF flow velocities introduced by the flow loop system or lumbar drain.

4.1 Physiologic Performance Considerations. Neurapheresis therapy was found to have nearly zero impact on CSF velocities in comparison to normal cardiac-induced physiologic CSF movement. Therefore, it is not expected that these alterations to CSF velocities would, on their own, have ramifications to the normal physiology. Previous research has shown that peak cardiac-induced CSF velocities in healthy people range from 2 to 4 cm/s within the intrathecal space [42–45]. Our findings show that Neurapheresis therapy induced CSF velocities ($U_{z-\text{mean}}$) do not exceed 0.08 cm/s for the Maximum Flow (Fig. 4). These scale proportionately smaller for the low flow case. As such, these cross-sectional average velocities are 1–2 orders of magnitude

smaller than normal peak cardiac-induced CSF velocities. Thus, for the boundary conditions applied in our study, it is likely that the impact of Neurapheresis flow is a relatively small change superimposed on normal cardiac pulsations. More information on Neurapheresis system safety in humans will be available following publication of the PILLAR trial (publication pending) and the ongoing Neurapheresis “PILLAR XT” clinical trial [31,46].

4.2 Impact of Neurapheresis Flow on Cerebrospinal Fluid Dynamics. Neurapheresis therapy increased $U_{z-\text{mean}}$ and $U_{ss}(z)$ greatly within the space between the return and the aspiration ports and to a lesser degree everywhere else in the model (Figs. 4 and 5). Local elevation of $U_{ss}(z)$ occurred near the first few return port holes that expelled $>80\%$ of the returning CSF (see the spikes highlighted with dotted lines in Fig. 5). $U_{ss}(z)$ was much higher for the maximum flow compared to no flow (Fig. 5). To put the numbers in context, the maximum value of $U_{ss}(z)$ within the region between the infusion ports was only 0.17 mm/s without Neurapheresis therapy (no flow) and 0.77 mm/s with Neurapheresis therapy (maximum flow) compared to peak cardiac-related CSF velocities that ranged up to ~ 25 mm/s. Thus, for the presented model boundary conditions, Neurapheresis therapy induced steady streaming velocities, $U_{ss}(z)$, were more than $35\times$ smaller than normal physiologic cardiac-related CSF velocities.

The effect of Neurapheresis system on steady streaming was localized to the SSS region between the aspiration and return ports. Titration of Neurapheresis procedure rate showed a corresponding decrease in $U_{z-\text{mean}}$ profiles and reverse flow showed a relatively equal, but opposite, effect on steady streaming compared to maximum flow between the aspiration and return ports (Figs. 4 and 5). All cases analyzed had nearly zero impact on streaming structures outside that region (above and below the ports). However, within the region above the return port, there is considerable steady streaming that is naturally introduced by the presence of vortices that form around spinal cord nerve roots due to CSF oscillations [35,47]. This can be observed by comparing maximum flow to dynamic mesh off (Figs. 4 and 5). Further research is needed to understand how Neurapheresis flow impacts advection and removal of specific solutes from the CSF and what impact the waste and CSF production rate may have on results.

4.3 Comparison of Results to Previous Studies in the Literature. To our knowledge, one study has been previously conducted by Tangen et al. [29] to examine CSF filtration. For that study, Tangen et al. used a bench top and multiphase CFD model to assess the efficacy of different lumbar drainage rates and patient orientations (incline, supine, upright) on blood removal from the CSF. The model used an anatomically idealized CSF system with cylindrical shaped spinal cord nerve roots and a rectangular-shaped intracranial compartment. They found that forced purification (lumbar to intracranial flow loop) in the upright position maximized blood clearance. CFD results compared favorably with in vitro experiments with a similar geometry. It is not possible to compare our CFD model results to Tangen et al., since our focus was on the impact of Neurapheresis flow on intrathecal CSF velocities and steady-streaming transport and not on its effect on solute removal.

Prior literature has applied various geometric and flow boundary conditions. Our CSF velocity profiles showed similar flow fields (Fig. 3) to previously published studies with spinal cord nerve roots [47–50]. Additionally, the present model with a catheter showed nearly identical results to our previous model having the same geometry, but without a catheter in place [35]. However, the previous studies incorporating spinal cord nerve roots did not investigate the impact of Neurapheresis flow or lumbar drain on CSF velocities. In both studies, we also utilized an anatomically realistic open-source three-dimensional intrathecal space model with spinal cord nerve rootlets [34] and a nonuniform moving boundary motion of the dura to replicate subject-specific CSF

flow along the SSS. An advantage of the open-source model is that it will allow direct comparison of CFD results of other researchers who use the model in the future. Future work may include building upon the model to understand impact on solute removal, validation of results against in vitro experiments, and comparison of CFD results using different solvers.

4.4 Potential Benefit of Neurapheresis System Computational Model for Cerebrospinal Fluid Filtration Protocol and Device Development. The CFD model presented offers a platform to understand intrathecal device behavior as well as envision alternative Neurapheresis system protocols and devices. For example, the presented platform can help quantify how different catheter designs and implantation locations may affect CSF velocities. This model also allows alteration of the SSS geometry and CSF flow pulsation along the spine to determine their individual affects. These alterations are not possible to conduct within humans and are also difficult, if not impossible, within animal models. Our initial study design was to investigate Neurapheresis therapy under a variety of flow rates and different flow-loop directions and compare results to a typical lumbar drain. Future studies are possible to conduct according to potentially clinically relevant questions and/or CSF filtration device designs.

5 Limitations

Our focus was only on the SSS, since the Neurapheresis system was located within that space. Therefore, this study did not take into account the impact of the cranial SSS. This model also lacks some of the fine anatomical structures such as arachnoid trabeculae, blood vessels, and denticulate ligaments. In addition, the catheter was positioned in the posterior SSS, because it is the most likely location where a catheter would be inserted. We did not investigate the impact of the catheter location around the spinal cord. Research has shown that catheter position can affect local solute distribution around the spinal cord on a small time scale (~ 1 s) [51]. It is unclear if these differences would propagate on a longer time scale.

We sought to verify the model with in vivo subject specific measurements of CSF flow rate at three axial locations along the spine. Our approach was to deform the dura to match MRI-derived CSF flow. In reality, it is possible that the dura does not deform at all, but rather, veins within the CSF are compressed. With current MR imaging techniques it is difficult to verify what is the exact location of deformation. Differences in the CSF pulse source location could, in principle, alter the results.

The MRI measurements used for this study did not allow direct validation of steady-streaming velocity results as these were <1 mm/s. Thus, the presented CSF velocity results are predictions to help elucidate the CSF velocities and steady-streaming flow patterns introduced by a CSF filtration device. Also, our modeling approach did not include respiratory component to CSF pulsations [52–54] because the MRI scanning time did not allow measurement of this parameter in addition to the other parameters used to formulate the model.

This study focused on the impact of Neurapheresis system on CSF flow velocities (advection) within the spine and how that compares with a lumbar drain. For these simulations, we did not investigate the impact of concentration gradients on movement of actual solutes such as blood products or inflammatory cells and exudates. We also did not include how blood may alter CSF viscosity. This is because the amount of blood in the CSF assumed in the model is small compared to the CSF volume (~ 300 mL) and not likely to significantly alter the viscosity. Further, as blood is slowly filtered out of the CSF, it is expected that CSF viscosity within the system could be time varying. The effect of gravity was not considered in this study since the density and viscosity of CSF were considered to be uniform in the model and the patient was assumed to be in the supine position. However, in principle, gravity can have an impact on CSF viscosity distribution within the

model. Taylor dispersion may affect how quickly blood is cleared from the CSF by enhancing solute spread within the cervical spine and also toward the aspiration port, as well as away from the aspiration port. Thus, consideration of advection only may overestimate actual blood clearance time.

6 Conclusion

Neurapheresis therapy may prove to assist removal of blood from CSF following SAH or enhance removal of other unwanted solutes. A subject-specific CFD model of intrathecal CSF dynamics was used to parametrically predict the impact of the Neurapheresis device on CSF dynamics under varying flow conditions. Results were compared to a typical lumbar drain used for blood removal from CSF. Neurapheresis therapy was found to significantly increase steady-streaming velocity magnitude compared to a lumbar drain. This effect was localized to the region within the Neurapheresis flow loop. The mean velocities introduced by the flow loop were small in comparison to normal cardiac-induced CSF velocities. Future multiphase simulations will be conducted to simulate multiphase solute transport for blood or other CSF solutes within the intrathecal space and validate model results against in vitro and/or in vivo measurements.

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Nomenclature

A	= area
A_{cs}	= cross-sectional area
CFD	= computational fluid dynamics
CSF	= cerebrospinal fluid
D_H	= hydraulic diameter
MRI	= magnetic resonance imaging
Q	= flow rate
Q_{max}	= peak flow rate
Q_{ss}	= nondimensional fraction of flow rate amplitude
Re	= Reynolds number based on hydraulic diameter
SAH	= subarachnoid hemorrhage
SSS	= spinal subarachnoid space
U	= velocity
U_{ss}	= steady-streaming velocity magnitude
U_{z-mean}	= cyclic mean z-velocity
V	= cell volume
μ	= dynamic viscosity (Pa · s)
ν	= kinematic viscosity ($m^2 s^{-1}$)
ρ	= density (Kg/m^3)

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