Time-SLIP MRI without cardiac gating for cerebrospinal fluid flow imaging: a phantom-controlled study

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Aims and objectives

In magnetic resonance imaging (MRI), the time-spatial labeling inversion pulse (Time-SLIP) is a form of spin labeling providing quantitative and selective inflow information by placing the inversion pulse before data acquisition and background suppression [1]. Time-SLIP is a variant ASL (Arterial Spin Labeling) sequence, initially designed for unenhanced MR angiography and later implemented for visualization of different body fluids, including cerebrospinal fluid, pancreatic juice [2] and even saliva in parotid glands [3]. Our team was interested in the feasibility of Time-SLIP for reliable CSF dynamics assessment at the levels of cerebral aqueduct and C1-C2. To this end, we created a dynamic phantom for pulse sequence calibration. We also considered substituting photoplethysmography-based (PPG) cardiac gating with a simulated one. Such a modification would simplify the use of Time-SLIP in routine practice. Another goal was to study quantitative parameters such as CSF length of motion (LOM) [4] at the levels of cerebral aqueduct and C1-C2. Finally, we validated modified Time-SLIP sequence for the assessment of linear CSF flow velocity.
Methods and materials

Pulse sequence and cardiac gating

We performed Time-SLIP MRI both in vitro (on a phantom) and in vivo. The prospective cohort consisted of 9 males and 12 females with the median age of 46 years (min 23 y.o., max 84 y.o.). Informed consent was obtained in all cases. Patient distribution was as follows:

- Study unremarkable (n=9)
- Multiple sclerosis (n=7)
- Postoperative changes (n=2)
- Subependymoma (n=1)
- Parasellar mass (n=1)
- Sylvian fissure arachnoid cyst (n=1)

We performed MRI on a 1.5T unit (ExcelArt Vantage, Canon Medical Systems Corporation, Japan) with the standard head four-channel coil. The Time-SLIP sequence had the following parameters: TR=8500 ms; TEeff=80 ms; sequence type Fast Advanced Spin Echo; slice thickness 5.0 mm; selective tag slice width 30 mm; number of excitations (NEX) 7; FOV 26 × 26 cm; reconstruction matrix 128 × 256; phase encoding steps=64; flip angle=90°; black blood time interval (BBTI)=2000/3000 ms; parallel imaging acceleration factor (SPEEDER)=2. The acquisition time was 2:16 min. We substituted cardiac gating with the PPG-based simulation (a light with a fixed frequency of 160 flashes per minute, i.e., exceeding the patient's heart rate). Our earlier tests did not reveal any major differences in MRI with the real PPG and a simulated one. High NEX value allows observing a broader range of possible CSF motion within a fixed time interval. In our experience, "true" cardiac gating is not required if during the scan a random high heart rate is simulated via PPG.

Phantom

We developed a phantom simulating oscillatory CSF motion. This phantom is a modification of the earlier one [5]. The phantom is a freely rotating pulley with two polyvinyl chloride tubes stretched over it, filled with distilled water. We attached vials with contents simulating various tissues (fat, brain, water) to the phantom. A brain tissue equivalent was produced with carrageenan gel and gadopentetic acid [6]. We used a 3-meter long inextensible thread and an elastic, stretchable belt so that the phantom's movements would be oscillatory and not translatory (Fig. 1a). The amplitude of oscillations was 1.5-4.0 cm, the frequency was 50-90 cycles per minute (CPM) as per the normal heart rate range. The phantom has a motor with a crank mechanism and variable rotation speed (Fig 1b).
### Image analysis and statistics

We evaluated the images on the Intrasense Myrian multimodal console. Regions of interest (ROIs) included CSF at the cerebral aqueduct and C1-C2 levels. We calculated the phantom's length of motion (i.e., distilled water) as the arc length. We manually assessed in vivo CSF LOM on sagittal Time-SLIP series with the same window width and level for BBTI of 2000 ms and 3000 ms, respectively (Fig 2c, 2d). LOM was measured from the nearest selective tag slice to the furthest pixels with significant contrast (i.e., hyperintense relative to non-tagged CSF). Statistical analysis was performed using Statistica 8.0 software package (StatSoft Inc., USA). We utilized the Mann-Whitney U test. We used non-parametric statistics due to the small (n = 21) and heterogeneous group (by age and pathology) for which the probability of a non-Gaussian distribution is higher than in a large uniform sample. This was particularly pronounced at C1-C2 levels.
Fig. 1: The phantom’s design. 1a - The pulley, description in the text. 1b - The rotator module. A rod is attached to the motor shaft, which creates oscillatory motions. The amplitude can be regulated by fasteners attached to the rod. The rotation speed is variable.

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Fig. 2: Time-SLIP images of the phantom: A - stationary, BBTI = 2000 ms; B - stationary, BBTI = 3000 ms; C - moving, set amplitude = 1.5 cm, measured LOM (A) = 1.7 cm, rotation frequency = 51 CPM, BBTI = 2000 ms; D - moving, BBTI = 3000 ms. Each vial is numbered according to its content: 1,2,3,8,9,10 - water; 4,6 - mineral oil; 5,7 - brain tissue simulation.

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Results

Phantom study

In the phantom study, we measured length of motion (LOM) for four different fixed values of the pulley rotation speed corresponding to the heart rate of 51, 54, 60 and 93 beats per minute. The displacement amplitude correlated well for BBTI of 2000 and 3000 with the maximum difference of 37% for BPM 51.

We also chose three fixed values of the oscillation amplitude (1.5 cm; 2.34 cm; 3.9 cm) (Fig. 2b). The combined data for BBTI of 2000 and 3000 is presented in Fig 5; R2=0.63; slope, a=0.49; interception, b=2.6 cm (Fig. 4). The average measurement error was 18% with a maximum of 37%. In some cases, we observed an asymmetrical LOM both clockwise and counterclockwise, more noticeable with BBTI 3000 (Fig. 2c, 2d). This is probably related to the direction of the FASE phase-encoding gradient set to anterior-posterior. Given the relatively large scatter of data obtained in vivo, the results may be biased. A more extensive study sample is needed to obtain reliable quantitative results. This includes phantom studies synchronized ("gated") with rotation and with cardiac gating simulation applying different frequency. The results of a statistical analysis of the patient cohort are presented in Fig. 5, Fig. 6.

Cerebral aqueduct study

In the study of CSF dynamics at the cerebral aqueduct using the modified Time-SLIP sequence (Fig. 3 a,b), median (25%-75% quartile) LOM for the BBTI of 2000 ms was 13.03 (9.53-16.00) mm, and 30.25 (23.68-35.27) mm for the BBTI of 3000 ms, i.e., 2.3 times higher (Fig. 5). This can be due to an intense turbulent flow in the cerebral aqueduct [7], resulting in an exchange of CSF between the 3rd and 4th ventricles with a high LOM over several cardiac cycles covered by the BBTI. Therefore, it is necessary to clarify the "stroke volume" concept from publications on CSF flow assessment via phase contrast MRI [8]. This concept may be applicable only to one cardiac cycle.

Knowing the heart rate and assuming that the CSF moves cyclically, it was possible to estimate the speed of oscillatory movements.

Given the oscillatory nature of CSF movement, its velocity can be represented as a sinusoid. The formula for CSF flow velocity with BBTI of 2000 ms is as follows: 

\[ V(t) = V_0 \sin \theta t \]

\[ A(t) = \# V_0 (\sin \theta t ) \ dt = -V_0/ \# \cos \theta t +C \]

\[ V_0 = A_0 * \# = A_0 * 2 *\#*# \]
whereas #0 stands for apparent in vivo CSF flow amplitude (LOM), # stands for patient’s heart rate (BPM) before Time-SLIP MRI.

The median values (25%-75% quartile) obtained in with this method are presented in Fig.5 with an additional scale indicating the variations. For BBTI 2000, the LOM was 8.86 (6.48-10.89) cm/sec. This value exceeds the literature data on the phase contrast MRI, whereas the average peak velocity in the cerebral aqueduct varied from 4.26 to 5.20 cm/sec [9], or the average systolic/diastolic velocity of 2.5 cm/sec [10]. This result is likely associated with an overestimation caused by turbulent flow and CSF stirring. As such, after 2-3 cardiac cycles, Time-SLIP recorded the unidirectional non suppressed spin propagation along the aqueduct in the direction of the 4th ventricle, leading to LOM overestimation.

**C1-C2 spine study**

In the study of CSF dynamics at the C1-C2 levels, LOM was slightly higher in the caudal direction, but these differences were not statistically significant (Fig. 6). Average LOM for BBTI 3000 is 1.64 times higher than for BBTI 2000. These differences were statistically significant in all cases, albeit lower when compared to the cerebral aqueduct (1.63 vs. 2.3 times). We observed significantly higher LOM values both cranially and caudally in the ventral subarachnoid space (compared to the dorsal) for BBTI 3000 (Fig. 6). According to Ohtonari et al. 2018 [4] LOM was higher in ventral subarachnoid space compared to the dorsal. We also calculated total LOM as the median of sum LOM for ventral and dorsal surfaces, cranial and caudal directions. The maximum total length of motion was 32.81 (29.57 - 37.03) mm, which is slightly lower than the normal values (35 ##) for Chiari malformation type I patients as determined by the T-SLIP method with cardiac gated data [4].
Fig. 3: The CSF flow visualization in vivo. Tag slice borders are shown with dotted lines. Each LOM is shown with a red line. A - the CSF flow at the cerebral aqueduct, BBTI = 2000 ms; B - the CSF flow at the cerebral aqueduct (same patient), BBTI = 3000 ms. C - the CSF flow at the C1-C2 level, BBTI = 2000 ms; D - the CSF flow at the C1-C2 level (same patient), BBTI = 3000 ms.

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Fig. 4: The phantom study graph. The mean ± STD values are presented. The mean for length of motion (LOM) was measured for four different fixed values of the pulley rotation speed corresponding to the heart rate of 51, 54, 60 and 93 beats per minute. R²=0.63; slope, a=0.49; interception, b=2.6 cm. The average measurement error was 18% with a maximum of 37%.

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Fig. 5: The cerebral aqueduct CSF flow study graph. The median and 25%-75% quartile LOM values for the BBTI of 2000 ms and 3000 ms are presented as blue bars. The median and 25%-75% quartile CSF velocity amplitude values for the BBTI of 2000 ms and 3000 ms are presented as orange bars.

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**Fig. 6:** The spine C1-C2 CSF flow study graph. The median and 25%-75% quartile LOM positive values for cranial direction flow (BBTI of 2000 ms and 3000 ms) are presented as blue bars. The median and 25%-75% quartile LOM negative values for caudal direction flow (BBTI of 2000 ms and 3000 ms) are presented as orange bars.

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Conclusion

The preliminary in vitro study showed a relatively good accuracy of fluid LOM measurement with the mean variation coefficient of 18.5% (max 37%). Our modified Time-SLIP pulse sequence with high number of acquisitions (NEX) does not require real cardiac gating (simulated PPG was used). It allows evaluating CSF flow length of motion (LOM) at the levels of cerebral aqueduct and C1-C2. The CSF velocity can also be evaluated using the acquired LOM value if a patient's heart rate is known. We observed a possible overestimation of the CSF flow velocities in cerebral aqueduct compared to literature data. The difference between CSF LOM in cerebral aqueduct for BBTI 2000 and 3000 ms can be attributed to a turbulent flow of CSF and fast exchange of CSF between the 3rd and 4th ventricle.
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