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HOW DOES THE PROTEIN CONTENT OF CSF AFFECT DWI THERMOMETRY?
- INITIAL RESULTS OF PHANTOM AND SUBARACHNOID HEMORRHAGE PATIENT STUDIES -

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ABSTRACT—Diffusion-weighted imaging (DWI) has already been incorporated as a regular sequence for patients. Although DWI-based thermometry has potential as a non-invasive temperature measurement method for inside the human brain, DWI might be influenced by the composition of cerebrospinal fluid (CSF). The purpose of this study was to investigate the influence of protein content in CSF for DWI thermometry on both phantom and patients. The phantom study showed that protein content <10 mg/ml did not affect DWI thermometry and low Fisher scale on DWI thermometry in patients with subarachnoid hemorrhage was unaffected by hemorrhage.

Key Words: brain temperature; diffusion-weighted imaging; cerebrospinal fluid; protein; subarachnoid hemorrhage

1. INTRODUCTION

Temperature is one of the most classical signs and has been utilized for monitoring vital condition based on a normal body temperature of around 37°C. Nevertheless, no direct, non-invasive methods for measuring internal body temperature have been established other than magnetic resonance imaging (MRI)-based methods [1, 2].

With MRI-based thermometry, the most clinically applicable method may be post-processing of diffusion-weighted imaging (DWI) [3, 4]. Although only applicable to non-restricted water, e.g., cerebrospinal fluid (CSF), this method is potentially useful in assessing the thermal physiology of the brain in both patients and healthy subjects. This method has already been applied to measuring deep brain temperature in healthy volunteers [3], for determining the relationship between tympanic temperature and deep brain temperature [4], clarifying the age-dependence of deep brain temperature in healthy volunteers [5], and applications for moya moya disease [6], head trauma [7], idiopathic normal-pressure hydrocephalus [8], and for assessing multiple sclerosis patients [9].

However, this DWI-thermometry might be influenced by the composition of CSF, which can be strongly affected by its viscosity and diffusivity [10]. We have also encountered cases showing temperature decline on DWI thermometry following head trauma [7]. In normal adults, the CSF protein concentration is in the range of 0.18-0.58 mg/ml [11]. The degree to which the protein concentration in CSF may affect the diffusion of water molecules remains in question.

The purpose of this study was to investigate the influence of protein content, which may be caused by the contamination of CSF in the brain by blood, on DWI thermometry using artificial CSF (ACSF) with variable protein concentrations at near-brain temperature. In addition, we assessed patients with subarachnoid hemorrhage (SAH), as one of the most common forms of brain hemorrhage, and discussed the effects of blood contamination on DWI thermometry.

2. METHODS

2.1 Phantom Study

2.1.1 ACSF Phantom

ACSF phantoms comprised 60 ml ARTCEREB® irrigation and perfusion solution for cerebrospinal surgery (Na^+, 145 mEq/l; K^+, 2.8 mEq/l; Mg^{2+}, 2.2 mEq/l; Ca^{2+}, 2.3 mEq/l; Cl^-, 129 mEq/l; HCO_3^-, 23.1 mEq/l; P, 1.1 mmol/l; glucose, 0.61 g/l; pH 7.3; Otsuka Pharmaceutical Factory, Naruto, Japan) and 0-10,004.8 mg albumin from bovine serum (pH 7; Wako Pure Chemical Industries, Tokyo, Japan).

2.1.2 DWI for ACSF phantom

DWI was acquired five times using a 1.5-T scanner (Sonata; Siemens, Erlangen, Germany) equipped with a receive-only CP head array coil. DWI was performed in the axial plane using a spin-echo echo planar imaging diffusion-weighted sequence (repetition time (TR), 3500 ms; echo time (TE), 79 ms; flip angle, 90°; bandwidth, 1955 Hz/pixel; slice thickness, 5.0 mm; matrix size, 128×128; field of view (FOV), 230 × 230 mm; number of excitations, 3; three slices; b value, 800 s/mm^2; motion-probing gradient (MPG), six directions; zero filling interpolation). Due to the maintenance of a consistent temperature for samples in the magnetic resonance magnet, we produced water-jacket-style thermal maintaining equipment (Fig. 1 [12]), and acquired images at a controlled temperature (around 37.0ºC, monitored using an MRI-compatible optical fiber thermometer).

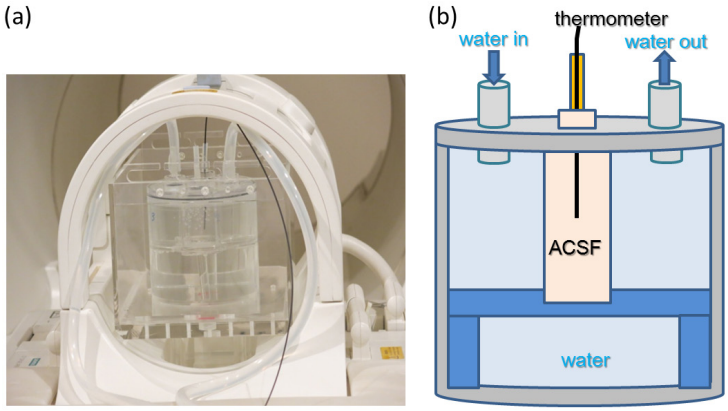

Figure 1. Water-jacket-style thermal maintenance equipment. (a) Set in head coil of MRI scanner. (b) Graphical representation of the equipment.

2.2 Patient Study

2.2.1 SAH Patients

This patient study was approved by the institutional review board (the Ethics Committee of Kyoto Prefectural University of Medicine) and informed consent was obtained from all subjects. DWI data for 9 SAH patients (2 men, 7 women; mean (± standard deviation) age, 55.8 ± 13.1 years; range, 35-66 years) were retrospectively used for assessing deep brain temperature. The hemorrhage severity of SAH patients were categorized to three levels (Fisher scale, 2-4) by an experienced radiologist (J.T.) using computed tomography (CT). The Fisher scale is summarized as follows: 1) no blood; 2) diffuse thin (<1 mm) SAH without clots; 3) localized clots and/or layers of blood >1 mm thickness; 4) intracerebral or intraventricular blood (±SAH). A demographic summary of SAH patients is shown in Table I.

Table I. Demographic summary of SAH patients.

#	FS[a]	Age	Sex	Vent[b]	Medu[c]	Scan day[c]	Case of SAH[e]
1	2	60	F	-	-	1	Basilar top aneu.
2	2	66	M	-	-	4	s/o ip-SAH
3	2	35	F	-	-	2	f-l-ICA aneu.
4	3	43	M	-	+	3	s/o ip-SAH
5	3	63	F	-	+	5	f-l-MCA aneu.
6	3	66	F	-	+	0	r-MCA aneu.
7	4	66	F	+	+	0	f-r-MCA aneu.
8	4	65	F	+	+	3	l-ICA aneu.
9	4	38	F	+	+	5	r-A-com aneu.

a) Fisher scale, b) hemorrhage in ventricle, c) hemorrhage in medullary cistern, d) scan after incident (day), e) aneu: aneurysm, ip: idiopathic perimesencephalic, f-: fraction, r-: right, l-: left, MCIA: middle cerebral artey, ICA: internal carotid artery, A-com: anterior communicating artery

2.2.2 DWI for SAH patients

All DWI was obtained using a 1.5-T whole-body scanner (Gyroscan Intera; Philips Medical Systems, Best, the Netherlands). Single-shot echo planar imaging (EPI) was used for DTI (TR, 6000 ms; TE, 71 ms; MPG, 15 orientations; b-values, 1000 s/mm^2; averaging of two images; FOV, 230 mm). A parallel imaging technique (SENSE) was used to record 128 × 53 data points, which could be reconstructed to images equivalent to a 128 × 106 matrix. Data were zero-filled to generate images with a resolution of 128 × 128. A total of 20 slices with a thickness of 3 mm each were obtained without inter-slice gaps. All trans-axial slices were obtained using a plane parallel to a line passing through the anterior and posterior commissures of the brain (AC-PC line).

2.3 Conversion of Diffusion Coefficient to Temperature

The diffusion coefficient along the direction of motion-probe gradient i was calculated by Equation (1) and converted to a temperature [3]:

$$D_i = \ln (S_0 / S_i) / b \quad (1),$$

where D_i is the diffusion coefficient [mm^2/s] along direction i, b is the applied diffusion weighting [s/mm^2], and S_0 and S_i are the voxel signal intensities of the reference and diffusion-weighted images along diffusion direction i, respectively. The value D_i was converted to the corresponding temperature using Equation (2):

$$T_i = 2256.74 / \ln (4.39221 / D_i) - 273.15 \quad (2),$$

where T_i is in units of degrees Celsius [°C]. Temperature within the lateral ventricle (LV) was determined according to the procedure described in this subsection. Mean temperature was calculated using a histogram curve-fitting method [4]. The region of interest was manually segmented on the b0 image. An optical fiber thermometer (FL-2400; Anritsu Meter, Tokyo, Japan) was used as a reference for phantom measurement.

2.4 Viscosity Measurement of ACSF

The viscosity of ACSF was measured at the same temperature as MRI acquisition (37.0ºC) using an Ubbelohde viscometer (#0; Sibata Scientific Technology, Saitama, Japan) and the method was based on Japan Industrial Standard K2283-2000. Mean kinematic viscosity (from five measurements) of ACSF was calculated as Ct, where C is the viscometer constant (0.003539 mm^2/s^2) and t is the ACSF migration time in the viscometer.

2.5 Statistics

Comparisons were performed using paired t tests (Matlab; The Mathworks, Natick, MA). Correlations showing values of $p<0.05$ were evaluated as significant.

3. RESULTS

3.1 Protein Concentration vs. Viscosity on ACSF

Figure 2 shows the relationship between albumin concentration and kinetic viscosity. The difference in kinetic viscosity between distilled water and ACSF was not significant ($p = 0.49$) at 37.0ºC. Kinetic viscosity increased linearly with ACSF solution albumin concentration ($R^2 = 0.9736$). The difference between distilled water and ACSF without albumin was 1.70%. The maximum albumin content (200 mg/ml, 1,000× normal human adult) was increased 68.1% from normal albumin content (0.5 mg/ml) at 37.0ºC.

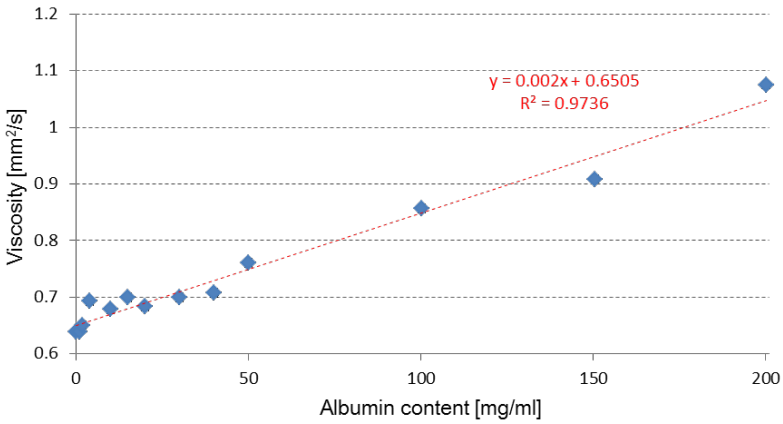

Figure 2. Relationship between albumin concentration and viscosity (37.0°C).

3.2 Protein Concentration vs. Diffusion Coefficient on ACSF

Figure 3 shows the relationship between albumin concentration and the diffusion coefficient obtained from DWI. No significant positive or negative relationships were identified between albumin concentration in ACSF solution (<10 mg/ml, 20× that of human adult in area A and diffusion coefficient), and the linearity between albumin concentration and diffusion coefficient was very low (R^2 = 0.0994). Conversely, when albumin concentration was >15 mg/ml (area B), a strong negative linear correlation existed between albumin concentration and diffusion coefficient (R^2 = 0.9914).

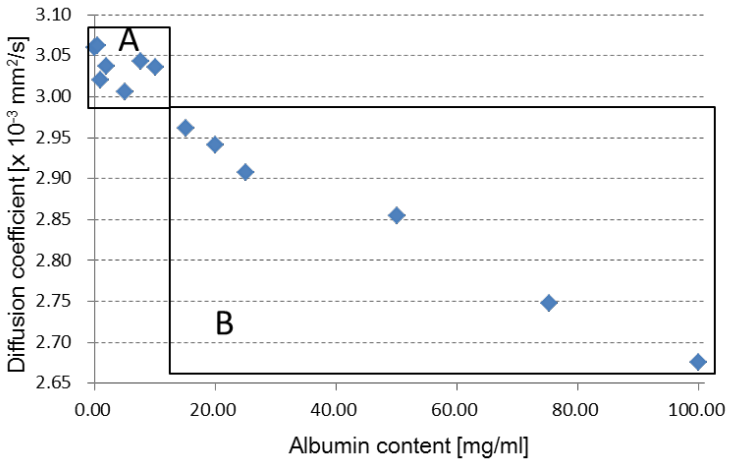

Figure 3. Relationship between albumin concentration and diffusion coefficient (around 37.0ºC).

3.3 Protein Concentration vs. DWI Thermometry on ACSF

Figure 4 shows the relationship between albumin concentration and results of DWI thermometry. No significant declining affect by content of albumin was seen when albumin concentration was <10 mg/ml (area A). Because DWI thermometry uses the diffusion coefficient, the same trend was observed in area B with Figure 3.

Figure 5A shows the Bland-Altman plot between the temperature setting and the results of DWI thermometry with lower albumin content (<10 mg/ml, area A in Fig. 4), while Figure 5B shows the Bland-Altman plot for area B (>15 mg/ml) in Figure 4. From the Bland-Altman analysis, no fixed or proportional biases were evident between temperature setting and the results of DWI thermometry in area A. In addition, all observed data in area A were within the 95% confidence interval. In contrast to area A, area B shows strong fixed and proportional biases between the temperature setting and the results of DWI thermometry.

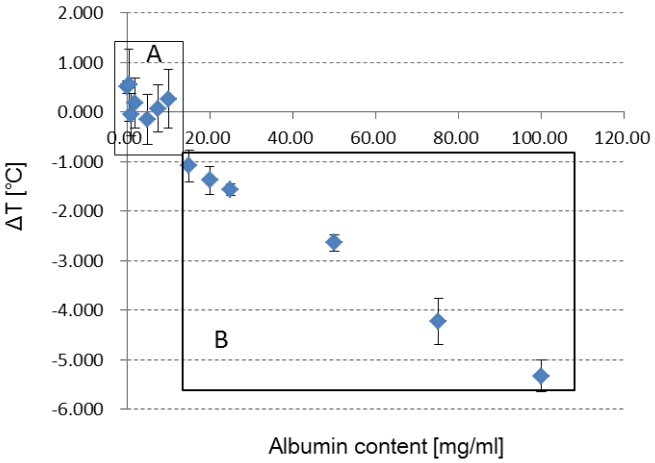

Figure 4. Relationship between albumin concentration and results of DWI thermometry (around 37.0ºC). ΔT represents the difference between temperature setting and observed temperature.

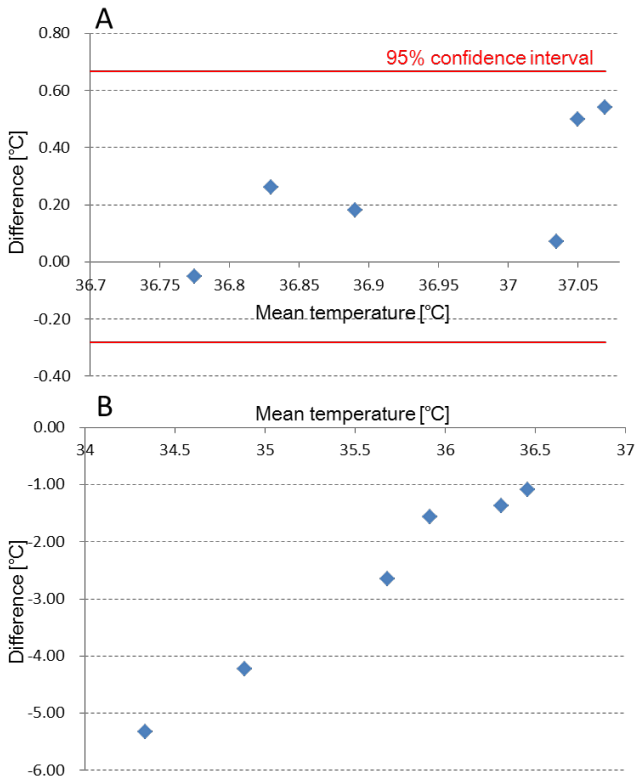

Figure 5. Bland-Altman plot between temperature setting and results of DWI thermometry.

3.4 Summary of SAH Patients

When the patient had an aneurysm in the brain and a high hemorrhage level according to the Fisher scale, blood was observed in the ventricle and medullary cistern. The presence of blood at the medullary cistern severely affects the results of DWI thermometry. DWI was performed at a variable duration after the hemorrhage incident (<5 days). This may also represent a parameter affecting the results of DWI thermometry in hemorrhage patients.

3.5 DWI Thermometry on SAH Patients

Figure 6 shows representative CT images from SAH patients categorized as Fisher scale 2-4 (FS2-FS4). Differences among Fisher scale and blood-covered area around the medullary cistern were well-depicted.

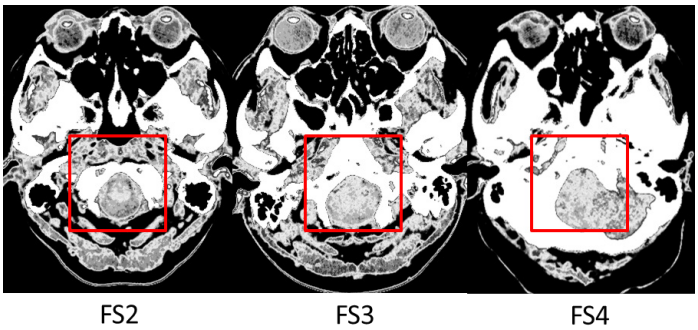

Figure 6. Representative CT images for SAH patients. The inside of the rectangle includes the region around the medullary cistern. White-colored voxels represent blood contamination.

Figure 7 shows the results of DWI thermometry for SAH patients. No strong correlation was apparent between severity of hemorrhage and temperature, and no significant group differences were evident based on Fisher scale (FS2-3, p=0.07; FS3-4, p=0.57; FS1-3, p=0.06). The FS2 group showed no effects on DWI thermometry when compared to FS2 and FS3.

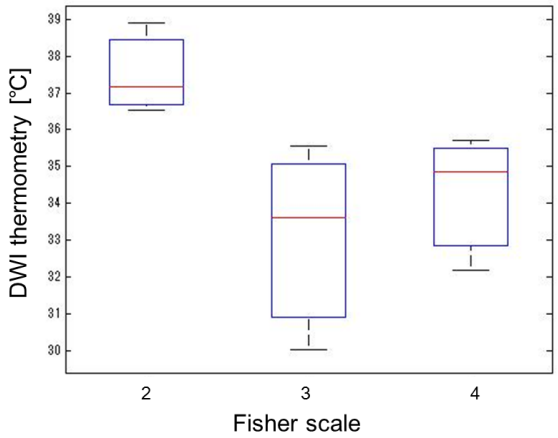

Figure 7. Relationship between hemorrhage severities of SAH patients based of Fisher scale and results of DWI thermometry.

Figure 8 shows the relationships between DWI thermometry and number of days between SAH and DWI. The day of DWI also differed among patients. When the Fisher scale was larger than 2 and the scan day was the same as the onset (0 day), the effect of hemorrhage on DWI thermometry was larger than under other conditions. This may clearly show the effect of hemorrhage on DWI thermometry in SAH patients.

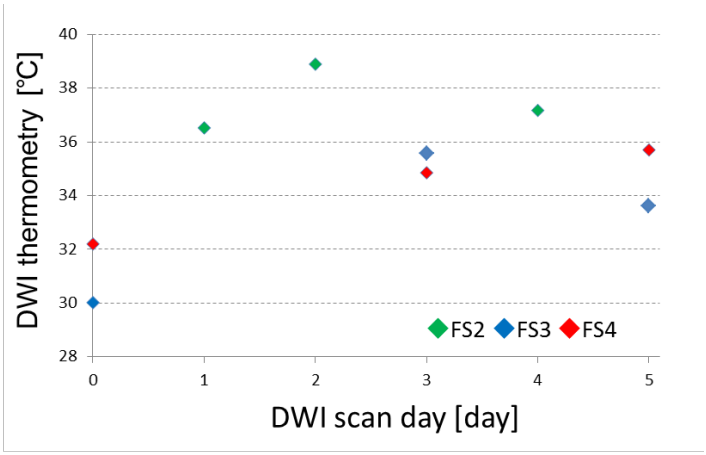

Figure 8. Relationships between DWI scan day and results of DWI thermometry. FS, Fisher scale.

4. DISCUSSION

From our ACF phantom measurement, albumin content <10 mg/ml did not affect the measurement of free diffusion of water molecules by DWI. DWI thermometry was thus effective under this condition. Although other water-soluble and -insoluble proteins existing in human blood should be considered, the effects of these proteins may show similar trends to those of albumin.

In this initial consideration of ACSF, we only treated protein content and viscosity as factors affecting DWI thermometry. Another extremely important factor for DWI thermometry in the human brain is the movement of CSF, which consists of not only diffusion, but also to-and-fro motion and fast flow. For reliable DWI thermometry of the human brain, CSF movements might be considered in further endeavors.

From the results of measurement in SAH, when Fisher scale was less than 3, hemorrhage had no effect on DWI thermometry. A small amount of hemorrhage, as with Fisher scale 2, thus has a negligible effect on DWI thermometry, allowing this method to be used for monitoring patient brain activity. The Fisher scale has already been widely recognized for estimating hemorrhage severity in the cranial region. This scale might thus be useful as a decision-making standard for DWI thermometry in patients with brain hemorrhage.

DWI thermometry uses LV area for calculating temperature. From this study of SAH patients, blood in the medullary cistern also affected the results of DWI thermometry. Hemorrhage in the medullary cistern and in other cisterns must therefore be considered when utilizing DWI thermometry.

In addition to the severity of hemorrhage, the timing of DWI also impacts the results of DWI thermometry. Our result showed that a reduction in hemorrhage affects DWI scan day for patients categorized as Fisher scale 3 or 4 (Fig. 8). If we can determine the most appropriate timing for DWI thermometry after severe hemorrhage, this method might still be useful for monitoring patient brain activity.

Although the ACSF study showed the effects of protein on DWI thermometry with increasing viscosity of ACSF solutions, no direct evidence has been accumulated for the relationship between hemorrhage and declining results of DWI thermometry in SAH patients. To obtain such evidence, we have to elucidate the relationship between protein content in CSF and effects on DWI

thermometry. In addition, further study is needed regarding whether declining results of DWI thermometry are attributable to the effects of blood contamination of CSF or declines in brain activity due to brain disorders.

Limitations: The present ACSF study only used albumin as a representative protein in human blood. Other proteins present in blood would presumably also affect DWI thermometry. Further studies are needed to identify the effects of those proteins. In the SAH patient study, we could only obtain results for 3 patients in each Fisher scale groups. Appropriate statistical power for group comparisons would require further investigation with a suitably larger cohort.

5. CONCLUSION

We assessed the temperature of both protein-contaminated ACSF and in SAH patients using DWI thermometry. The ACSF phantom showed that protein content <10 mg/ml did not markedly affect DWI thermometry, while DWI thermometry in SAH patients with low Fisher scale was unaffected by hemorrhage**.**

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