Hemodynamic-independent Analysis of Water Molecules Fluctuation in Brain Using MRI

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(Received on October 19, 2011. In final form on January 4, 2012)

Abstract: To evaluate the hemodynamic-independent biomechanical-information of the brain, we determined changes in the regional apparent diffusion coefficient (ADC) and total cerebral blood flow (tCBF) during the cardiac cycle using magnetic resonance imaging (MRI). The water fluctuation index (WFI), which was defined as a ratio of the regional ADC and the tCBF changes during the cardiac cycle (delta-ADC and delta-tCBF), was obtained from ECG-triggered single-shot diffusion echo planar imaging and phase-contrast cine MRI, respectively. The WFI was assessed in patients with idiopathic normal pressure hydrocephalus (I-NPH, n = 2), brain atrophy or asymptomatic ventricular dilation (VD, n = 2) and in healthy volunteers (control group, n = 9). WFI's in I-NPH were clearly higher than those in VD and control because the water molecules in cerebral white matter in I-NPH easily fluctuate owing to the arterial blood volume loading of the cranium, due to the decreasing the lower compliance in I-NPH, compared with that in control. On the other hand, delta-ADC in I-NPH was higher than that in control while delta-tCBF in I-NPH was lower. However, the differences between them were lower than the WFI. WFI analysis makes it possible to obtain biomechanical information as the fluctuation of the water molecules hemodynamic-independently in the brain, and may assist in the diagnosis of I-NPH.

Key words: magnetic resonance imaging (MRI), normal pressure hydrocephalus (NPH), fluctuation apparent diffusion coefficient (ADC), cerebral blood flow (CBF)

1. Introduction

Normal pressure hydrocephalus (NPH) was introduced by Adams and Hakim in the 1965 [1]. The clinical symptoms in idiopathic NPH (I-NPH) consisted of a triad (gait disturbance, dementia, and incontinence) that improved with the removal of cerebrospinal fluid. Concerning the types of NPHs, it is particularly difficult to diagnose an I-NPH, compared with an NPH of known cause, such as trauma, subarachnoid hemorrhage, and stroke [2-4]. There are still many unsolved problems with I-NPH in terms of the diagnostic criteria and selection of appropriate patients for shunt surgery [5]. Supplemental tests are crucial to differentiate I-NPH from other diseases with clinical symptoms similar to I-NPH. The guideline for I-NPH suggests that a combination of supplemental tests can increase predictive accuracy, thus assisting in the diagnosis of I-NPH [4]. Many studies have demonstrated the usefulness of a variety of supplemental tests (e.g., tap test, saline infusion test, MRI of the brain, cerebrospinal fluid (CSF) stroke volume in the aqueduct of the cerebrum, and intracranial compliance using a phase-contrast cine MRI) [6-13]. Above all, Miyati et al. have reported that intracranial compliance calculated from the temporal waves of arterial flow, venous flow, CSF flow, and displacement of the spinal cord to the cranium during the cardiac cycle, is low in I-NPH using phase-contrast cine-MRI [14]. This suggested that the measurement of intracranial compliance as a biomechanical property of the brain can assist in the diagnosis.

On the other hand, the apparent diffusion coefficient (ADC) changes during the cardiac cycle (delta-ADC) in I-NPH increases in cerebral white matter (WM), because intracranial compliance decreases in I-NPH, even though minimizing the bulk motion effect of the brain parenchyma. Moreover, this change was synchronized with the intracranial volume change mainly related to arterial inflow [15, 16]. These authors also showed that ADC changes during the cardiac cycle provide biomechanical properties of the brain. However, the delta-ADC may depend on the hemodynamic states such as cerebral blood flow (CBF). Therefore, the aim of this study was to evaluate hemodynamic-independent biomechanical-information of the brain using regional ADC and CBF changes during the cardiac cycle.

2. Materials and methods

2.1 Confirmation of relation between ADC and tCBF changes.

Diffusion-weighted images (DWI) during the cardiac cycle in each b-value were obtained using electrocardiographic (ECG) triggered multi-phase single-shot diffusion echo planar imaging (ss-EPI), which is largely insensitive to motion. However, ss-EPI is not able to completely eliminate the bulk motion effect of the brain parenchyma, thus ss-EPI was combined with sensitivity encoding (SENSE), half-scan and rectangular field of view (FOV) techniques to minimize this effect [15]. ADC
maps in each cardiac phase were then calculated from DWI using the following equation (1) on a pixel-by-pixel basis:

\[
ADC = \frac{\ln S_1 - \ln S_2}{b_2 - b_1}
\]

where \(S_1\) and \(S_2\) are signal intensities for each b-value, and \(b_1\) and \(b_2\) are 0 and 1000 sec/mm\(^2\), respectively.

We set the transverse plane at the basal ganglia level (Fig.1(a)), and draw regions of interest (ROIs) in frontal WM on a high resolution T\(_2\)-weighted image, except for the periventricular high intensity areas (Fig.1(b)). Finally, the maximum-minus-minimum ADC values (delta-ADC) of all cardiac phase images was calculated on a pixel-by-pixel basis (Fig.1(c)). To measure the temporal wave of total CBF (tCBF) during the cardiac cycle, a retrospective cardiac-gated phase-contrast cine-MRI was then performed at a C2 level of the vertical slice plane against a midpoint on the long axis of the aqueduct (Fig.2(a)). We set ROIs in the arterial vessels on velocity-mapped images in each cardiac phase to measure the flow velocities of bilateral internal carotid arteries and vertebral arteries using the method of Alperin et al for lumen segmentation [17] (Fig.2(b)). The baseline offset due to eddy currents was then corrected using a subtraction process [18].

We multiplied the cross-sectional areas of the arterial vessels by their velocity, and the flow of four vessels was added to obtain a tCBF wave during the cardiac cycle. Finally, the maximum-minus-minimum tCBF values (delta-tCBF) of all cardiac phase images was calculated (Fig.2(c)). We then assessed the relation between delta-ADC and delta-tCBF in healthy volunteers.

2.2 Measurement of water fluctuation index (WFI)

Water fluctuation index (WFI) defined as ratio of delta-ADC value to delta-tCBF, was determined. We evaluated the WFI, delta-ADC, and delta-tCBF in I-NPH, asymptomatic ventricular dilation of brain atrophy (VD), and healthy volunteer (control). In addition, we do not make a clinical diagnosis of healthy volunteers.

2.3 Imaging conditions and study subjects

The imaging parameters of ECG-triggered ss-EPI were set at 70-100 ms echo time (TE), 256mm FOV, 0 and 1000s/mm\(^2\) b factor, 64×62 imaging matrix, 8-32 cardiac phases (Dependent heart rate), 90-degree flip angle, 2 SENSE factor, 0.61 half-scan factor, and 2 signal averaging.

The Scan parameters of a retrospective cardiac-gated phase-contrast cine-MRI were 20 ms TE, 140 mm FOV, 256×128 imaging matrix, 32 cardiac phases, 20-degree flip angle, and 80 cm/s velocity encoding.

WFI analyses were performed in patients with I-NPH (n =2, 76 +/- 0.0 years), VD (n=2, 80 +/- 2.83 years), and control (n=9, 30.3 +/- 9.13 years). Criteria for selection of I-NPH based on clinical evidence from symptoms, brain imaging and successful CSF tap test following the Japanese guidelines. It is currently recognized that VD, has a negative result of CSF tap test, is difficult to differentiate from I-NPH. Because the CSF tap test is a one of major supplemental tests for diagnosis of I-NPH that has a high positive predictive value of successful shunting, but it has the low sensitivity predicting outcome of surgery and it has clinical symptoms similar to I-NPH and Evans index greater than 0.3. The purpose and procedures of all studies were sufficiently explained to all patients.

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![Fig.1](image.png)

**Fig.1** (a) Slice plane, (b) location of regions of interest in cerebral white matter, and (c) procedure for delta-ADC.
patients, and studies were performed only after obtaining consent from each patient.

3. Result

Fig.3 shows relation between delta-ADC and delta-tCBF. There was a significantly positive correlation between delta-tCBF and delta-ADC ($R^2 = 0.55, p = 0.0133$).

The average WFI of the I-NPH group was $28.9 \times 10^{-3}$ mm$^3$/L (SD = 8.13) compared with $16.8 \times 10^{-3}$ mm$^3$/L (SD = 0.487) for the VD group and $6.12 \times 10^{-3}$ mm$^3$/L (SD = 1.35) for control group. The WFI in I-NPH was clearly higher than those in VD and control (Fig.4, Fig.7(a), (b) and (c)).

On the other hand, the average delta-ADC was higher in

**Fig.2** (a) Slice plane, (b) location of regions of interest (No. 1, 2, 3 and 4 regions of interest are the right and left internal carotid arteries, and the right and left vertebral arteries, respectively.) and (c) definition of delta-tCBF.

**Fig.3** Relation between delta-ADC and delta-tCBF in control ($R^2 = 0.556, P = 0.0133$).

**Fig.4** WFI in patients with I-NPH, VD and control.

**Fig.5** Delta-ADC in patients with I-NPH, VD and control.
the I-NPH group (mean ± SD, 0.302 ± 0.0445 ×10⁻³mm²/s) than in the VD (0.216 ± 0.0836×10⁻³mm²/s) and control groups (0.0847 ± 0.0186×10⁻³mm²/s) (Fig.5, Fig.7 (d), (e) and (f)), whereas delta-tCBF in the I-NPH (0.639 ± 0.0872 L/min) was lower than that in the VD (0.775 ± 0.321 L/min) and control (0.876 ± 0.294 L/min) (Fig.6). However, the differences of delta-ADC and delta-tCBF between I-NPH and VD were lower than the WFI.

4. Discussion

We devised a method to evaluate hemodynamic-independent biomechanical-information of the brain. Nakamura et al. have indicated that the ADC values in WM during the cardiac cycle were significantly altered and synchronized with intracranial volume change during the cardiac cycle that mainly related to the arterial flow, even though minimizing the bulk motion effect of brain parenchyma [15]. Ohno et al. applied this result, evaluated the delta-ADC in I-NPH which decreased the intracranial compliance [16]. As a described in the introduction, however, delta-ADC depends on the hemodynamic states such as cerebral blood flow (CBF). It is due to that delta-ADC is the complex hemodynamics-tissue interactions in the brain. The fact that there was significantly positive correlation between the delta-ADC and delta-tCBF (Fig.3) supports this assumption. This result also means that there is a linear system between them in a limited extent.

Since the diagnosis of I-NPH remains unclear, numerical techniques are used to identify patients with I-NPH. In particular, the simplest supplemental test for diagnosing I-NPH, i.e., a CSF tap test, shows a highly positive predictive value in successful shunt surgery, though it has the relatively low sensitivity and is invasive [6, 7]. Therefore, we attempted WFI analysis using MRI as a noninvasive examination. Fig.4 shows that the WFI in I-NPH was clearly higher than those in VD and control possibly, because the water molecules in WM in I-NPH were easily fluctuated by arterial blood volume loading of the cranium, due to the decreasing intracranial compliance in I-NPH [14]. As intracranial condition change, such as I-NPH, the power for transmission of vascular pulsation to water fluctuation in intracranial tissues is thought to change in accordance with the degree of damping the arterial pulsation. Namely, the water fluctuation of I-NPH is larger than that of VD and control. Although the delta-ADC in VD was a similar value in I-NPH, the WFI in I-NPH was greater than that in VD, because of the increase in delta-tCBF. On the other hand, the fact that the delta-ADC in I-NPH was higher than that in VD and control (Fig.5) coincided with a recent finding [10], while the delta-tCBF in I-NPH was lower than that in VD (Fig.6). However, the differences in these indices between I-NPH and VD were lower than those in WFI, despite the demonstrated contrasts between I-NPH and VD. This result also shows that delta-ADC analysis alone may not suffice to differentiate between them since delta-ADC depends on delta-tCBF, i.e., the hemodynamic state (Fig.7). In contrast, WFI
analysis is independent of the hemodynamics, and can also obtain both delta-ADC and delta-tCBF values, thus increasing the amount of clinical information.

5. Conclusion

WFI analysis makes it possible to obtain biomechanical-information based on the hemodynamically independent analysis of water molecular fluctuation in the brain, and may assist in the diagnosis of I-NPH.

References


