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# Effects of free breathing on cerebrospinal fluid hydrodynamics: a study based on real-time phase-contrast MRI

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## Summary of Main Findings

Using real-time phase contrast MRI, the effect of free breathing on multiple parameters of CSF at the aqueduct and at the second-to-third cervical vertebrae were successfully quantified. During the expiratory phase, the amplitude, average stroke-volume and cardiac period of CSF increased.

## Synopsis

The effect of breathing on CSF is not well understood. Real-time phase-contrast MRI can quantify CSF flow continuously. A time-domain multi-parameter analysis method was developed to quantify the effect of free breathing on CSF. It was found that the cardiac period and the average stroke volume of CSF at second-to-third cervical vertebrae level and at the aqueduct were significantly increased during the expiratory phase, while the net flow of CSF was notably decreased.

## Introduction

A better understanding of the cerebrospinal fluid (CSF) hydrodynamics is essential for the diagnosis of a number of neurological disorders<sup>1,2</sup>. In addition to the cardiac contribution, breathing also affects CSF dynamics. Unfortunately, conventional phase contrast sequences with the aid of cardiac gating can only provide a reconstructed mean cardiac cycle flow curve and thus cannot study the effect of breathing on CSF<sup>3</sup>. An increasing number of studies are beginning to use real-time phase contrast (RT-PC) sequences to study the effect of breathing on CSF dynamics<sup>4-8</sup>.

Most of these studies quantify the effect of different breathing patterns on CSF by power spectrum analysis. However, this method can only quantify the effect of breathing on the net CSF flow rate. Compared to other breathing patterns, the effect of free breathing (E-Fb) on CSF is smaller and more difficult to quantify. Therefore, this study aims to quantify the E-Fb on CSF using a multiparametric time-domain analysis method.

## Methods

### - Image acquisition

10 healthy volunteers (age: 19~29; 5 women) were examined using a clinical 3T scanner, and a 32 channels head coil. A chest belt was set up to record the free breathing signals.

The RT-PC used in this study was a multi-shot, gradient-recalled echo-planar imaging sequence with a Cartesian trajectory and parallel acquisition technology. Parameters were as follows: SENSE=2.5, EPI-factor=7, FOV=140\*140mm<sup>2</sup>, pixel size acquisition=70\*70mm<sup>2</sup>. VENC, time resolution, TE/TR and number of images are shown in Fig.1-B. Direction from foot to head is defined as positive.

As shown in Fig.1-A, RT-PC sequences were acquired from two planes to quantify the CSF flow: at the aqueduct (Fig.1-C) and at the second-to-third cervical vertebrae position (C2-C3) (Fig.1-D).

### - Image Processing

All image and signal processing were performed using software – Flow 2.0<sup>9,10</sup>.

First, the continuous CSF flow rate signal is extracted after segmentation and background field correction process. Then, from this signal, the software automatically locates the maximum or minimum value of each CCFC to obtain multiple independent CCFCs (Fig.1-E red points). Each CCFC contains five parameters: net flow rate, net stroke-volume (Net-StV), amplitude, average stroke-volume (Aver-StV) and cardiac period.

### - Reconstruction of the average CCFC

The average CCFC was reconstructed using all CCFCs to quantify the CSF parameters (Fig.2-A&C). Net-StV is the sum of the positive and negative stroke-volume, and Aver-StV is the average of the absolute values of the positive and negative stroke-volume.

### - Quantification of the E-Fb on CSF

The time-domain multi-parameter analysis method has been used in previous studies<sup>11,12</sup>. The inspiratory and expiratory phases were defined using the breathing signal (Fig.2-B), and then the CCFCs within the inspiratory phase were reconstructed as CCFC-Inspi; similarly, with CCFC-Expi. From CCFC-Expi and CCFC-Inspi, the difference between expiratory and inspiratory phases ( $Diff_{Ex-In}$ ) was calculated for each parameter (Fig.2-D).

We assumed that a non-zero phase delay (*Shift*) maximizes the value of  $Diff_{Ex-In}$  for each parameter. Only by finding the appropriate *Shift* the E-Fb intensity can be correctly quantified. For this purpose, a curve with *Shift*, as the independent variable, and  $Diff_{Ex-In}$ , as the dependent variable, was automatically estimated by the software. For each parameter, the maximum or minimum  $Diff_{Ex-In}$  and its corresponding *Shift* were extracted (Fig.3).

## Results

The stroke volume of CSF at C2-C3 and in the aqueduct is  $657 \pm 163$  mm<sup>3</sup> and  $61 \pm 33$  mm<sup>3</sup>, respectively (Fig.4).

CSF at C2-C3 shows a greater tendency to flow toward the spinal canal during the expiratory phase than during the inspiratory phase. Likewise, a greater volume of CSF is drained from the aqueduct into the fourth ventricle during the expiratory phase (Net-StV in Fig.4). During the expiration, the average stroke-volume of CSF at C2-C3 and in the aqueduct is increased (Aver-StV in Fig.4).

The E-Fb ( $Diff_{Ex-In}$  and  $Shift$ ) on Net-StV is correlated with the E-Fb on Net-Flow. The E-Fb on Aver-StV and Cardiac period are correlated (Fig.5).

## Discussion

The values of CSF parameters quantified in this study using RT-PC are in reasonable agreement with the previous studies<sup>13,14</sup>. Net-flow and Net-StV values are mainly influenced by the background field correction resulting from image processing, which makes these values rather irrelevant<sup>15</sup>. However, what could be indeed a clinically relevant parameter is the E-Fb on Net-flow and Net-StV.

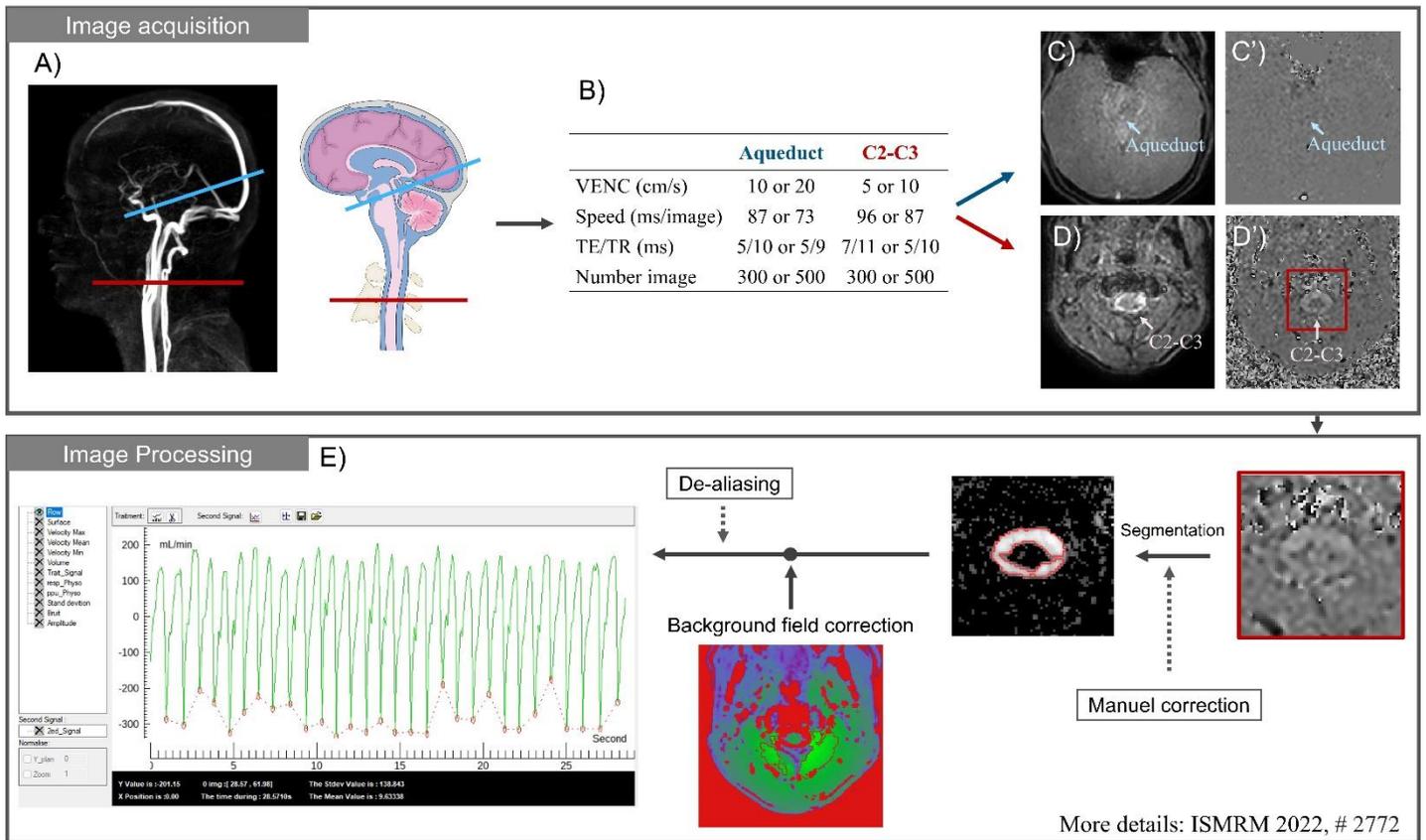
The E-Fb on multiple CSF parameters was successfully quantified using a time-domain analysis method proposed in this study. It is also confirmed that the E-Fb on each parameter can only be correctly quantified by considering a phase shift.

E-Fb on Net-StV and Aver-Stv are two very important parameters of CSF hydrodynamics and their  $Shift$  were shown to be different. For example, the E-Fb on CSF at C2-C3 during the expiratory phase increases in the cardiac period ( $Diff_{Ex-In}=7.7\%$ ,  $Shift=34\%$ ) and in the Aver-StV ( $Diff_{Ex-In}=122\text{ mm}^3$ ,  $Shift=38\%$ ), while it decreases in Net-StV ( $Diff_{Ex-In}=-263\text{ mm}^3$ ,  $Shift=6.5\%$ ). This interesting phenomenon seems to be a positive response to stabilize intracranial pressure. Evaluation of E-Fb on CSF may suggest potential markers for the diagnosis of some neurological disorders.

## Conclusion

Using RT-PC combined with post-processing software and analysis methods, the effect of free breathing on multiple CSF parameters was successfully quantified despite its complex hydrodynamics. These new findings will provide a valuable reference for subsequent studies on the effects of breathing on cerebral circulation and clinical diagnosis.

## Figures (5/5)



**Figure 1: Workflow diagram of image acquisition and processing.** The locations of the intracranial plane (blue) and extracranial plane (red) are shown in angiography images (A). The CSF information in the aqueduct (C) and at C2-C3 level (D) is extracted by RT-PC (B). After image processing (segmentation, background field correction, ...) the continuous flow signal of CSF is obtained. The software automatically locates the minimum value of each cardiac cycle flow curve (CCFC) as a split point to extract multiple independent CCFCs (E).

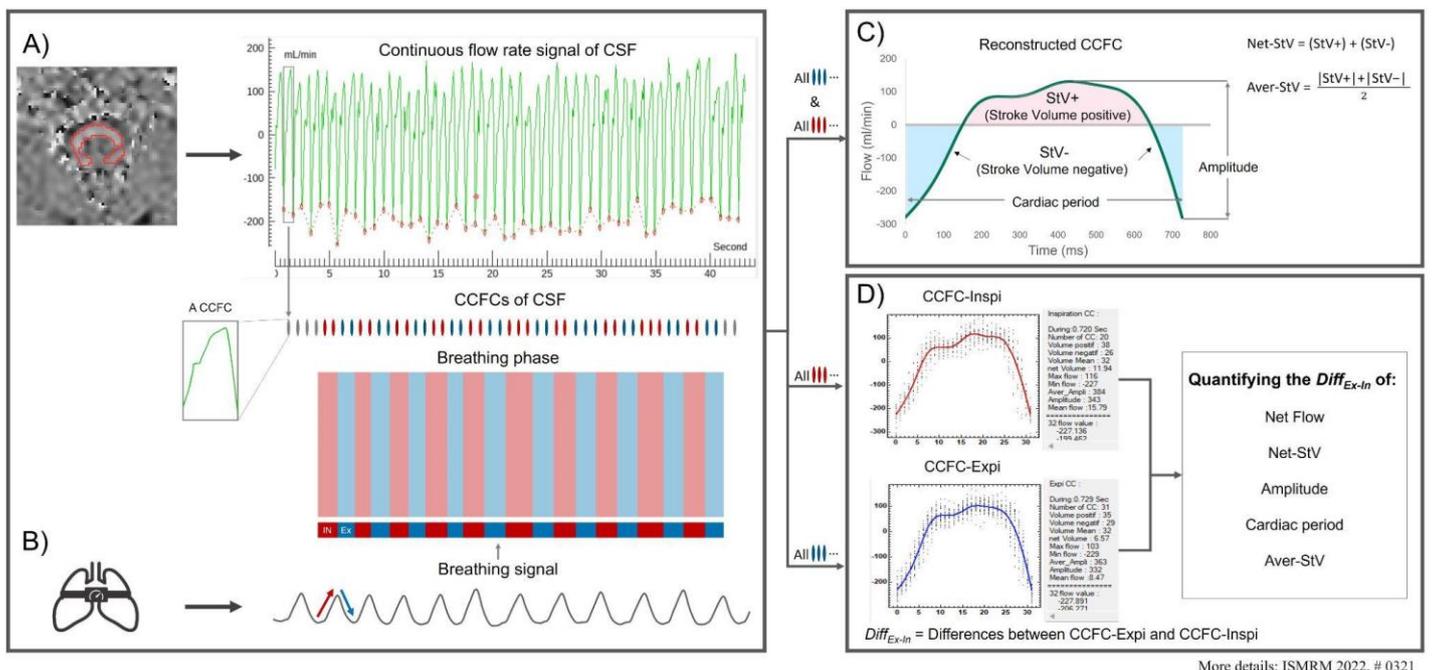


Figure 2: **Workflow chart for reconstruction of average CCFC, CCFC-Inspi and CCFC-Expi.** Multiple CCFCs are first extracted from the continuous signal (A), and then inspiratory and expiratory cycles are defined using the breathing signal (B). The average CCFC is reconstructed using all the CCFCs (C). CCFC-Inspi and CCFC-Expi are reconstructed using the inspiratory and expiratory CCFCs, respectively (D). The  $Diff_{Ex-In}$  of each parameter is calculated by comparing CCFC-Inspi and CCFC-Expi (D).

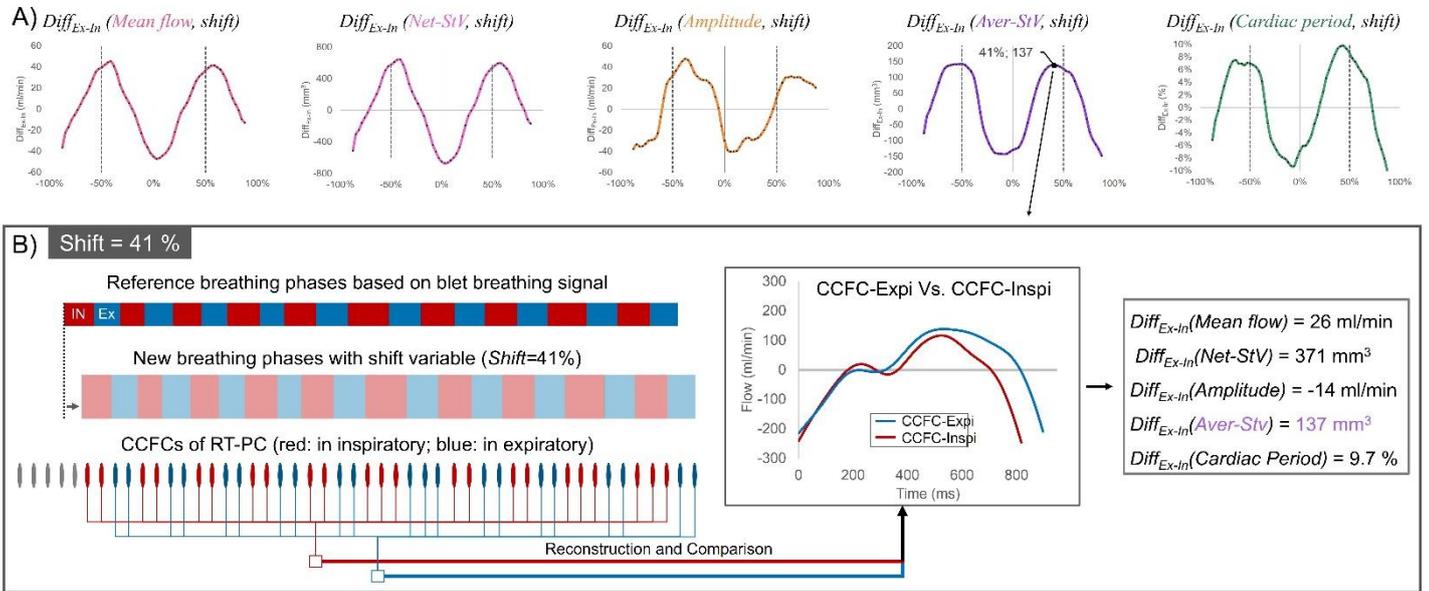
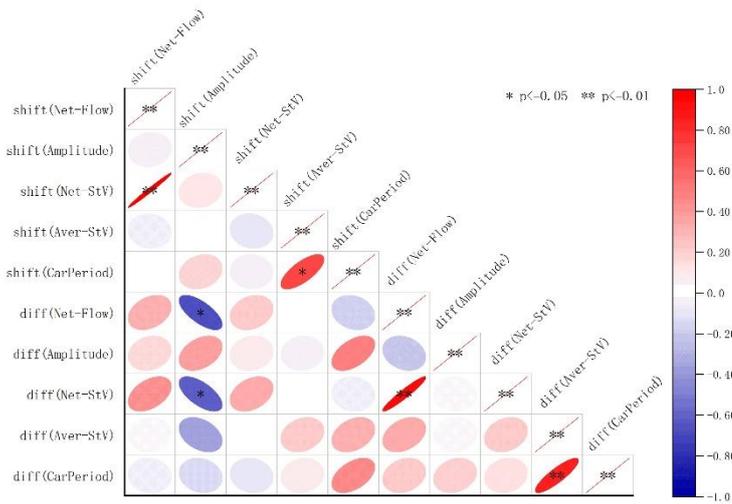


Figure 3:  $Diff_{Ex-In}(shift)$  curves for each parameter evaluated (A). Influence of Shifts(%) variation in  $Diff_{Ex-In}$ . A Shift equals to 10% indicates that the breathing signal is shifted to the right by a distance of (average breathing period  $\times$  10%) seconds. B shows an example where the  $Diff_{Ex-In}$  on each parameter is calculated for a Shift equal to 41%. For this Shift, the  $Diff_{Ex-In}$  on Aver-StV, for example, presents the maximum value.

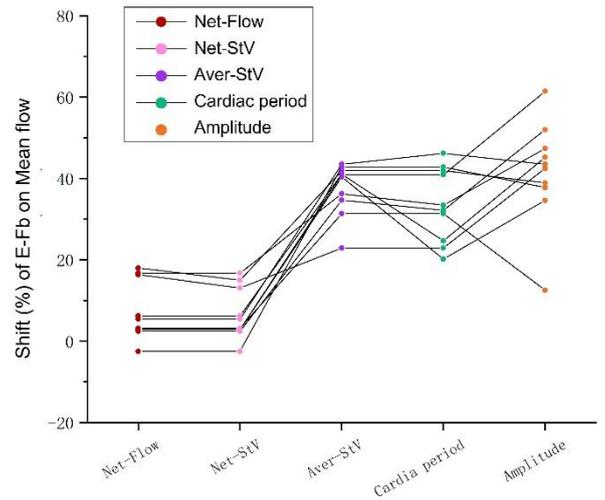
	C2-C3			Aqueduct		
	Mean value	$Diff_{Ex-In}$	Shift (%)	Mean value	$Diff_{Ex-In}$	Shift (%)
Surface (mm <sup>3</sup> )	164 $\pm$ 48			11 $\pm$ 1.8		
Net flow (ml/min)	12 $\pm$ 3.6	-19 $\pm$ 12	7.2 $\pm$ 6.8	0 $\pm$ 1.2	-4 $\pm$ 1.6	12 $\pm$ 8.5
Net-StV (mm <sup>3</sup> )	180 $\pm$ 61	<b>-263 <math>\pm</math> 170</b>	<b>6.5 <math>\pm</math> 6</b>	-6 $\pm$ 17	<b>-53 <math>\pm</math> 24</b>	<b>12 <math>\pm</math> 9.6</b>
Amplitude (ml/min)	391 $\pm$ 92	17 $\pm$ 8.4	42 $\pm$ 12	30 $\pm$ 12	4 $\pm$ 1.8	27 $\pm$ 16
Aver-StV (mm <sup>3</sup> )	<b>657 <math>\pm</math> 163</b>	<b>122 <math>\pm</math> 68</b>	<b>38 <math>\pm</math> 6.1</b>	<b>61 <math>\pm</math> 33</b>	<b>12 <math>\pm</math> 8.4</b>	<b>27 <math>\pm</math> 8.8</b>
Cardiac period (%)	.84 s $\pm$ .12 s	7.7 $\pm$ 3.4	34 $\pm$ 8.7	.83 s $\pm$ .12 s	7.2 $\pm$ 4.4	28 $\pm$ 11

Figure 4: **CSF parameters estimated at two locations (C2-C3 & aqueduct), and their E-Fb ( $Diff_{Ex-In}$  & Shift).** In both locations, during the expiratory phase, the E-fb on Net-StV decreases and on Aver-Stv increases. Net-Stv = net stroke-volume, Aver-Stv = average stroke-volume.

**A)** Correlation of  $Diff_{Ex-In}$  and  $Shift$  of each parameter of CSF (C2-C3 level)



**B)** Shift of each parameter of CSF at C2-C3 level



**Figure 5: Correlation matrix of  $Diff_{Ex-In}$  and  $Shift$  (A) and the  $Shift$  distribution (B) of each parameter. A strong correlation is presented between the E-Fb on Net-StV and on Net-Flow. The E-Fb on Aver-StV is correlated with the E-Fb on cardiac period. \* indicates  $p < 0.05$ , and \*\* indicates  $p < 0.01$  for Spearman's test. CarPeriod indicates Cardiac Period.**

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