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Changing the Currently Held Concept of Cerebrospinal Fluid Dynamics Based on Shared Findings of Cerebrospinal Fluid Motion in the Cranial Cavity Using Various Types of Magnetic Resonance Imaging Techniques

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Abstract

The "cerebrospinal fluid (CSF) circulation theory" of CSF flowing unidirectionally and circulating through the ventricles and subarachnoid space in a downward or upward fashion has been widely recognized. In this review, observations of CSF motion using different magnetic resonance imaging (MRI) techniques are described, findings that are shared among these techniques are extracted, and CSF motion, as we currently understand it based on the results from the quantitative analysis of CSF motion, is discussed, along with a discussion of slower water molecule motion in the perivascular, paravascular, and brain parenchyma. Today, a shared consensus regarding CSF motion is being formed, as follows: CSF motion is not a circulatory flow, but a combination of various directions of flow in the ventricles and subarachnoid space, and the acceleration of CSF motion differs depending on the CSF space. It is now necessary to revise the currently held concept that CSF flows unidirectionally. Currently, water molecule motion in the order of centimeters per second can be detected with various MRI techniques. Thus, we need new MRI techniques with high-velocity sensitivity, such as in the order of 10 μm/s, to determine water molecule movement in the vessel wall, paravascular space, and brain parenchyma. In this paper, the authors review the previous and current concepts of CSF motion in the central nervous system using various MRI techniques.

Key words: cerebrospinal fluid, magnetic resonance imaging, perivascular space, paravascular space, glymphatic system

Introduction

According to the historical medical literature, cerebrospinal fluid (CSF) was first described by a Venetian physician, Massa, who depicted the presence of fluid within the ventricles.[1,2] Later, Cotugno[3] described the presence of a similar fluid also at the surface of the spinal cord. The term "CSF" that is used today was first coined by Magendie,[4] and it has since been used by many researchers and clinicians to describe the fluid that is widely distributed throughout the subarachnoid space and ventricular system (CSF space) at the surfaces and within the brain and spinal cord.

Cerebrospinal fluid is constantly in motion, maintaining communication among the brain, spinal cord, nervous system, and lymphatic and vascular systems.[5–12] In so doing, CSF has physical significance (buffer and buoyancy effects against external forces; transmitting vascular pulsation; buffer function of excess brain pulsation), as well as physiological significance (heat produced by neural activity; draining

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unnecessary substances from brain parenchyma; substance exchange among the brain parenchyma, spinal cord, and nervous system), thereby playing a crucial role in facilitating maintenance of nervous system function.[13–21] Thus, for CSF to fully display these functions, it cannot stagnate as fluid in the CSF space and must always be moving. Until recently, the dynamics of CSF had been described as "CSF flow" or "CSF circulation." Cathelin,[22] a French physician, is considered to be the first person to use the term "CSF circulation", and Cushing[23] later called it the "third circulation," distinguishing CSF circulation from the circulation of blood, lymph, and interstitial fluid (ISF). To visualize this CSF circulation, tracers such as air,[24] oil,[25] radioisotope,[26] and/or contrast material[27] were injected into the ventricles or the subarachnoid space to observe the bolus movement of the tracer over time. By following the movement of the tracer, a concept termed "CSF flow," analogous to unidirectional river flow, emerged. Specifically in "CSF flow," CSF in the ventricles seemingly descends in the caudal direction within the ventricles, ascends in the cephalic direction from the lower back area once it flows through the surface of the spinal cord, and mobilizes from the basal cistern to the Sylvian fissure laterally, ultimately reaching the convexity of the cerebrum.[26] Conveniently, the arachnoid granulations and villi are present around the major venous sinuses in this convexity of the cerebrum, and Key and Retzius[9] demonstrated that dye administered into the subarachnoid space accumulates at these arachnoid granulations and villi. Based on their observation, it was believed that CSF is absorbed at this site to return to the bloodstream and is secreted again from the choroid plexus, completing the CSF circulation. However, according to the traditional studies, Sweet et al.[28] concluded that the choroid plexuses do not appear to be necessary for the exchange of water between blood and CSF by studies with heavy water in normal human subjects in 1950. Hassin[29] proposed that CSF does not circulate, it acts as tissue fluid, it is not secreted by the choroid plexus, and it is not absorbed through the arachnoid granulation on pathological studies. Later, Milhorat[30] emphasized that the removal of substances from the brain parenchyma through the lymphatic role of the CSF becomes truly important. As a result, the currently held theory of bulk flow in the CSF space of CSF from the production site of the choroid plexus to the site of absorption at the arachnoid granulations or villi has been criticized.

With the emergence of magnetic resonance imaging (MRI),[31–37] findings that encourage a revision in the concept of "CSF flow" and "CSF circulation" have been discovered.[38] Every MRI method understandably has advantages and disadvantages based on its unique principle of imaging. However, it would be possible to determine the essence of CSF motion by taking findings that are shared among the imaging methods and aggregating them as the greatest shared factors. In this review, shared findings that were obtained through observing CSF motion in the CSF space using various types of MRI techniques are described, and the physiological significance of such findings is summarized.

Analysis of CSF Motion in the Ventricular System

CSF motion in the Sylvian aqueduct and foramen of Monro

Because of its luminal structure within the brain and because anatomically it is in the center of the cranium, many CSF motion studies focused on the Sylvian aqueduct. Feinberg et al.[32] used velocity density imaging to identify the CSF velocity through the Sylvian aqueduct; this study showed bi-directional CSF motion at the Sylvian fissure. Presumably, this was the first study to use MRI techniques to document CSF motion in the intracranial cavity. On phase contrast (PC) imaging, volumetric, almost sinusoidal, CSF motion through the Sylvian aqueduct during one cardiac cycle was shown by Bradley et al.[39] They also stated that CSF motion in the systolic phase was toward the caudal direction, and during diastole, CSF motion was in the cephalic direction.[39,40] Following this research, many investigators published similar research results using PC,[41–47] time-resolved three-dimensional phase contrast (3DPC),[48–51] echo-planar imaging (EPI),[52] and time-spatial labeling inversion pulse (Time-SLIP).[53,54] Investigation of dynamic improved motion-sensitized driven-equilibrium steady-state free precession (dynamic iMSDE SSFP) showed turbulent CSF motion that surged up from the Sylvian aqueduct to the third ventricle.[37] Currently, real-time imaging of cardiac and respiratory components of CSF velocity using simultaneous multi-slice PC EPI shows inspiration phase CSF directed superiorly into the ventricles and the foramen magnum, and it is reversed in the expiration phase, giving bi-directional respiratory motion.[55]

Changing the viewpoint to the foramen of Monro, there has been less investigation of the foramen of Monro than of the Sylvian aqueduct. However, when we review the investigations of the foramen of Monro, they reached the same conclusion that CSF shows bi-directional motion, and cardiac-related CSF motion was observed.[42,48] Surprisingly, Time-SLIP

and dynamic iMSDE SSFP demonstrated blow-up CSF motion from the third ventricle through the foramen of Monro.[37,54] To summarize the results, at the foramen of Monro and the Sylvian aqueduct, which connect each ventricular system, CSF shows bi-directional motion. Figures 1–3 show typical CSF motion in volunteers with different MRI sequences.

CSF motion in the ventricles

When understanding CSF motion in the ventricles, it is easy to understand the physical perspective, not only directional CSF motion and velocity imaging in the ventricles, but also by grasping the acceleration of the CSF in the ventricles. There have been few studies focusing on the quantitative analysis of physical variables.[50,56] In Fig. 4, representative previous results show the acceleration in various parts of the intracranial cavities.[56] Quantitative analysis of CSF acceleration in the ventricular system showed that CSF acceleration was greater in the third and fourth ventricles than in the lateral ventricle. Imaging analysis using 3DPC, Time-SLIP, and dynamic iMSDE SSFP showed increased CSF velocity, and marked turbulent motion in the third and fourth ventricles was noted by several researchers.[37,42,49,54,57,58] Thus, both imaging and quantitative evaluations resulted in the same conclusion that the third and fourth ventricles are in a hyperdynamic state. The third ventricle is anatomically located at the center of CSF movement in the ventricular system; it is small and has an important function in CSF motion in the ventricular system, and it is caught between the two thalami. O'Connell[59] proposed that capillary flow into the brain parenchyma during the systolic phase causes expansion of the brain parenchyma. Thus, squeezing of both sides of the thalami at the third ventricle was thought to be the driving force of CSF pulsation; presumably this squeezing leads to acceleration of CSF motion in the third ventricle, and, for this reason, the third ventricle acts as a CSF pump. Another approach to CSF motion using MRI described by Sunohara et al.[60,61] determined the correlation between the velocity waveforms, as well as the delay time, and found that the CSF motion of the ventral surface of the brainstem is correlated with that of the third and fourth ventricles. It may be possible to surmise from these findings that the origin of the CSF motion in the third ventricle is pulsation of the arteries. However, the velocity propagation of the pulsation is extremely fast compared with the lateral ventricle, and different results are also obtained depending on the location of reference, indicating the need for additional studies. CSF motions of the fourth ventricle and ventral surface of the brainstem are also highly correlated,[60–62] likely due to the CSF communication between the fourth ventricle and the subarachnoid space around the brainstem that is directly connected through the foramen of Magendie and the foramen of Luschka.

Quantitative analysis of CSF motion shown in Fig. 4 demonstrated a gentle CSF acceleration at the trigone compared with other ventricles,[56] consistent with results from 3DPC imaging evaluations.[48,56] Focusing on the ventricular system, although it has been classically described that CSF pulsation originates from the choroid plexus,[63] it has been reported that the choroid plexus of the trigone at the very least does not undergo a large enough volumetric change to become a driving force of CSF.[48,56] This finding is accepted by clinicians, because this pulsation in the choroid plexus has also been questioned when observed under neuroendoscopic examination.[64] On the other hand, CSF motion in the lateral ventricles, far from the basal cistern, has a poor correlation with the CSF motion in the ventral surface of the brainstem,[60,62] and, in particular, the CSF motion in the trigone of the lateral ventricles, farthest away from the basal cistern, has a lower correlation with the CSF motion in the ventral surface of the brainstem.[61] Figures 1–3 show typical CSF motion in volunteers with different MRI sequences.

CSF motion in the subarachnoid space

Cerebrospinal fluid motion in the subarachnoid space of the ventral surface of the brainstem is quite vigorous on 3DPC, Time-SLIP, and dynamic iMSDE SSFP.[37,48,50,54,65] Because a bony structure (the clivus) is present at the front of the subarachnoid space on the ventral surface of the brainstem, and the vertebro-basilar artery is traveling in the subarachnoid space on the ventral surface of the brainstem over a long distance, which extends along the perpendicular direction inside the subarachnoid space, and is surrounded by CSF, the anatomical structure is set up such that the heartbeat easily propagates through arteries to the subarachnoid space.[48] On the upper cervical spine, the venous plexus of the epidural space pulsates in response to intrathoracic pressure changes, and this vigorous CSF motion related to respiration may be spread in the ventral surface of the brainstem and propagate in the upward direction, thereby causing CSF motion to become active, with both arterial and respiratory elements complementing each other. These results are consistent with those of other studies that have used EPI and showed that respiration and cardiac pulsation both affect CSF movement at the cervical level.[66,67]

Within the Sylvian fissure, vigorous CSF motion in the proximal Sylvian fissure decreased laterally,

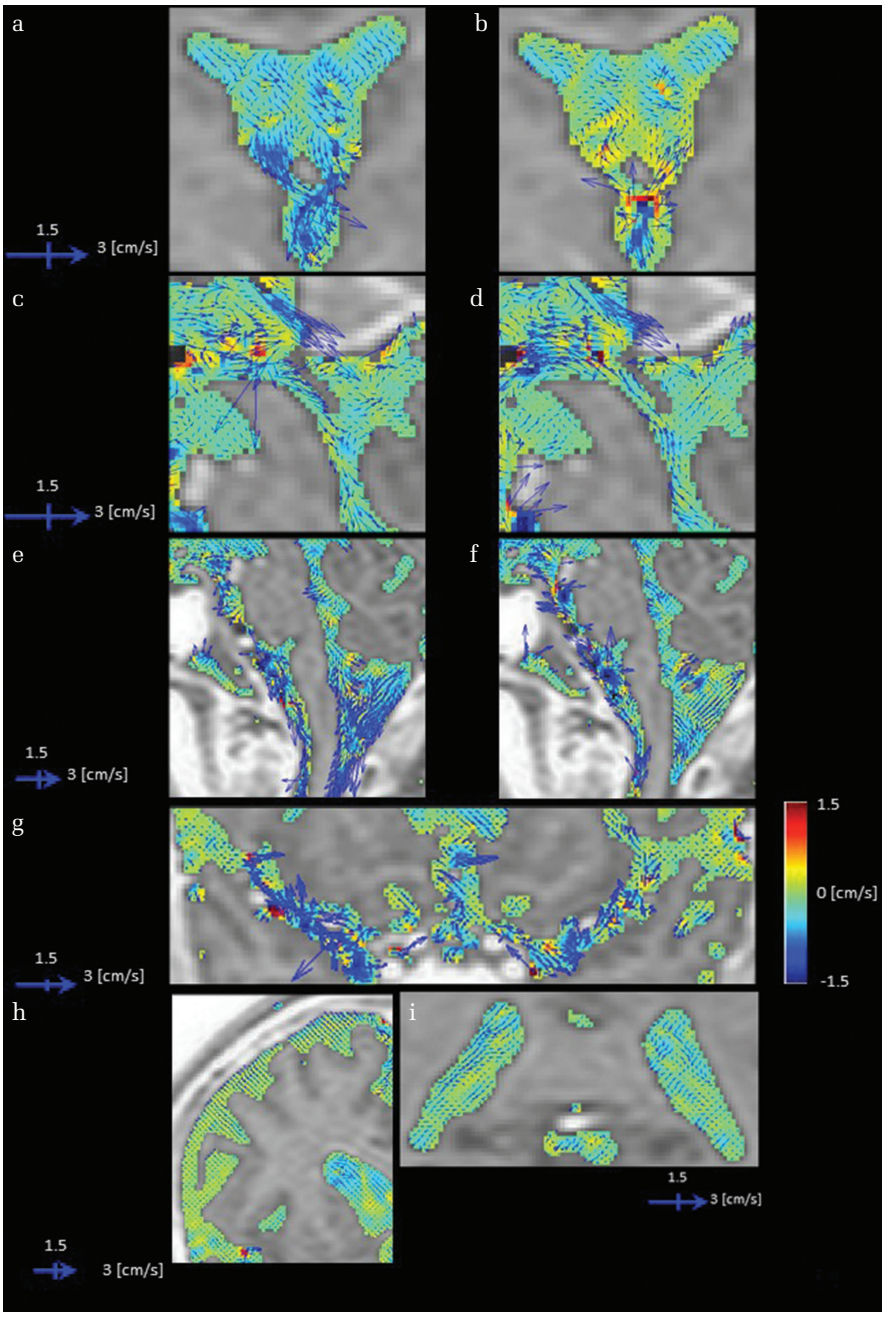


Fig. 1 Images of cerebrospinal fluid (CSF) velocity with 3DPC in a healthy volunteer. CSF velocity in each imaging plane is represented by the vector length and direction, while the velocity orthogonal to the imaging plane is shown by color coding. The vectors and color scales are as displayed. Sites with irregular motion show long vectors that point in various directions with colors that also change. In addition, blood flow-derived velocity components (non-CSF components) arising from inside the blood vessels were subtracted and removed from the images. Rotational motion within the anterior horn as a vector (a), and the antero-posterior direction as changes on a color scale (b). A motion that ascends toward the lateral and the third ventricle (b and d) and conversely descends toward the third and fourth ventricle (a and c). Irregular motions are evident in the third ventricle based on rotational motion expressed as long vectors and the large change in color display that represents motion orthogonal to the imaging plane (a–d). In the fourth ventricle, augmented motion is observed (e and f). A gentle motion is observed in the trigone (i). A strong motion is shown to strengthen toward the subarachnoid space of the upper cervical spine (e and f). An active CSF motion proximal to the Sylvian fissure that attenuates as it transmits laterally (g), although motion is gradually attenuated toward the distal Sylvian fissure. An augmented motion in a limited area near the vascular structure (g). A suppressed motion seen in convexity (h).

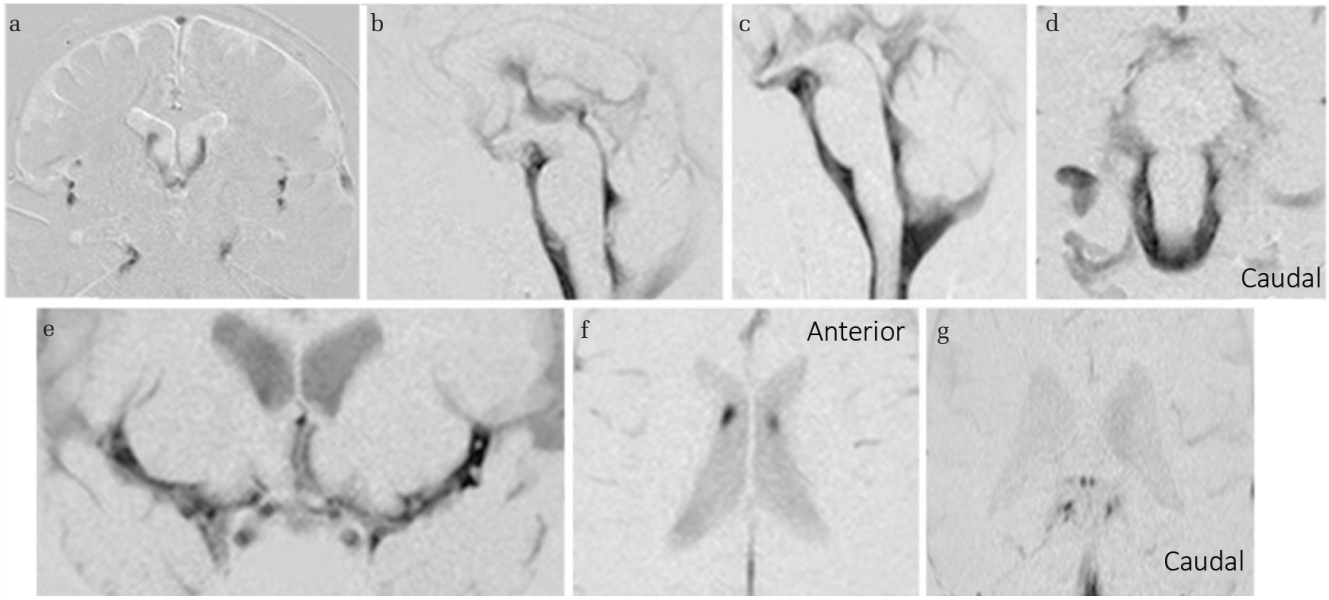


Fig. 2 Cerebrospinal fluid (CSF) motion in a healthy individual visualized using dynamic improved motion-sensitized driven-equilibrium steady-state free precession (dynamic iMSDE SSFP). In dynamic iMSDE SSFP, the dark regions on the grayscale images indicate vigorous CSF motion. The image contrast is achieved by the signal attenuation induced by irregular motions in each site compared with the surrounding site where CSF moves relatively mildly. With dynamic iMSDE SSFP, irregular motion is observed at the anterior horn, but not at the posterior half of the lateral ventricles (a and b). A motion that sprayed upward from the third ventricle to the anterior horn is visualized (a and b). Augmented motion at the Sylvian aqueduct is observed (b). Turbulent motions are evident in the third and fourth ventricles (b and c). Increased turbulent motion around the brainstem is observed (c and d). A turbulent motion proximal to the Sylvian fissure that attenuates as it transmits laterally (e). Although this augmented motion gradually attenuates toward the distal part of the Sylvian fissure, it also shows limited turbulence near the vascular structure (e). However, motion that attenuates toward the convexity of the cerebrum is not subsequently affected by additional driving forces and is visualized to maintain a suppressed movement (e). Depressed turbulent motion in the convexity is observed (a). Suppressed motion is observed in the trigone (f and g).The axial image shown in (f) confirms irregular motion propagated from the foramen of Monro at the anterior horn, but not at the posterior half of the lateral ventricles.

and anatomically, arachnoid trabeculae exist in a complex manner along with the vascular system.[68,69] It is postulated that, due to these structures, CSF motion becomes buffered as it moves from the center toward the distal part of the cranial cavity.[37,48] At the areas distal to the Sylvian fissure, which is part of the subarachnoid space, and at the convexity of the cerebrum, slow CSF motion is predominantly observed; however, it has been reported that CSF motion increases, although in a limited manner, around the vascular structure within this area.[56] It is evident from this finding that there is irregularity in the movement of CSF around the vascular structure within the subarachnoid space.

At the convexity of the cerebrum far from the basal cistern, CSF appeared to be stagnant on Time-SLIP,[70] and minimal CSF motion was observed on dynamic iMSDE SSFP and 3DPC.[37,48,50,56] With Time-SLIP, it is possible to observe CSF motion for 1–6 s after applying a radio frequency pulse to the region of interest,[54] and it appeared that CSF was stagnant at the convexity of the cerebrum during these 1–6 s. 3DPC showed decreased velocity and acceleration of CSF at the convexity of the cerebrum.[48,50,56] When the shared findings of the 3DPC, dynamic iMSDE SSFP, and Time-SLIP methods were extracted, the movement of CSF appeared to be quite suppressed at the convexity of the cerebrum. These findings, specifically that CSF motion was attenuated as it passed through the basal cistern and transmitted to the convexity of the cerebrum, are consistent with results demonstrated in many other articles.[37,48,50,54,56] Figures 1–3 show typical CSF motion in volunteers with different MRI sequences. The quantitative analysis and imaging analysis of CSF motion described above showed the mutual findings listed in Table 1.

Representative typical MRI studies to describe CSF motion

Every MRI method understandably has advantages and disadvantages based on its unique principle of imaging. However, it would be possible to determine

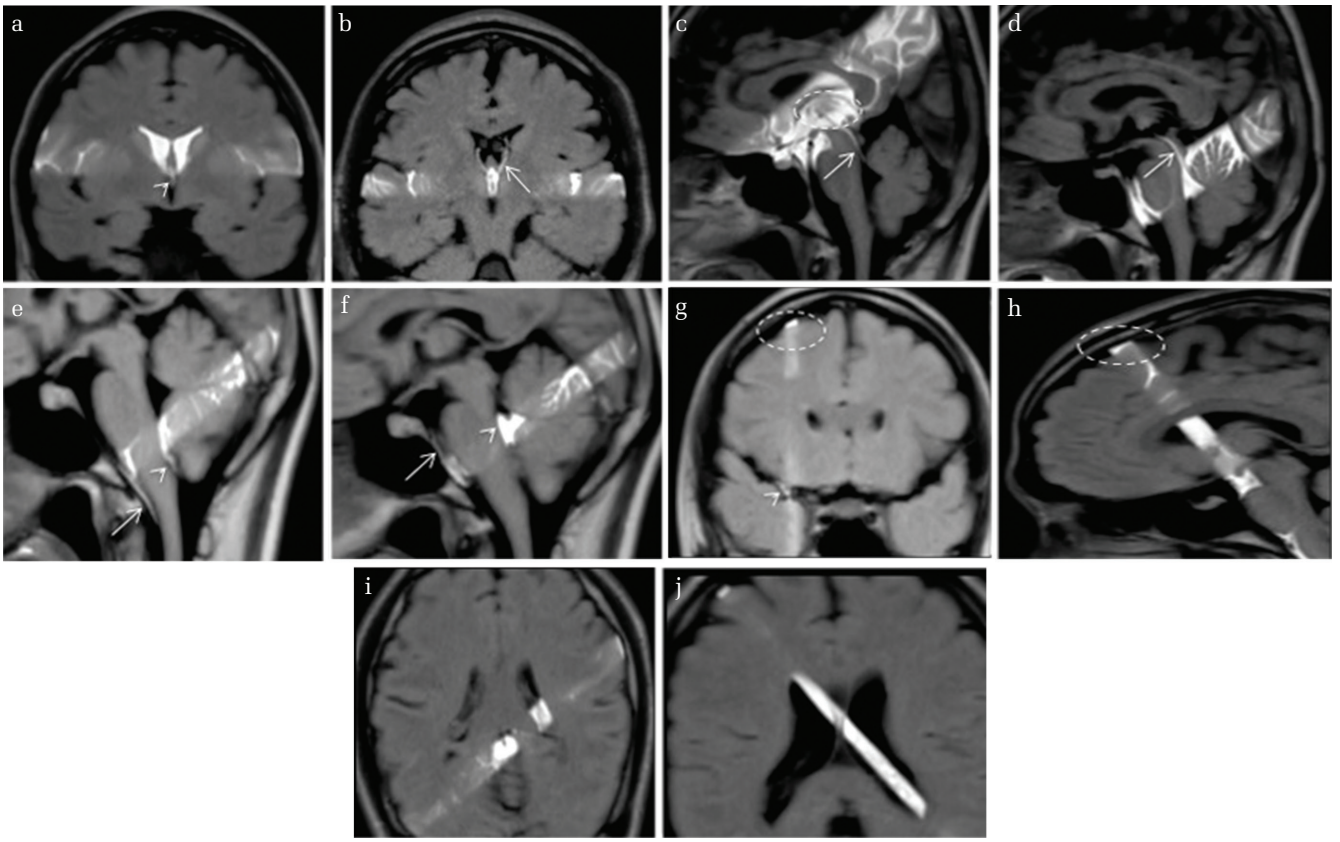


Fig. 3 Cerebrospinal fluid (CSF) motion in a healthy individual visualized using time-spatial labeling inversion pulse (Time-SLIP). Time-SLIP enables observation of the movement of labeled CSF, shown in white on the image slab, in the first 1–6 s after starting the imaging. Conversely, unlabeled CSF flowing into the specified slab is visualized in black. Motion of labeled (*white band*) CSF to the third ventricle at the anterior horn and conversely to the anterior horn at the third ventricle is observed (a and b). CSF motion that ascends toward the third ventricle (d) and conversely descends toward the fourth ventricle (c). Irregular motions (*black unlabeled turbulent wake in the white labeled area*) are evident in the third ventricle (c *circle*). Motion in both caudal and cephalic directions in the fourth ventricle and the ventral surface of the brainstem (e and f). An image showing (g) lateral movement in the Sylvian fissure (*arrow*), but no movement is observed in the convexity of the cerebrum (*circle*). A sagittal image visualizes CSF that appears to be stagnant, with no movement at all (h *circle*). Labeling around the choroid plexus does not show marked CSF movement (i and j).

the essence of CSF motion by taking findings that are mutual between each imaging method and aggregating them as the greatest common factors. In this review, the shared findings that were obtained through observing CSF motion in the CSF space using typical MRI techniques are described, and the physiological significance of such findings is described. The characteristics of each imaging technique discussed in this review are presented in Table 2.

Cardiac- or respiratory-related CSF motion

Recent studies that examined CSF motion linked to the changes in intrathoracic pressure from respiration were reviewed. Time-SLIP, dynamic iMSDE SSFP, and EPI visualize CSF motion that contains both cardiac pulsatile and respiratory elements because the images are taken during free breathing; however, it is not feasible to separate cardiac pulse- and respiratory-related CSF motion for visualization or to conduct a quantitative evaluation of CSF motion.[52,54,66,67,71] On the other hand, 3DPC takes images with the peripheral arterial pulse and ECG or chest wall movements as a trigger[33,72] while visualizing CSF motion that contains both cardiac pulsatile and respiratory elements; however, there is also a risk that the part of the respiratory aspect that is longer than the cardiac cycle is not taken into account.[70,71] Measurement of respiratory fluctuation-induced distance of CSF movement was therefore attempted, where quantitative analysis of the distance of CSF moving in the cephalic and caudal directions was performed.[71] Additionally, Kao et al.[73] and Chen et al.[55] used an EPI velocity phase

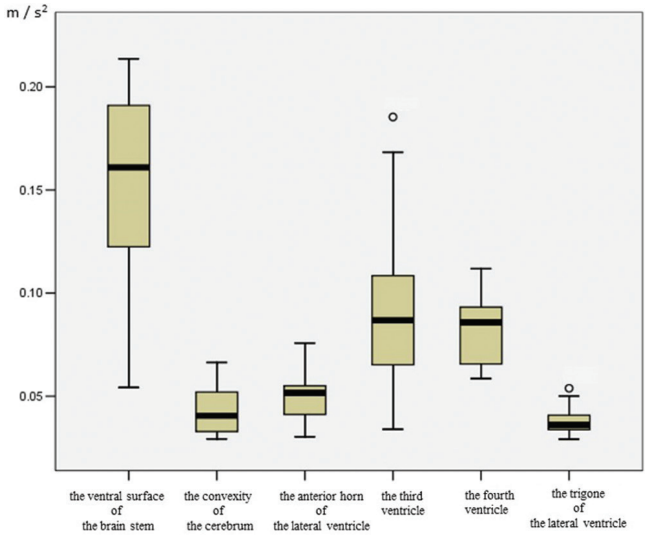


Fig. 4 Quantitative value of CSF acceleration in the ventricular system and subarachnoid space of healthy volunteers. Healthy volunteers (age range 28–73 years, male = 6, female = 6). Acceleration of CSF is shown as the rate of velocity change per unit time. From a fluid mechanics perspective, sites with small volumes, such as the subarachnoid space at the ventral surface of the brainstem, are considered to have increased fluid velocity compared with sites with large volumes, such as the trigone; however, because acceleration is less affected than velocity by the volume of the site in which the fluid is present, it is excellent for fluid mechanics analysis that compares sites with different volumes. Circles indicate outliers. Reprinted from Takizawa et al.[56] (Fig. 4). The quantitative value indicating augmented acceleration in the anterior horn is increased compared with that of the trigone. High CSF acceleration in the third and fourth ventricles. CSF motion demonstrates a gentle CSF acceleration at the trigone compared with other ventricles, consistent with results from other imaging (Figs. 1–3) evaluations. CSF acceleration corroborates the finding that CSF motion in the subarachnoid space from the ventral surface of the brainstem is elevated, whereas acceleration at the convexity of the cerebrum is suppressed.

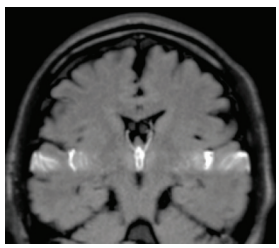
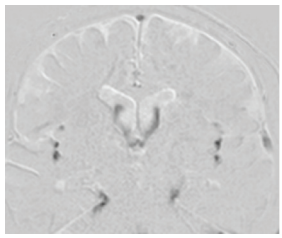
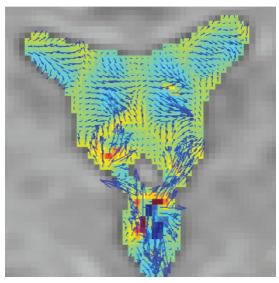
contrast technique to perform frequency analysis of CSF motion associated with heartbeat and respiratory fluctuations. Furthermore, frequency analyses of CSF motion have recently been attempted by some researchers, visualizing CSF motion during free breathing or controlled breathing with the PC method and analyzing the results with various methods.[62,74,75] These researchers recently published their success in separating cardiac pulsatile and respiratory components of CSF motion.[62,75] A frequency analysis, albeit not evaluated quantitatively, concluded that the respiratory element is more dominant than the cardiac pulsatile element in CSF motion.[76] On the other hand, some have concluded that CSF motion is greatly impacted by cardiac pulsation, and that the large movements of CSF are affected by respiratory elements; in other words, cardiac pulsation affects the basic pulsation of

Table 1 Shared findings of CSF movement in the cranial cavity

In general	Moves, not a circulatory flow.
	Moves, unstable very complex motion.
	Moves, repeats acceleration and deceleration, not only a simple dispersion.
	Related to cardiac gate, respiratory cycle, and daily human activities.
Subarachnoid space	Augmented at ventral surface of the brainstem.
	Strengthened at the center of the cranial cavity, weakened toward the distal part.
	Suppressed in the convexity.
Ventricular system	Augmented in the third and fourth ventricles.
	Suppressed in the trigone.

CSF: cerebrospinal fluid.

Table 2 Characteristics of each imaging technique presented in this review

Time-SLIP		Directly observes the signal intensity change due to transference of water protons from certain slab-like regions, in which the proton spins are excited sometime before (about 1–6 s).
Dynamic iMSDE SSFP		Detects and visualizes irregular movement of water protons as signal attenuation induced by phase dispersion in each voxel.
3DPC		Quantifies and visualizes time-resolved CSF velocity in 3D space, and thus enables characterization of CSF motion in a quantitative manner.

Time-SLIP: time-spatial labeling inversion pulse, Dynamic iMSDE SSFP: dynamic improved motion-sensitized driven-equilibrium steady-state free precession, 3DPC: time-resolved three-dimensional phase contrast.

CSF, and respiration affects the large pulsations.[62,75] Traditional pressure wave research by Hamit et al.[77] has shown that arterial blood pressure is an important factor in maintaining the static pressure of the CSF. However, strong dynamic changes in the pressure of the CSF are affected mainly through venous channels.[77] Wszedybyl-Winklewska et al.[78] showed that increased inspiratory resistance is associated with large swings in the heart-generated dynamic relationship between blood pressure and subarachnoid oscillations in healthy subjects. In particular, if CSF motion reaches a far distance due to respiratory fluctuations, it would indicate that such movements greatly impact substance mobilization, and this would be an essential study that gives significance to the relationship between respiration and CSF motion.[78] All these studies concern the frequency analysis of CSF motion that started around 2015, and future developments and progress are anticipated.

Approach to CSF motion

There are two approaches to study CSF that mobilizes in the cranium and spinal canal: 1) understanding physiological CSF motion in healthy individuals, and 2) pathological elucidation of a condition that induces CSF motion abnormalities. In this review, findings that were shared among the different types of imaging methods were extracted, and the physiological aspects of CSF motion in healthy individuals are described. For the pathological elucidation of various types of disorders, a more sophisticated analysis has become feasible today by combining multiple imaging techniques, based on their specific characteristics, as described above.

Future direction: need detection of slower water molecule motion

The main sources of ISF are blood and CSF.[10] With respect to the pathway of CSF flow into and out of the brain parenchyma, many researchers have been focusing on perivascular movement,[10,11,79,80] paravascular movement,[7,10,81–84] and dural lymphatic drainage.[84–89] The most significant exchange between vessels and brain parenchyma happens at the capillary level.[10] ISF re-enters the basement membrane at the capillary level, and the ISF is eliminated along the tunica media and tunica adventitia of the major cerebral arteries.[90–93] Mathematical models indicate perivascular transport of ISF by the reflection (reverse direction to the flow of blood; reverse direction to the major pulse wave) motion that follows each vascular pulsation.[90] Research from the group of Carare and Weller[91,94,95] has suggested an alternative route along the vasculature. They injected tracer into the basal ganglia, and the tracer distributed in the brain parenchyma, but the tracer was also simultaneously present in the laminin in the basement membranes of capillaries and in the basement membranes in the tunica media of arteries.[91] Additionally, amyloid beta has almost the same distribution as tracers that are draining from the brain parenchyma along basement membranes in the walls of capillaries and arteries, not around the venous channels.[91,96] Mestre et al.[97] performed a quantitative analysis of CSF perivascular flow in live mice. Their research showed that the CSF moves into the brain parenchyma through the pariarterial (perivascular space around the artery) area and drains from the brain parenchyma through the same vessel wall route. The radioactive tracer appears in the intracranial arteries and disappears at the wall of the carotid artery in the neck,[93] and this phenomenon strongly suggests that ISF is eliminated in the artery wall to drain into the cervical lymphatic system,[92] completing the perivascular ISF drainage system.

Many studies have shown the radioactive tracer activity recognized at the cervical lymph node after injection of tracer into the brain parenchyma.[98–100] The discovery of lymphatic structure in the dura mater provides new insights into how ISF and CSF reach the cervical lymphatic system[6,85] other than the perineural space. However, the black box between the brain and lymphatic structure in the dura mater is still far from being completely understood. We are still missing the connecting bridge between the CSF spaces and/or brain parenchyma and the meningeal lymphatic system,[87] which cleans up the unnecessary substances and heat produced by neural activity. The term glymphatic system has appeared as a bridge between water clearance and the lymphatic system and has attracted a great deal of attention by many researchers. The glymphatic system was proposed by Iliff et al. This concept was the basis for *in vivo* two-proton imaging of fluorescent tracers.[8] The glymphatic system shows that CSF moves into the brain parenchyma along paravascular spaces that surround penetrating arteries (Virchow–Robin space);[101,102] CSF entering from the CSF space into brain parenchyma pass through aquaporin-4 (AQP4), which are water-selective channels that regulate osmotically driven water transport through the cell membrane that is present on the astrocyte endfeet and ependymal cells; mixed CSF and ISF moves by the mechanism of convective solute transport in the brain parenchyma; and parenchymal ISF is eliminated by the paravenous (perivascular space around the vein) drainage pathway.[7,103,104] An early study by Rennels et al.[105] reported that apparent

convective tracer influx may be facilitated by transmission of the pulsations of the cerebral arteries to the microvasculature, and that fluid circulation through the central nervous system occurs through paravascular pathways. Bedussi et al.[81] showed that the paravascular space extends from the CSF space into the brain parenchyma and provides the possibility for unnecessary substance removal that could be facilitated by a mixing action generated by pressure pulsation in the CSF space. Ohashi et al.[106] showed strong contrast enhancement around the vein of Labbe after intravenous administration of gadolinium, and, at the same time, Naganawa et al.[107] showed that intravenously administered gadolinium leaks from the cortical veins into the surrounding subarachnoid space. Today, many researchers are trying to identify the routes by which CSF enters into and drains from brain parenchyma, but the theory of the glymphatic system is not yet established.

Smith et al.,[108] writing against the glymphatic system, showed that AQP4 deletion does not impair transfer of solutes from CSF into the brain parenchyma; movement of fluorescence of different sizes through the brain parenchyma is consistent with their diffusion coefficients; and local movement of solute in the brain parenchyma is not impaired immediately after cardiorespiratory arrest. These results do not support the glymphatic clearance mechanism that transfer of water molecules from CSF to ISF requires AQP4-dependent convection in the brain parenchyma.[108] Thus, the precise mechanism of drainage from where interstitial fluid mixes with CSF remains controversial.[109] The water molecule movement of the brain parenchyma is also unresolved. A computational model by Asgari et al.[110] showed that arterial pulsation may lead to fast paravascular water molecule transport by dispersion, and that glymphatic water molecule transport does not require bulk flow. Faghih and Sharp[109] showed that the glymphatic circulation driven by steady pressure is implausible, given current estimates of anatomical and fluid dynamics. Jin et al.[111] discussed, using their mathematical model, that significant convective transport requires a sustained pressure difference of several mmHg between the para-arterial and paravenous fluid, and it is not affected by pulsatile pressure fluctuations; diffusion (without convection) in the extracellular space is adequate to account for experimental transport studies in brain parenchyma. Therefore, their modeling results do not support a physiologically important role for local parenchymal convective flow in solute transport through brain extracellular space.[111] A traditional anatomical study showed that the final route of mixed ICF and CSF from brain parenchyma though the paravenous space is not obviously developed compared with the para-arterial space, which was seen in a classical pathological study in human spacemen.[112] Recently, Abbott et al.[113] presented an excellent review, a comprehensive re-evaluation of the previously proposed glymphatic concepts in favor of a new system that better considers basic cerebrovascular physiology and fluid transport considerations. Currently, research on the glymphatic system versus the perivascular system remains a major debate. The discovery of the glymphatic system was done under non-physiological conditions such as tracer injected into the cisterna magna and ventricular infusion, and two-proton imaging detected a limited surface of the cortex through two small cranial windows. In the studies of slow water molecule motion, tracer studies were mostly used. It should be noted that the injection of tracers into the cranium is very sensitive to pressure and volume disturbances, and excess injection speed and/or volume of the tracers may lead to non-physiological conditions in the cranium.[10] Thus, a method for monitoring water movement in the brain other than tracer studies is required. Therefore, use of MRI is desired to identify the slow water movement in the central nervous system as a non-tracer study.

In the present review, the detection of water protons by MRI in the order of centimeters per second was presented. Thus, imaging techniques with higher velocity sensitivity, such as several tens of micrometers per second are needed. They include diffusion tensor imaging analysis along the perivascular space,[114] brain surface motion imaging,[115] double diffusion encoding oscillatory gradient spin technique,[116] microscopic diffusional kurtosis imaging with symmetrized double diffusion encoding EPI,[117] q-space imaging,[84,118,119] and ultrafast magnetic resonance encephalography.[120] Such techniques will greatly improve our knowledge in the near future.

Conclusion

The classical concepts of "CSF flow" and "CSF circulation" should be amended. Furthermore, the expression "CSF motion" is appropriate from a physics perspective when evaluating the various directionalities and dynamics of CSF in the space where it exists. Moreover, CSF repeats acceleration and deceleration not only through simple dispersion of water, but also through pressure gradients and rotation, resulting in very complex motions with the addition of movements associated with activities of daily living. Furthermore, it is postulated

that CSF mixes with newly produced CSF and is absorbed near the production site at times or after it is transported far from the production site through respiratory fluctuation or human movements, thereby maintaining homeostasis of the central nervous system. As described above, CSF constantly maintains its movement, acting as a mediator of draining metabolites and metabolic heat generated by neural activities. When CSF is stagnant, the CSF space simply becomes a "garbage sink" and increases the concentration of CSF protein, which restricts CSF motion in the CSF space.

In future, detection of slower water molecule motion in the perivascular and/or paravascular and brain parenchyma spaces are needed. Much more work remains using imaging techniques with higher velocity sensitivity, such as several tens of micrometers per second.

The conclusion of this review is an aggregation of the greatest shared factors obtained through various MRI techniques that ascertain the movement of protons of water molecules in the order of centimeters per second regarding CSF motion in the CSF space, providing an understanding of CSF motion at the present time (2018) that can be accepted by many researchers.

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Conflicts of Interest Disclosure

The authors report no conflict interest concerning the materials or methods used in this study or the findings specified in this paper.

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