Quantification of Oscillatory Shear Stress from Reciprocating CSF Motion on 4D Flow Imaging

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ABSTRACT

BACKGROUND AND PURPOSE: Oscillatory shear stress could not be directly measured in consideration of direction, although cerebrospinal fluid has repetitive movements synchronized with heartbeat. Our aim was to evaluate the important of oscillatory shear stress in the cerebral aqueduct and foramen magnum in idiopathic normal pressure hydrocephalus by comparing it with wall shear stress and the oscillatory shear index in patients with idiopathic normal pressure hydrocephalus.

MATERIALS AND METHODS: By means of the 4D flow application, oscillatory shear stress, wall shear stress, and the oscillatory shear index were measured in 41 patients with idiopathic normal pressure hydrocephalus, 23 with co-occurrence of idiopathic normal pressure hydrocephalus and Alzheimer-type dementia, and 9 age-matched controls. These shear stress parameters at the cerebral aqueduct were compared with apertures and stroke volumes at the foramen of Magendie and cerebral aqueduct.

RESULTS: Two wall shear stress magnitude peaks during a heartbeat were changed to periodic oscillation by converting oscillatory shear stress. The mean oscillatory shear stress amplitude and time-averaged wall shear stress values at the dorsal and ventral regions of the cerebral aqueduct in the idiopathic normal pressure hydrocephalus groups were significantly higher than those in controls. Furthermore, those at the ventral region of the cerebral aqueduct in the idiopathic normal pressure hydrocephalus group were also significantly higher than those in the co-occurrence of idiopathic normal pressure hydrocephalus with Alzheimer-type dementia group. The oscillatory shear stress amplitude at the dorsal region of the cerebral aqueduct was significantly associated with foramen of Magendie diameters, whereas it was strongly associated with the stroke volume at the upper end of the cerebral aqueduct rather than that at the foramen of Magendie.

CONCLUSIONS: Oscillatory shear stress, which reflects wall shear stress vector changes better than the conventional wall shear stress magnitude and the oscillatory shear index, can be directly measured on 4D flow MR imaging. Oscillatory shear stress at the cerebral aqueduct was considerably higher in patients with idiopathic normal pressure hydrocephalus.

ABBREVIATIONS: AD = Alzheimer-type dementia; iNPH = idiopathic normal pressure hydrocephalus; OSI = oscillatory shear index; OSS = oscillatory shear stress; TAWSS = time-averaged wall shear stress; WSS = wall shear stress.
in the pathogenesis of flow-mediated arterial dilation or atherosclerosis.\textsuperscript{11-20} Oscillating low WSS due to turbulent flow at the arterial bifurcation is associated with atherosclerotic plaque,\textsuperscript{11,16-18} whereas chronic high WSS contributes to expansive or outward remodeling of vessels in response to a sustained increase in flow.\textsuperscript{19,20}

In the CSF dynamics, the normal CSF movements generated by the directional beating of motile cilia on the ependymal cells lining the ventricular surface maintain a calm environment in the ventricles; however, increased reciprocating bidirectional CSF movements might induce the disruption of motile cilia and ependymal gliosis, which has been shown to be directly associated with ventriculomegaly.\textsuperscript{21-26} Therefore, we hypothesized whether oscillatory shear stress (OSS) due to bidirectional CSF movements at the cerebral aqueduct may also be associated with the size of the cerebral aqueduct and ventricles in iNPH. However, OSS could not be directly measured, which was different from the conventional WSS magnitude without direction information or the oscillatory shear index (OSI), indicating direction changes. Therefore, a novel method to directly measure OSS using 4D flow MR imaging was successfully developed. This study aimed to evaluate the significance of OSS at the cerebral aqueduct and foramen of Magendie in iNPH by comparing it with the conventional WSS magnitude and OSI. Furthermore, shear stress parameters were compared with apertures and stroke volumes at the foramen of Magendie and cerebral aqueduct among patients with iNPH only, patients with co-occurrence of iNPH and Alzheimer-type dementia (AD), and age-matched controls.

**MATERIALS AND METHODS**

The ethics committees for human research of Rakuwakai Otowa Hospital approved the study design and protocol (Nos. Rakuto-Rin-17–041 and R2019-227). After obtaining written informed consent from patients or their relatives, the private information was anonymized in a linkable manner. Data collection, anonymization, image acquisition, and data-processing methods of 4D flow MR imaging were described in our previous study.\textsuperscript{10} In brief, 64 patients diagnosed with iNPH and 9 age-matched controls who underwent MR imaging examinations from January 28, 2017, to August 30, 2019, using a 3T MR imaging system (Magnetom Skyra; Siemens) were included in this study. All patients with iNPH had gait disturbance, cognitive impairment, and/or urinary incontinence, which improved after the CSF tap test, and ventricular dilation, an enlarged Sylvian fissure, and narrow sulci at the high convexity on conventional CT or MR imaging. A total of 23 patients with iNPH also had clinical AD based on the comprehensive assessment of their symptoms and findings on MR imaging and SPECT. Furthermore, 9 participants 60 years of age or older were recruited as controls because they had no symptoms of iNPH, AD, and/or Alzheimer-type dementia (AD), and age-matched controls. Of Monro to the upper cervical subarachnoid spaces. All 4D flow analyses were conducted using the 4D flow application in an independent 3D volume analyzer workstation (Synapse 3D; Fujifilm Healthcare). To increase the accuracy of fine anatomic information of \(<1\) mm, we used volumetric data on a T2-weighted 3D spin-echo sequence with sampling perfection with application-optimized contrasts by using different flip angle evolution (SPACE sequence; Siemens). Sequence parameters (TR, 2800 ms; TE, 286 ms; FOV, 230 mm; matrix, 192 \(\times\) 192; and voxel size, 0.6 \(\times\) 0.6 \(\times\) 0.9 mm) were superimposed on 3D phase images using a trilinear interpolation algorithm, and a 3D polygon mesh of ventricles and subarachnoid spaces was created from this high-resolution volumetric data using a marching cubes algorithm (Online Supplemental Data). In all 4D flow analyses, stress parameters were measured after confirming the absence of phase aliasing or motion artifacts. The anterior-posterior diameters of the foramen of Magendie, the lower and upper ends of the cerebral aqueduct, and the midbrain were measured on the midsagittal plane of T2-weighted 3D SPACE MR imaging (Online Supplemental Data).

The 3D flow velocities (centimeters/second) and volumes (milliliters/second) of the reciprocating CSF movements through 12 ROIs were measured from the bilateral foramina of Monro to the lower end of the second cervical vertebra. The stroke volume was calculated by adding the absolute forward and backward CSF flow volumes, and reversed flow rate (%) by the absolute backward flow volume divided by the absolute forward flow volume. The surface mesh of CSF spaces was generated by increasing the image resolution and applying maximum smoothing, with an
heartbeat, we calculated the TAWSS vector without direction information.
The flow velocity vector in the nth phase parallel to the wall was the TAWSS vector.

The conventional WSS vector in the nth phase \( \vec{v}(n) \) was calculated as

\[
\vec{v}(n) = \mu \frac{\Delta \vec{v}(n)}{\Delta z},
\]

where \( \Delta z \) was the distance perpendicular to the wall, \( \Delta \vec{v}(n) \) was the flow velocity vector in the nth phase parallel to the wall, and \( \mu \) was the dynamic viscosity. In this study, \( \Delta z \) was set at 0.8 mm considering the resolution and average diameter of the cerebral aqueduct, and \( \mu \) was set 1.0 \( \times \) 0.001 (pascal \( \times \) second) based on the CSF modeled as an incompressible Newtonian fluid with hydrodynamic characteristics of water.

The WSS magnitude \( |\vec{v}(n)| \) was defined as an absolute value without direction information.

To evaluate the cumulative effect of WSS vector during 1 heartbeat, we calculated the TAWSS vector \( \vec{T} \) as

\[
\vec{T} = \frac{\sum_{n=1}^{N} \vec{v}(n)}{N},
\]

where \( N \) was the total number of phases during 1 cardiac cycle and TAWSS magnitude \( |\vec{T}| \) was defined as a scalar quantity of the TAWSS vector.

The angle between the nth phase direction of the WSS vector and the TAWSS vector as the principal axis was defined as \( \theta(n) \), and the scale for converting \( \theta(n) \) into a binary value of +1 or -1 was defined as \( \delta[\theta(n)] \), calculated as

\[
\delta[\theta(n)] = \begin{cases} +1 & (-90^\circ < \theta(n) < 90^\circ) \\ -1 & (90^\circ < \theta(n) < 270^\circ) \end{cases},
\]

where \( \delta(\theta) = +1 \) indicates the same direction as \( \vec{T} \) and \( \delta(\theta) = -1 \) indicates a 180° opposite direction. As shown in Fig 1, the WSS magnitude multiplied by +1 or -1 was defined as OSS calculated as

\[
\text{OSS} = |\vec{v}(n)| \times \delta[\theta(n)].
\]

The OSI amplitude was calculated as the maximum minus the minimum OSS value.

OSI that monitors the direction changes of the WSS vector during 1 cardiac cycle was calculated as

\[
\text{OSI} = \frac{1}{2} \left( \frac{1}{N} \sum_{n=1}^{N} \vec{v}(n) \right) \left( \frac{1}{N} \sum_{n=1}^{N} |\vec{v}(n)| \right).
\]

Shear Stress Parameters
The conventional WSS vector in the nth phase \( \vec{v}(n) \) (N/m^2) was calculated as

\[
\vec{v}(n) = \mu \frac{\Delta \vec{v}(n)}{\Delta z},
\]

where \( \Delta z \) was the distance perpendicular to the wall, \( \Delta \vec{v}(n) \) was the flow velocity vector in the nth phase parallel to the wall separate from \( \Delta z \), and \( \mu \) was the dynamic viscosity. In this study, \( \Delta z \) was set at 0.8 mm considering the resolution and average diameter of the cerebral aqueduct, and \( \mu \) was set 1.0 \( \times \) 0.001 (pascal \( \times \) second) based on the CSF modeled as an incompressible Newtonian fluid with hydrodynamic characteristics of water.

The WSS magnitude \( |\vec{v}(n)| \) was defined as an absolute value without direction information.

To evaluate the cumulative effect of WSS vector during 1 heartbeat, we calculated the TAWSS vector \( \vec{T} \) as

\[
\vec{T} = \frac{\sum_{n=1}^{N} \vec{v}(n)}{N},
\]

where \( N \) was the total number of phases during 1 cardiac cycle and TAWSS magnitude \( |\vec{T}| \) was defined as a scalar quantity of the TAWSS vector.

The angle between the nth phase direction of the WSS vector and the TAWSS vector as the principal axis was defined as \( \theta(n) \), and the scale for converting \( \theta(n) \) into a binary value of +1 or -1 was defined as \( \delta[\theta(n)] \), calculated as

\[
\delta[\theta(n)] = \begin{cases} +1 & (-90^\circ < \theta(n) < 90^\circ) \\ -1 & (90^\circ < \theta(n) < 270^\circ) \end{cases},
\]

where \( \delta(\theta) = +1 \) indicates the same direction as \( \vec{T} \) and \( \delta(\theta) = -1 \) indicates a 180° opposite direction. As shown in Fig 1, the WSS magnitude multiplied by +1 or -1 was defined as OSS calculated as

\[
\text{OSS} = |\vec{v}(n)| \times \delta[\theta(n)].
\]

The OSI ranges from 0 to 0.5, where 0 indicates a complete unidirectional flow and 0.5 indicates oscillatory flow only.

The WSS magnitude and OSI were automatically calculated per pixel and displayed on the 3D surface display using a scalable color map of the 4D flow application on Synapse 3D.

Data and codes used in this study are not available within the public domain because of the commercially available workstation.

The WSS magnitude, OSS, and OSI were automatically measured using 5 dotlike ROIs with the highest WSS magnitude at the ventral (ROI 1) and dorsal (ROI 2) regions of the foramen magnum and dorsal (ROI 3) and ventral (ROI 4) regions of the cerebral aqueduct and interpeduncular cistern (ROI 5).

Statistical Analysis
The Kruskal-Wallis rank sum test was used to compare the mean values [SD] for age and several MR imaging measurements among the 3 groups. In addition, the Wilcoxon rank sum test was used to compare continuous variables between patients with iNPH with co-occurrence of iNPH and AD or controls. The Fisher exact test was used to compare the 3 proportions. The Pearson correlation coefficient (r) and 95% CI were used to determine relationships between shear stress and morphologic parameters or stroke volume. Statistical significance was assumed at a P value < .05. All missing data points were treated as deficit data that did not affect other variables. Statistical analyses were performed using R statistical and computing software (Version 3.6.2; http://www.R-project.org).

RESULTS
During 1 cardiac cycle, the CSF moved in the cranioaudal and caudocranial directions periodically through the cerebral

FIG 2. Oscillation of WSS due to bidirectional CSF flow through the cerebral aqueduct. The numbers 1, 2, and 3 demonstrate temporal changes of the reciprocating CSF motion during 1 cardiac cycle in a 77-year-old man diagnosed with iNPH. The colored path lines (lower figures) show the flow as a moving trajectory of the virtual particle through the middle part of the cerebral aqueduct in 1 heartbeat. The color and length of 3D streamlines (upper figures) indicate the flow velocity as pink for fast and blue for slow. The sampling interval of streamlines and path lines was set at 0.2 mm after the trilinear interpolation. The arrows indicate the WSS vector produced by the flow parallel to the wall surface. The size and direction of the arrows indicate the magnitude and direction of the WSS vector. Temporal changes of the WSS vector at the dorsal region (yellow arrows) were larger than those at the ventral region (white arrows).
Bidirectional CSF movements at the dorsal region of the cerebral aqueduct were larger than those in the ventral region in patients with iNPH. Chronologic WSS magnitude changes in the dorsal region of the foramen magnum (ROI 2, yellow) and dorsal (ROI 3, red) and ventral (ROI 4, blue) regions of the cerebral aqueduct in 1 cardiac cycle. Considering the shear stress direction, these changes were completely different.

**FIG 3.** Distributions and fluctuations of shear stress parameters per heartbeat in iNPH. The colored surfaces in the ventricles show the distribution of WSS magnitude (A) and OSI (B) in the same patient with iNPH, as shown in Fig 2. Red indicates high and blue indicates low. Line-graphs C and D show chronologic changes of WSS magnitude and OSS at the dorsal region of the foramen magnum (ROI 2) and dorsal (ROI 3) and ventral (ROI 4) regions of the cerebral aqueduct in 1 cardiac cycle. Considering the shear stress direction, these changes were completely different.

**Table 1: Clinical and morphologic characteristics of the study population**

|                  | iNPH Only | iNPH with AD | Control | P Value |
|------------------|-----------|--------------|---------|---------|
| Total number     | 41        | 23           | 9       | .332    |
| Male/female      | 28:13     | 13:10        | 4:5     | .207    |
| Age (yr)         | 78.2 [SD, 6.62] | 79.8 [SD, 5.83] | 75.7 [SD, 5.70] | .207 |
| Anteroposterior diameter (mm) | | | | |
| Foramen of Magendie | 5.72 [SD, 1.77] | 5.88 [SD, 2.04] | 2.02 [SD, 0.44] | <.001 |
| Lower end of cerebral aqueduct | 4.44 [SD, 0.87] | 4.25 [SD, 1.41] | 2.23 [SD, 0.70] | <.001 |
| Upper end of cerebral aqueduct | 3.65 [SD, 0.66] | 3.45 [SD, 0.73] | 2.30 [SD, 0.54] | <.001 |
| Midbrain         | 8.56 [SD, 0.88] | 8.43 [SD, 0.92] | 9.32 [SD, 1.57] | .230 |
| Stroke volume (µL/heartbeat) | | | | |
| Foramen of Magendie | 32.9 [SD, 22.6] | 37.4 [SD, 37.6] | 21.1 [SD, 11.7] | .448 |
| Lower end of cerebral aqueduct | 37.6 [SD, 28.9] | 39.6 [SD, 43.7] | 17.8 [SD, 13.0] | .083 |
| Upper end of cerebral aqueduct | 49.0 [SD, 33.3] | 52.6 [SD, 32.5] | 18.9 [SD, 10.5] | .002 |
| Foramina of Monro | 96.5 [SD, 41.0] | 97.8 [SD, 39.1] | 62.6 [SD, 44.6] | .042 |

*Data are means. P value is from the Kruskal–Wallis rank sum test.*

aqueduct (Fig 2 and Online Supplemental Data). The distribution of WSS magnitude (Fig 3A) was somewhat different from that of the OSI (Fig 3B). The bimodal high WSS magnitude in Fig 3C at the dorsal region of the foramen magnum (ROI 2) and cerebral aqueduct (ROI 3) was changed to the periodic oscillation by converting OSS (Fig 3D). In other words, 1 of the 2 WSS magnitude peaks during a heartbeat was converted to the negative OSS.

A total of 73 participants comprising 41 patients diagnosed with iNPH only, 23 with co-occurrence of iNPH and AD, and 9 age-matched controls were included in this study (Table 1). The difference in mean OSS amplitude, TAWSS, and OSI at the ventral (ROI 1) and dorsal (ROI 2) regions of the foramen magnum and interpeduncular cistern (ROI 5) was not significant among the 3 groups. Therefore, the amplitude, maximum, and
minimum OSS values; TAWSS; and OSI at the dorsal (ROI 3) and ventral (ROI 4) regions of the cerebral aqueduct are shown in Table 2. The mean OSS amplitude at the dorsal and ventral regions of the cerebral aqueduct in the iNPH groups was approximately 3 times higher than that in the controls because the maximum OSS in the iNPH groups was twice as high and the minimum OSS was considerably lower. Remarkably, the mean amplitude and maximum OSS values at the ventral region of the cerebral aqueduct in the iNPH-only group were twice as high as those in the iNPH with AD group. The mean TAWSS magnitude at the dorsal region of the cerebral aqueduct in the iNPH-only group was also significantly higher than that in the controls. Furthermore, patients with iNPH-only had a significantly higher mean TAWSS magnitude at the ventral region of the cerebral aqueduct compared with those with iNPH with AD. The median and distribution of the OSS amplitude and TAWSS magnitude at the dorsal and ventral regions of the cerebral aqueduct among the 3 groups are shown as boxplots in Fig 4. Both the OSS amplitude and TAWSS magnitude at the dorsal region of the cerebral aqueduct in the iNPH groups were significantly higher than those in the controls, whereas the OSS amplitude at the ventral region of the cerebral aqueduct in the iNPH-only group was significantly higher than that in the iNPH with AD group and controls. The difference in OSI was not significant among the 3 groups.

The TAWSS magnitude was strongly associated with the amplitude and maximum and minimum OSS values at the dorsal (r = 0.89, 0.93, and −0.77) and ventral (r = 0.88, 0.93, and −0.73) regions of the cerebral aqueduct (Online Supplemental Data).

**Relationships between Shear Stress Parameters and Anterior-Posterior Diameter or Stroke Volume**

The amplitude and maximum and minimum OSS values and TAWSS magnitude at the dorsal region of the cerebral aqueduct were significantly associated with the anterior-posterior diameters of the foramen of Magendie and the lower end of the cerebral aqueduct (Table 3) and were strongly associated with stroke volume at the upper and lower ends of the cerebral aqueduct and foramen of Magendie, respectively (Table 4). The amplitude and maximum and minimum OSS values and TAWSS magnitude at the ventral region of the cerebral aqueduct were significantly-but-weakly associated with stroke volumes at the lower and upper ends of the cerebral aqueduct. However, OSI was not significantly associated with anterior-posterior diameters or stroke volumes at any locations.

**DISCUSSION**

The reciprocating bidirectional CSF movements increase the bi-modal WSS magnitude at the cerebral aqueduct during a cardiac cycle in iNPH. The conventional WSS magnitude was calculated as an absolute value of the WSS vector without the direction information by converting to a scalar quantity. However, the actual shear stress was produced by the bidirectional CSF flows from positive to negative values, not in a bimodal waveform. Therefore, a novel parameter, OSS with plus/minus directional information in addition to the WSS magnitude, was developed. On the basis of our literature review, this study is the first report that directly measures the OSS on 4D flow MR imaging. The maximum value of positive OSS drastically fluctuated to the minimum value of negative OSS during a heartbeat due to the reciprocating CSF movements in iNPH. Conversely, the maximum WSS magnitude value was either of the 2 peaks, whereas the minimum value was nearly zero consistently. However, the TAWSS magnitude was significantly associated with the OSS amplitude.

The distribution and magnitude of OSI were different from those of OSS or WSS magnitude. In contrast to steady flow conditions, pulsatile bidirectional flows cause large OSS fluctuations.

In this study, the OSS amplitude at the dorsal region of the cerebral aqueduct was significantly associated with both the foramen of Magendie diameters and stroke volumes at the upper and lower ends of the cerebral aqueduct and foramen of Magendie, respectively. Our previous study demonstrated that the stroke volume at the cerebral aqueduct had the strongest association with the foramen of Magendie diameter. These findings indicate that the dilation of the foramen of Magendie may be the first trigger for increased OSS amplitude at the dorsal region of the cerebral aqueduct due to increased aqueductal stroke volume. On the basis of study on oscillating flow dynamics, chronic high OSS at the cerebral aqueduct may be involved in the expansive remodeling of the aqueductal lumen diameter and may

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**Table 2: Mean value [SD] of parameters at the cerebral aqueduct in the study population**

|                      | All (n = 73) | iNPH Only (n = 41) | iNPH with AD (n = 23) | Control (n = 9) | P1 | P2 | P3 |
|----------------------|-------------|-------------------|----------------------|----------------|----|----|----|
| **Dorsal region of the cerebral aqueduct** |             |                   |                      |                |    |    |    |
| OSS amplitude        | 52.5 [SD, 33.9] | 59.7 [SD, 34.1] | 52.9 [SD, 32.2] | 19.8 [SD, 13.3] | .483 | <.001 | .004 |
| Maximum OSS          | 35.9 [SD, 16.0] | 38.7 [SD, 15.5] | 37.3 [SD, 16.1] | 19.7 [SD, 6.3] | .566 | <.001 | .002 |
| Minimum OSS          | −16.7 [SD, 19.8] | −21.0 [SD, 20.2] | −15.6 [SD, 18.9] | −0.1 [SD, 9.6] | .277 | .001 | .043 |
| TAWSS                | 18.2 [SD, 8.9] | 19.7 [SD, 8.7] | 18.8 [SD, 9.3] | 9.9 [SD, 2.2] | .678 | <.001 | .008 |
| OSI                  | 0.21 [SD, 0.13] | 0.24 [SD, 0.12] | 0.19 [SD, 0.14] | 0.16 [SD, 0.11] | .234 | .077 | .614 |
| **Ventral region of the cerebral aqueduct** |             |                   |                      |                |    |    |    |
| OSS amplitude        | 27.2 [SD, 28.4] | 36.0 [SD, 32.2] | 18.1 [SD, 19.8] | 11.9 [SD, 11.1] | .022 | .020 | .363 |
| Maximum OSS          | 23.6 [SD, 15.9] | 28.8 [SD, 17.9] | 18.2 [SD, 10.9] | 14.2 [SD, 6.4] | .017 | .011 | .246 |
| Minimum OSS          | −3.6 [SD, 13.9] | −7.1 [SD, 15.9] | 0.14 [SD, 10.1] | 2.3 [SD, 7.5] | .080 | .091 | .592 |
| TAWSS                | 12.2 [SD, 7.1] | 14.3 [SD, 8.1] | 10.1 [SD, 4.9] | 8.1 [SD, 2.7] | .038 | .020 | .458 |
| OSI                  | 0.15 [SD, 0.15] | 0.15 [SD, 0.15] | 0.10 [SD, 0.14] | 0.11 [SD, 0.15] | .114 | .355 | .910 |

*P1 indicates probability value of iNPH only versus iNPH with AD by the Wilcoxon rank sum test; P2, probability value of iNPH only versus controls by the Wilcoxon rank sum test; and P3, probability value of iNPH with AD versus controls by the Wilcoxon rank sum test.*
subsequently increase the pulsatile CSF inflow. However, this study has not yet proved this evidence.

Increased OSS amplitude may be associated with symptoms or pathologies of iNPH. We found that patients with iNPH-only had significantly higher OSS amplitude only at the ventral region of the cerebral aqueduct compared with those with co-occurrence of iNPH and AD. This finding was consistent with our previous result that patients with iNPH-only had not only smaller ventricular volume but also larger basal cistern and Sylvian fissure volumes than those with co-occurrence of iNPH and AD.27 AD is known as the most common comorbidity with iNPH due to CSF stagnation;28-32 hindering the clearance of neurotoxic molecules such as amyloid-$\beta$ or $\tau$.33,34 Recently, pulsatile CSF inflow to the ventricular systems during sleep was reportedly associated with large, coupled low-frequency oscillations in the neuronal activity and hemodynamic oscillations.35 Decreased CSF pulsation may be associated with AD onset through the pathway in suppressed electrophysiological slow waves that impair amyloid-$\beta$ and $\tau$ excretion into the brain interstitial fluid and CSF during sleep.36-39 Therefore, direct OSS measurement in future studies will help determine whether CSF oscillations are associated with the AD onset.

This study had some limitations as described in our previous study.10 In particular, influences of respiration, wall motion, eddy currents, and background noise on the 4D flow MR imaging sequence were not assessed. Second, OSS and WSS magnitudes calculated by 4D flow MR imaging may be underestimated compared

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**FIG 4.** Boxplots for the amplitude of OSS and TAWSS at the dorsal and ventral regions of the cerebral aqueduct among 3 groups. A, Distribution of the OSS amplitude at the dorsal region of the cerebral aqueduct. B, Distribution of the TAWSS at the dorsal region of the cerebral aqueduct. C, Distribution of the OSS amplitude at the ventral region of the cerebral aqueduct. D, Distribution of the TAWSS at the ventral region of the cerebral aqueduct.
Table 3: Relationships with anterior-posterior diameter by the Pearson correlation coefficient (95% confidence intervals)

|                      | Foramen of Magendie | Lower End of Cerebral Aqueduct | Upper End of Cerebral Aqueduct | Midbrain |
|----------------------|---------------------|--------------------------------|--------------------------------|----------|
| **Dorsal region of the cerebral aqueduct** | OSS amplitude | 0.55 (0.36–0.69) | 0.47 (0.26–0.63) | 0.28 (0.05–0.48) | NS |
|                      | Maximum OSS | 0.53 (0.34–0.68) | 0.41 (0.20–0.59) | NS | NS |
|                      | Minimum OSS | −0.51 (−0.66 to −0.31) | −0.46 (−0.63 to −0.26) | −0.32 (−0.51 to −0.10) | NS |
|                      | TAWSS | 0.56 (0.37–0.70) | 0.40 (0.18–0.58) | NS | NS |
|                      | OSI | NS | NS | NS | NS |

| **Ventral region of the cerebral aqueduct** | OSS amplitude | NS | 0.27 (0.04–0.47) | NS | NS |
|                      | Maximum OSS | NS | 0.31 (0.08–0.50) | NS | NS |
|                      | Minimum OSS | NS | NS | NS | NS |
|                      | TAWSS | 0.26 (0.04–0.47) | 0.33 (0.10–0.52) | NS | NS |
|                      | OSI | NS | NS | NS | NS |

**Table 4: Relationships with stroke volume by the Pearson correlation coefficient (95% confidence intervals)**

|                      | Foramen of Magendie | Lower End of Cerebral Aqueduct | Upper End of Cerebral Aqueduct | Foramina of Monro |
|----------------------|---------------------|--------------------------------|--------------------------------|--------------------|
| **Dorsal region of the cerebral aqueduct** | OSS amplitude | 0.48 (0.28–0.64) | 0.53 (0.34–0.68) | 0.63 (0.47–0.76) | NS |
|                      | Maximum OSS | 0.50 (0.31–0.66) | 0.56 (0.37–0.70) | 0.66 (0.50–0.77) | NS |
|                      | Minimum OSS | −0.41 (−0.59 to −0.20) | −0.46 (−0.63 to −0.26) | −0.55 (−0.70 to −0.37) | NS |
|                      | TAWSS | 0.43 (0.22–0.60) | 0.53 (0.34–0.68) | 0.73 (0.60–0.82) | NS |
|                      | OSI | NS | NS | NS | NS |

| **Ventral region of the cerebral aqueduct** | OSS amplitude | NS | 0.30 (0.07–0.50) | 0.25 (0.02–0.46) | NS |
|                      | Maximum OSS | NS | 0.32 (0.10–0.52) | 0.29 (0.07–0.49) | NS |
|                      | Minimum OSS | NS | −0.24 (−0.45 to −0.01) | NS | NS |
|                      | TAWSS | NS | 0.37 (0.15–0.55) | 0.34 (0.12–0.53) | NS |
|                      | OSI | NS | NS | NS | NS |

**Note:** NS indicates not significant (P ≥ .05) by the Pearson correlation analysis.

with the true values, though their distribution is considered reasonably accurate.\(^40\) Third, the AD comorbidity was not pathologically confirmed through brain biopsy, CSF biomarkers, or amyloid imaging in this study. Finally, we were unable to determine a causal relationship between the dilated cerebral aqueduct and increased OSS amplitude because this study had a cross-sectional design. Therefore, a causal relationship should be investigated in a prospective cohort study or basic research.

**CONCLUSIONS**

OSS as a novel parameter combining the conventional WSS magnitude with a positive or negative sign indicating the WSS direction can be quantitatively measured at any point on 4D flow MR imaging. Therefore, the OSS amplitude produced by reciprocating bidirectional CSF movements reflects WSS vector changes better than the conventional scalar quantities of the WSS magnitude and OSI. Quantitative OSS measurement may help elucidate the pathophysiologic mechanism of ventricular dilation in iNPH or symptom progression. OSS brings a new perspective to the study of slowly and intricately moving CSF in the complex shapes of the ventricles and the subarachnoid space.

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