Evaluation of Cardiac- and Respiratory-driven Cerebrospinal Fluid Motions by Applying the S-transform to Steady-state Free Precession Phase Contrast Imaging

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Purpose: To extract the status of hydrocephalus and other cerebrospinal fluid (CSF)-related diseases, a technique to characterize the cardiac- and respiratory-driven CSF motions separately under free breathing was developed. This technique is based on steady-state free precession phase contrast (SSFP-PC) imaging in combination with a Stockwell transform (S-transform).

Methods: 2D SSFP-PC at 3 T was applied to measure the CSF velocity in the caudal-cranial direction within a sagittal slice at the midline (N = 3) under 6-, 10-, and 16-s respiratory cycles and free breathing. The frequency-dependent window width of the S-transform was controlled by a particular scaling factor, which then converted the CSF velocity waveform into a spectrogram. Based on the frequency bands of the cardiac pulsation and respiration, as determined by the electrocardiogram (ECG) and respirator pressure sensors, Gaussian bandpass filters were applied to the CSF spectrogram to extract the time-domain cardiac- and respiratory-driven waveforms.

Results: The cardiac-driven CSF velocity component appeared in the spectrogram clearly under all respiratory conditions. The respiratory-driven velocity under the controlled respiratory cycles was observed as constant frequency signals, compared to a time-varying frequency signal under free breathing. When the widow width was optimized using the scale factor, the temporal change in the respiratory-driven CSF component was even more apparent under free breathing.

Conclusion: Velocity amplitude variations and transient frequency changes of both cardiac- and respiratory-driven components were successfully characterized. These findings indicated that the proposed technique is useful for evaluating CSF motions driven by different cyclic forces.

Keywords: cardiac, cerebrospinal fluid, free breathing, phase contrast, respiration

Introduction

Recently, the understanding of the motion of cerebrospinal fluid (CSF) has dramatically evolved. Moreover, CSF motion can be categorized as cardiac- and respiratory-driven in addition to bulk flow. Cardiac-driven motion results from the expansion and contraction of the major arteries and brain parenchyma, which are induced by cardiac pulsation. Respiration alters the intrathoracic pressure, which then alters the venous return, causing a pressure change in the veins in the intracranial space. The motion induced by this pressure change is referred to as respiratory-driven motion. Bulk flow is the slow flow of CSF, possibly related to the clearance of waste via the glymphatic system. Recently, a report suggested that CSF flow in perivascular space is driven by cardiac pulsation, although the relationship between the flow and respiration remains unclear.
Therefore, investigating cardiac- and respiratory-driven CSF motions under free breathing is important for understanding the fluid dynamics of the central nerves system. To the best of our knowledge, cardiac- and respiratory-driven CSF motions under free breathing for patients with neurodegenerative diseases (such as hydrocephalus) have not been reported.

A comprehensive understanding of CSF dynamics is currently unattainable, primarily because the bulk flow is much slower than the other two motions, rendering it substantially more difficult to monitor. However, from the perspective of various neurological diseases (such as hydrocephalus, brain tumors, and cognitive disorders), it may be related to CSF motion and interstitial fluid dynamics. Although the fine bulk flow is not monitored, the cardiac- and respiratory-induced motions may reflect the status of these diseases.

Cardiac-driven CSF motion has been investigated using cardiac-gated cine phase-contrast (PC) in addition to PC being applied to three spatial dimensions, which are referred to as 4D-flow.\(^{11-17}\) The 4D-flow analysis visualizes the CSF motion as vectors and color-coding. There are a number of alternative techniques that can be applied to visualize CSF motion. Time-spatial labeling inversion pulse (time-SLIP) has also been applied to CSF motion in deep respiration and breath-holding states,\(^{18}\) in which the technique visualizes the displacement of CSF. Dynamic improved motion-sensitized driven-equilibrium steady-state free precession (iMSDE SSFP) can be employed to visualize the intracranial CSF motion in quasi-real-time.\(^{19}\) Cardiac-driven CSF motion has been investigated using cardiac-gated cine phase-contrast (PC) in addition to PC being applied to three spatial dimensions, which are referred to as 4D-flow.\(^{11-17}\) A report using dynamic iMSDE SSFP analyzed the respiratory-driven CSF motion with respiratory instruction and under free breathing.\(^{1}\) Furthermore, cardiac- and respiratory-driven CSF motions in 6-s respiratory cycles have been analyzed using real-time SSFP-PC imaging.\(^{22}\) Meanwhile, a related review with imaging of the lymphatic system using MRI has been reported in recent years.\(^{23}\) One of the techniques to visualize perivascular space is gadolinium-based contrast-enhanced fluid-attenuated infrared spectroscopy (FLAIR) imaging.

Although 4D-flow is one of the most established methods for visualizing blood flow quantitatively, the technique is not sufficient for CSF motion because cardiac gating would hide the respiratory motion, whose cycle may significantly vary over time. To develop a technique that separates the two major motions when investigating the clinical relevance with the aforementioned diseases, an appropriate time-frequency analysis method is required, particularly for motions under free breathing. We focused on the Stockwell transform (S-transform), which is one of the short-time Fourier transformation methods for analyzing signals with time-varying frequency, as this was expected to separate the cardiac- and respiratory-driven CSF motions under free breathing.\(^{24}\) In the present study, the S-transform was used in conjunction with quasi-real-time SSFP-PC to separate the cardiac- and respiratory-driven CSF motions under instructed regular respiration and free breathing in healthy volunteers.

### Materials and Methods

The internal review board of our institution approved this study. All volunteers were examined after their informed consent was obtained, as per the terms of the internal review board’s approval.

#### S-transform

The S-transform was developed to extract signals with a time-varying frequency (such as earthquake waves), which has been described in detail.\(^{24,25}\) Briefly, the S-transform produces a time-frequency representation called a spectrogram of velocity waveform, as shown in the following equation:

\[
S(\tau, f) = \frac{|f|}{k\sqrt{2\pi}} \int_{-\infty}^{\infty} v(t)e^{-\frac{(t-\tau)^2}{2f^2}} e^{-i2\pi ft} dt, k > 0, \quad (1)
\]

where \(S(\tau, f)\) is the spectrogram, \(v(t)\) is the velocity waveform, \(f\) is the frequency, \(t\) and \(\tau\) are the time, and \(k\) is a scale factor (1 in this study), which controls the number of oscillations in the window.\(^{26,27}\) Equation (1) consists of a Fourier transform and Gaussian window terms. The variance of the Gaussian window is changed according to the frequency and \(k\)-factor, as denoted by \((k/f)^2\). The window width becomes narrower than the signal period in the time domain when the \(k\)-factor > 1. The time integral of the spectrogram is the Fourier spectrum of the time domain signal, as follows:

\[
V(f) = \int_{-\infty}^{\infty} S(\tau, f) d\tau. \quad (2)
\]

Theoretically, the original velocity waveform can be completely reconstructed by the inverse Fourier transforms of Equation (2).

Based on the convolution theorem, Equation (1) can be rewritten as

\[
S(\tau, f) = \int_{-\infty}^{\infty} V(a + f) e^{-\frac{(a+f)^2}{2f^2}} e^{i2\pi f a} da, f \neq 0. \quad (3)
\]

In practice, Equation (3) is used because it is more efficient with discrete calculations.

#### Cardiac- and respiratory-driven velocity measurements by SSFP-PC imaging

A 2D SSFP-PC technique using 3-T MRI was performed on three healthy volunteers (two males and one female with mean ± standard deviation (SD) ages of 51 ± 3 years).
under free breathing conditions. Scans were performed in the evening in a fasting state. To compare free breathing with breathing instruction, an in-house audio instruction system directed the volunteers to breathe in 6-, 10-, and 16-s periods. An electrocardiogram (ECG) was used to measure the cardiac pulsation frequency, and a bellows-type pressure sensor was placed on the abdomen of each volunteer to obtain the respiratory frequency. Asynchronous PC images were acquired under the following conditions: sequence = SSFP; flow encoding direction = caudal–cranial; TR = 6.0 ms; TE = 3.9 ms; flip angle (FA) = 10°; parallel imaging factor = 4; acquisition matrix = 89 × 128 (half-Fourier); reconstruction matrix = 256 × 256; field of view (FOV) = 28 cm × 28 cm; slice thickness = 7 mm; velocity encoding (VENC) = 10 cm/s; and slice directions = sagittal. PC image acquisition with 217 ms (4.61 fps) of temporal resolution was repeated 256 times, resulting in approximately 56 s of total acquisition time for each volunteer. The resultant frequency resolution (0.018 Hz) was sufficient to characterize the cardiac- and respiratory-driven components in the frequency domain.

Separation of cardiac- and respiratory-driven components from CSF motion based on the S-transform

In the separation procedure, it was assumed that the frequencies of the cardiac- and respiratory-driven CSF motions in the intracranial space were either identical or close to those of cardiac pulsation and respiration, respectively. The CSF velocity was obtained by SSFP-PC imaging, and the cardiac and respiratory signals were converted to spectrograms by S-transform. To separate the cardiac- and respiratory-driven components in the CSF velocity spectrogram, the frequencies of the cardiac pulsation and respiration during the scan were determined as the frequencies at peak amplitude in the spectrograms of the cardiac and respiratory signals. The cardiac- and respiratory-driven components were then extracted from the spectrogram of the CSF velocity by applying Gaussian bandpass filters. The center frequencies of these filters (0.2 Hz) were at the center frequencies of the ECG and respiration monitor frequencies and the band widths (standard deviations of the Gaussian functions).

Results

Figure 1 presents an example of the separation results of the cardiac- and respiratory-driven CSF velocity components at the foramen magnum of a healthy volunteer with a 6-s respiratory cycle. The CSF velocity, ECG signal, and respiration monitor signal were converted to the spectrogram using an S-transform. The color of the CSF velocity spectrogram represents the amplitude of the velocity waveform. Two Gaussian bandpass filters were applied to the CSF velocity spectrogram to extract the cardiac- and respiratory-driven components. Their frequencies changed with time according to the central frequencies of the ECG and respiration monitor signals. Only the frequency band < 1.5 Hz was extracted to eliminate noise in the high-frequency band. The results for the 6-, 10-, and 16-s respiration and free respiration cases were similar, as exhibited in Fig. 2. Furthermore, the cardiac-driven component was clearly recognizable in all cases. The respiratory-driven component under the 6-, 10-, and 16-s respiratory cycles could also be clearly identified, while that under free breathing dispersed with time. Furthermore, the respiratory-driven components were lower during the longer respiratory cycle. The cardiac- and respiratory-driven CSF velocity waveforms were then extracted from the spectrograms, as shown in Fig. 3. Although the cardiac component was similar for all respiratory conditions, the respiratory component changed for each condition.

Figure 4 presents the spectrograms under a 6-s respiratory cycle with different k-factors of the S-transform. The cardiac signal is plotted in Fig. 4a–4c when the respiratory signal was on 4d–4f. When k was lower than 1, the amplitude of the velocity wave varied largely. When k = 0.1, the width of the temporal Gaussian window was approximately 0.1 s, which resulted in the broad spectrogram for the cardiac component shown in Fig. 4(a). Similarly, when k = 0.1, the window width was approximately 0.67 s, making the respiratory waveform oscillate, as shown in Fig. 4(d). In contrast, the spectrogram ridge line became narrower for both cardiac- and respiratory-driven components when the k-factor was > 1, as shown in Fig. 4(c, f).

The CSF spectrograms under free breathing for three healthy volunteers are exhibited in Fig. 5. The cardiac-driven components were clear in all cases by setting k = 4. The respiratory components were also recognizable at k = 1.5. The k-factor for the cardiac component was set to a high value because the frequency was almost unchanged with time, while that for the respiratory was between 1 and 2 since the frequency was varied.

Discussion

To explore the relationship between CSF dynamics and the state of hydrocephalus, and to investigate the driving force of the neuro-waste clearance system via CSF motion, a new technique for analyzing CSF motion was developed. The technique was based on applying an S-transform to the CSF velocity waveform measured by real-time SSFP-PC, allowing the separation of the cardiac- and respiratory-driven CSF motions. Traditional blood flow velocity measurements (such as 4D-flow) assume the use of cardiac-gated PC. However, this is not suitable for CSF motion because both the cardiac- and respiratory-driven components are mixed. In particular, under free breathing (which is preferable for most patients with neurodegenerative diseases related to CSF motion), the respiratory component of CSF is expected to have an irregular cycle. Hence, it is mandatory to extract the time-varying CSF motion. Accordingly, the present study...
was performed under both regular and free breathing to determine the practicality of the technique for both conditions.

Recently, relationships between blood pressure and subarachnoid space (SAS) width oscillations in cranium under various respiratory conditions such as 10 breaths per min, that is 0.1 Hz respiratory frequency, were evaluated, which presented the increase in the amplitude of the blood pressure and SAS width oscillations at respiratory frequency.

**Fig. 1** Example of the separation results of cardiac- and respiratory-driven CSF velocities by ST of a male, healthy volunteer aged 54 years. The CSF velocity obtained by the SSFP-PC, ECG signal, and respiratory signal of the bellows-type pressure sensor is shown in the first column on the left-hand side. Each of these waveforms was converted to a spectrogram by the S-transform, as shown in the second column. Gaussian bandpass filters (0.2-Hz bandwidth) and the center frequency matched with the ECG or respiratory signal were applied to the CSF. The cardiac- and respiratory-driven components separated by the filters are shown in the right-hand column. CSF, cerebrospinal fluid; ECG, electrocardiogram; SSFP-PC, steady-state free precession phase contrast; ST, S-transform.

**Fig. 2** Spectrograms of the cardiac- and respiratory-driven CSF velocity components under 6-, 10-, and 16-s respiratory cycles and free breathing state of the same volunteer, as in Fig. 1. The cardiac and respiratory frequencies are depicted with black solid lines in each spectrogram. The behavior of the cardiac-driven component was not varied for those respiratory conditions. The respiratory spectrogram indicated that the amplitude and peak frequency were different in each respiratory condition. CSF, cerebrospinal fluid.
band under controlled slow breathing compared with spontaneous respiration. A report indicated that deep inspiration decreases the stroke volume and deep expiration increases the volume. In addition, the stroke volume variation leads to the change in the blood pressure. Thus, the slow breathing, that is deep respiration, enhanced the respiratory...
component of the blood pressure oscillation. Meanwhile, CSF motion is expected to be affected by the blood pressure change induced by cardiac pulsation and respiration because it propagates through vessels to major arteries in intracranial space such as basilar artery. Moreover, respiration may affect the CSF motion by changing the intrathoracic pressure. Further investigation for the CSF motion in relation to the blood pressure and respiration should be conducted to clarify the driving source of the cardiac- and respiratory-driven motions.

The results demonstrated that the cardiac- and respiratory-driven velocities in the spectrogram were clearly separated in

Fig. 5 Spectrograms of the cardiac- and respiratory-driven CSF velocities at the foramen magnum under free breathing of three healthy volunteers. The (a and b) results are for a male aged 54 years, (c and d) are for a male aged 48 years, and (e and f) for a female aged 51 years. Cardiac-driven CSF velocity components are shown in the left column, while the respiratory components are in the right column. Frequencies of the cardiac- and respiratory-driven CSF velocities are indicated as black lines. The $k$-factor of the S-transform is presented at the top of each image. CSF, cerebrospinal fluid.
all respiratory conditions using the Gaussian bandpass filter. The cardiac-driven CSF velocity was investigated using cardiac-gated PC imaging, while observation of the respiratory-driven CSF motion was conducted with various techniques. By comparison, SSFP-PC, in combination with S-transform, allowed visual characterization of the real-time cardiac- and respiratory-driven CSF motions under free breathing.

In the separation results (6-, 10-, and 16-s respiratory cycle and free breathing), high CSF velocity bands appeared in the cardiac and respiratory frequency ranges. This indicated that the cardiac- and respiratory-driven CSF velocities under respiratory instruction (and free breathing) can be separated in the spectrogram successfully using the presented technique. However, an occasional decrease in respiratory-driven CSF velocity amplitude in the spectrogram was observed under free breathing. This might be attributable to a change in the physiological status, although the respiratory monitor signal continued during the data acquisition in each of the free breathing cases. The reason for such an occasional discontinuity of the CSF spectrogram requires further investigation.

The k-factor of the S-transform changed the cardiac- and respiratory-driven CSF velocity spectrograms dramatically. Moreover, both cardiac- and respiratory-driven components in the spectrograms had a narrower ridge line when using a larger k-factor. The cardiac-driven component using k = 1 had broad lines in the frequency range because the temporal resolution of SSFP-PC was relatively too low to extract the cardiac-driven CSF velocity. Nevertheless, the cardiac-driven component was extracted due to the cardiac frequency being relatively stable during the scan. Higher k-factors (< 4) yielded a clearer central frequency. For the respiratory-driven component, a k-factor of 1-2 elicited favorable results for free breathing. Accordingly, adaptive optimization of the k-factor may be required. Despite the approximate selection of the k-factor, the present technique separated the cardiac- and respiratory-driven CSF velocities under free breathing. The frequencies of the cardiac- and respiratory-driven components in the spectrogram were identical to the ECG and respiration monitor signal frequencies, although the intensity of the respiratory-driven component varied temporally. Although the cardiac- and respiratory-driven CSF velocity spectrograms can be inversely transformed to those velocity waveforms in the time domain, there is a side effect in the inverse transform of the spectrogram where a filter was applied.

One limitation of this study is that the temporal resolution of the SSFP-PC acquisition was 217 ms (corresponding to a sampling frequency of 4.61 Hz), which may not be sufficient to extract the cardiac-driven CSF velocity. To accelerate acquisition, the use of echo-planar imaging (EPI) and/or compressed sensing should be adopted. Second limitation was optimization of the k-factor, particularly for the respiratory component under free breathing. Another limitation was a few volunteers. In this study, variety between volunteers has not been evaluated. Since the optimal k-factor may be different in an individual, the variety would be evaluated in future study.

Conclusion
The presented technique uses the S-transform based on SSFP-PC imaging, which is useful for clarifying the properties of cardiac- and respiratory-driven CSF motions under free breathing and instructed breathing (with a regular period). A relatively high k-factor of the S-transform can characterize the frequency of the cardiac-driven CSF velocity component, while k = 1 extracted that of the respiratory-driven component. In addition to accelerating the acquisition and optimization of the k-factor, a comparison of cardiac and respiratory components of the CSF motion in patients with neurodegenerative disease (such as hydrocephalus) is required to investigate the relevance of the disease with these motions.

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Conflicts of Interest
Satoshi Yatsushiro is an employee of BioView, Inc., in Japan, and Kagayaki Kuroda is an adviser of BioView, Inc., in Japan. Kagayaki Kuroda, Mitsunori Matsumae, and Hideki Atsumi received a research grant from the Terumo Life Science Foundation. The other authors declare that they have no conflicts of interest.

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