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Brain-core temperature of patients before and after orthotopic liver transplantation assessed by DWI thermometry

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Abstract

Purpose To assess brain-core temperature of end-stage liver disease patients undergoing orthotopic liver transplantation (OLT) using a temperature measurement technique based on the apparent diffusion coefficient of the cerebrospinal fluid in the lateral ventricles.

Materials and methods The study group was composed of 19 patients with a model for end-stage liver disease (MELD) score of 23.7 who underwent MR imaging before and after OLT. MR imaging studies were performed with a 1.5T MR scanner. Brain-core temperature (T : °C) was calculated using the following equation from the apparent diffusion coefficient (D) of the cerebrospinal fluid in the lateral ventricles: $T = 2256.74/\ln(4.39221/D) - 273.15$ measured with a DWI sequence (b value 1000 s/mm²). We compared brain-core temperature of all patients before and after OLT.

Results Brain-core temperature measurements were successfully taken in all patients before and after OLT. The measured brain-core temperature mean \pm standard deviation was 38.67 ± 1.76 °C before OLT and 38.60 ± 0.99 °C after OLT, showing no significant difference ($P = 0.643$).

Conclusions Brain-core temperature was stable in patients undergoing OLT. DWI thermometry may provide a supplementary brain biomarker to confirm that cerebral blood flow and metabolism are stable in patients undergoing OLT.

Keywords Diffusion-weighted imaging temperature · DWI thermometry · MR imaging · Ventricular temperatures · Orthotopic liver transplantation

Abbreviations

ASL Arterial spin labeling

CBF Cerebral blood flow

CMRO₂ Cerebral metabolic rate for oxygen

CSF Cerebrospinal fluid

DWI Diffusion-weighted imaging

FLAIR Fluid-attenuated inversion recovery

FSE Fast-spin-echo

FOV Field of view

LV Lateral ventricles

MELD Model for end-stage liver disease

MR Magnetic resonance

MRI Magnetic resonance imaging

OTL Orthotopic liver transplantation

PWI Perfusion-weighted imaging

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Introduction

Neurologic complications affect up to 15–30% of liver transplant recipients, and their etiology is significantly related to immunosuppressant neurotoxicity and opportunistic infections occurring after the transplantation rather than cerebral hemodynamic and metabolic abnormality occurring during the surgical procedure [1, 3]. On the other hand, liver transplantation is also known to substantially affect the cerebral blood flow (CBF) [2, 3]. During orthotopic liver transplantation (OLT), and after graft reperfusion, cerebral autoregulation is impaired due to cerebrovascular dilatation. Cerebral

blood flow, which becomes uncoupled from cerebral metabolic rate for oxygen (CMRO₂) may vary uncontrollably [2]. Changes in CBF and cerebral metabolism associated with the hemodynamic imbalance, which can occur during OLT, can be extremely dangerous for brain perfusion [3]. Though OLT rapidly restores normal liver function, there are little data available regarding the variation of cerebral hemodynamics and metabolism in patients undergoing OLT [3]. The improvement in the cerebral metabolism is difficult to assess in the acute post-transplant period with standard magnetic resonance (MR) imaging techniques [3]. Few studies have shown that changes in the basal ganglia and white matter can be reversible. They have shown that morphological change by MR imaging and metabolites on MR spectroscopy can be restored in months after OLT [4, 5].

Cerebral metabolism is responsible for the production of brain heat. The generated heat is removed mainly through the circulation of blood in the intracranial vessels and the circulation of the cerebrospinal fluid (CSF) in the ventricular system. The balance between heat production and heat removal allows maintenance of a stable temperature in the brain parenchyma. Due to the neuronal metabolism, the brain temperature is usually approximately 1 °C higher than the body-core temperature [6]. MR with diffusion-weighted imaging (DWI) is a relatively new, easy, and non-invasive method to assess the brain temperature, feasible in routine clinical MR imaging. This method is based on the measured apparent diffusion coefficient of the CSF in lateral ventricles to calculate the temperature of the cerebrospinal fluid [7].

The purpose of our study was to evaluate the brain-core temperature of adult patients with end-stage liver disease before and after OLT. We employed the DWI sequence routinely used for the standard brain MR imaging protocol as a non-invasive temperature measurement technique based on the apparent diffusion coefficient of the cerebrospinal fluid in the lateral ventricles.

We tried to evaluate if brain-core temperature is coupled with brain metabolism and brain perfusion and its fluctuations in response to brain hemodynamics or metabolic changes during OLT could be used as a potential biomarker for hemodynamic or metabolic impairment occurring during OLT that can lead to acute neurologic complications.

Materials and methods

Patient population

Our retrospective cohort study was reviewed and approved by the Institutional Research Review Board (IRRB) of our institute, and informed consent form was waived; however, informed written consent to the MR was obtained from all patients.

Brain MR exams of 59 patients who were eligible for OLT were collected retrospectively from January, 2014 to January, 2017.

These MR exams were part of another research project aimed at assessing the preexistence of cerebral risk factors in patients who were candidates for liver transplantation at our institute.

Among the 59 patients, we selected only 27 patients, who then underwent brain MR imaging at 1.5T with the same MR unit and with the same DWI MR sequence parameters to avoid differences in DWI temperature calculation among different MR units or DWI sequence parameters. Patients with poor DWI image quality ($n=8$) were excluded from the study.

Ultimately, the study group consisted of 19 patients (16 men, 3 women; age range 42–70 years, mean age 57.9 ± 7.4 years). The mean score for the Model for End-Stage Liver Disease (MELD) [8] was 23.7 (range 18–31, $SD \pm 3.3$).

All of the patients underwent brain MR imaging within 30 days (range 7–26 days, mean 13.4 days, median 12 days) before OLT, and within 30 days (range 10–23 days, mean 14.3 days, median 13 days) of OLT. The etiology of end-stage liver disease was diagnosed as follows: $n. 1$ drug-related fulminant hepatic failure; $n. 3$ non-alcoholic steatohepatitis, $n. 8$ hepatocellular carcinomas, $n. 3$ HCV/HBV/HDV-infection-related, $n. 1$ primary biliary cholangitis, $n. 1$ acute liver failure on chronic sclerosing cholangitis, $n. 1$ cryptogenic cirrhosis, and $n. 1$ liver cirrhosis.

Neurologic evaluation of all patients before and after OLT was done to assess the presence of acute neurological deficits before OLT and the possible onset of acute neurological complications after the surgical procedure.

MR examination

The MR exams were done on a 1.5T MR scanner (Signa Excite, General Electric Medical Systems, Milwaukee, USA).

The DWI images were acquired with the following parameters: repetition time (TR), 6000 ms; echo time (TE), 88 ms; b value, 1000 s/mm²; image averaging, two times; field of view (FOV) 230 mm; motion-sensitizing gradients applied in 15 directions; and 42 3-mm-thick sections obtained without intersection gaps. The duration of gradient pulse and the interval between the gradient pulses (Δ/δ) were 64.1/40.9 ms. Diffusion time was 50.5 ms. Acquisition time was 3 min.

Additional conventional MR imaging protocols included axial and sagittal fast-spin-echo (FSE) T2 W [5100/110 (TR/TE)] images, axial fluid-attenuated inversion recovery (FLAIR) [8000/140/2400 (TR/TE/TI)] images, along with axial, sagittal, and coronal non-enhanced and

contrast-enhanced (0.1 mmol/Kg gadobutrol-Gadovist, Bayer, Leverkusen, Germany) FSE T1 W [650/15 (TR/TE)] images with an FOV of 22 cm, matrix 320×320 , slice thickness 5 mm, intersection gap 1 mm, and number of excitations 2.

Image analysis and temperature estimation

The kinetic theory states that a direct relationship exists between the absolute temperature and the diffusion coefficient. MR can be adopted to measure the diffusion coefficient of non-restricted water molecules [9]. Studies by Mills [10] and Kozak et al. [11] found that the temperature of the CSF can be estimated using the diffusion coefficient detected by MR.

The lateral ventricle regions for each patient were extracted using an automatic region-growing segmentation procedure, in which lateral ventricle area is segmented by using region growing with the probability 0.1–1.0 on the CSF existing ratio map as previously described [12, 13] (Fig. 1). The apparent diffusion coefficient of the lateral ventricle regions extracted was calculated using the following, previously reported, equation [11, 12]:

$$D = \frac{\ln(S_0/S)}{b},$$

in which D is the apparent diffusion coefficient (square millimeters per second), b is the applied diffusion weighting (seconds per square millimeter), and S_0 is the voxel signal intensities on echo-planar images with no diffusion weighting ($b=0$ s/mm²) to obtain signal decline due to diffusion phenomena by diffusion-weighted imaging and S is the voxel signal intensity in DWI ($b=1000$ s/mm²) images. The brain-core temperature (T in °C) was calculated using the following equation, applying the calculated D value:

$$T = \frac{2256.74}{\ln\left(\frac{4.39221}{D}\right)} - 273.15.$$

The temperature estimation of CSF is calculated within the lateral ventricles, because this method is only applicable to non-restricted water, and the diffusion of the CSF is almost equal to the free diffusion of pure water. The estimated temperature of the lateral ventricle was compared in patients before and after OLT.

Statistical analysis

Statistical analysis was done using a non-parametric Mann–Whitney U test to compare the patient's brain-core temperature before and after OLT. The test is based on

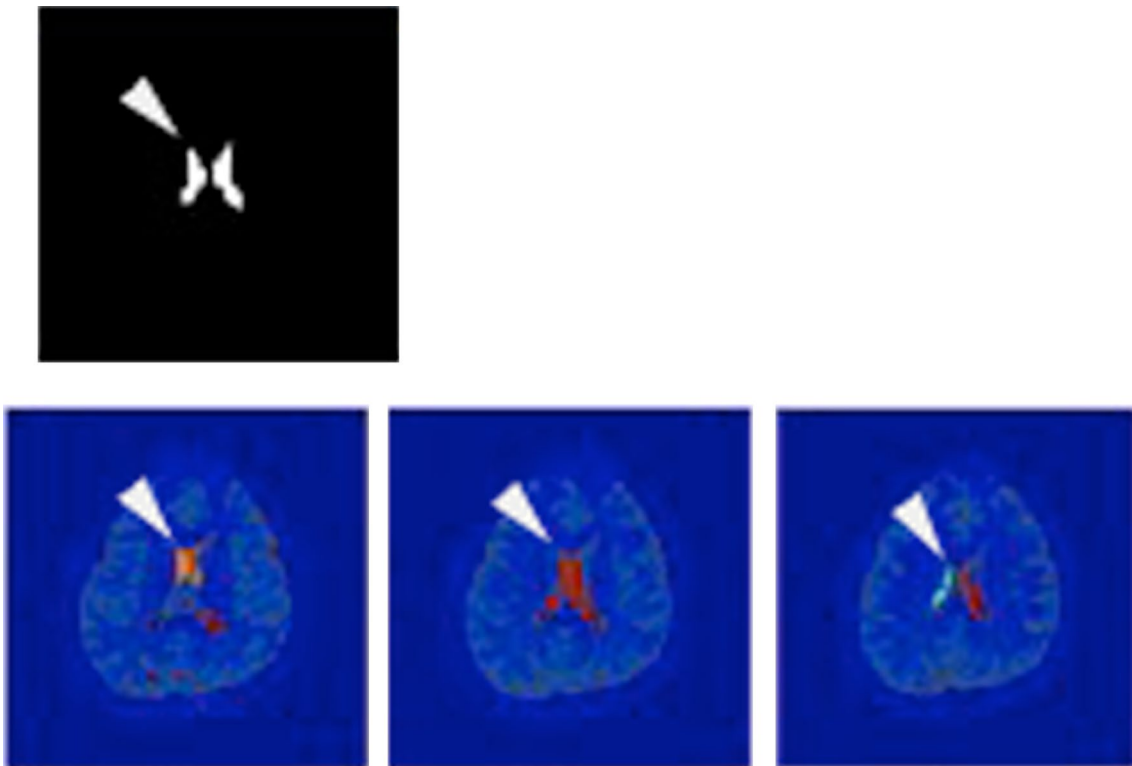


Fig. 1 Lateral ventricle regions (arrowhead) extracted using an automatic region-growing segmentation procedure

the null hypothesis that it is equally likely that a randomly selected brain-core temperature value from a sample measured before OLT will be less than or greater than a randomly selected brain-core temperature value from sample measured after OLT.

A $p < 0.05$ was considered statistically significant for the correlation. The statistical analysis was done using SPSS Statistics software (SPSS, Chicago, IL, USA). As the sample size for this study was small, we assessed the power of the Mann–Whitney U test with the analysis software G*Power version 3.1.9.2 (Heinrich-Heine-University Düsseldorf, Germany) to ensure that statistical power of 0.90 for the result was achieved comparing the brain-core temperature of 19 patients before and after OLT.

Results

The brain-core temperature was successfully measured non-invasively in all patients before and after OLT using magnetic MR diffusion-weighted imaging thermometry technique. The mean \pm standard deviation of the brain-core temperature measured before and after OLT was 38.67 ± 1.76 and 38.60 ± 0.99 °C, respectively (Fig. 2). There was no statistically significant difference between the

estimated temperature before and after liver transplantation ($P=0.643$, risk of beta-error=0.90). In all patients, no acute neurological deficits were found before OLT, and no neurological complications were found following the surgical procedure.

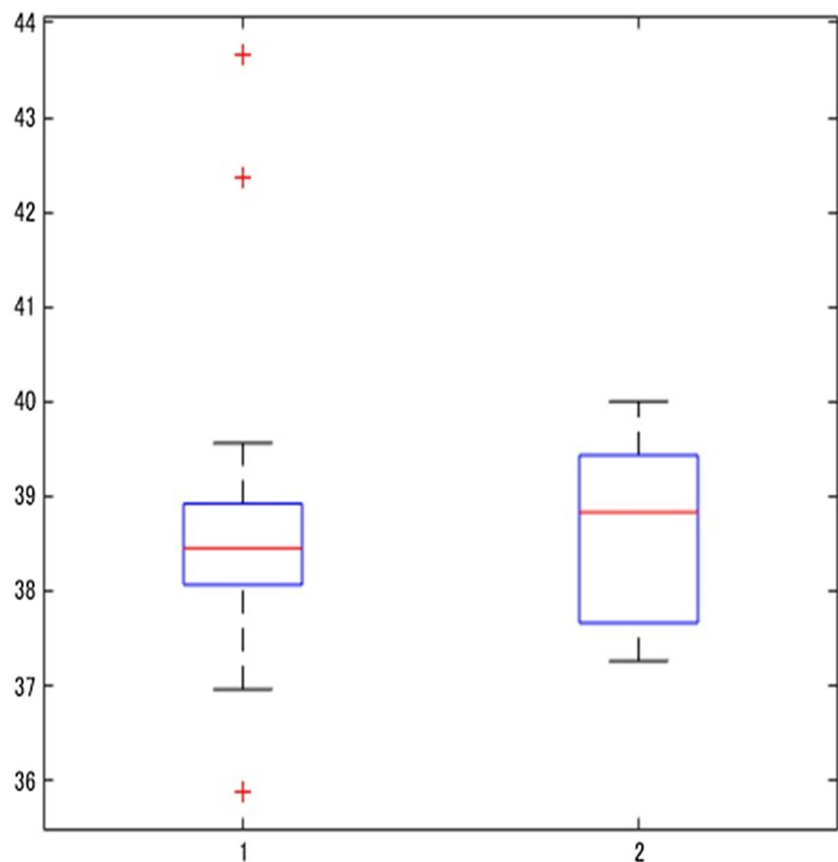
Discussion

The results of this study evidenced no statistically significant difference in brain-core temperature, measured with DWI thermometry, in patients before and after OLT. To the best of our knowledge, no other study has investigated the brain-core temperature using DWI thermometry in patients who have undergone OLT.

Though OLT rapidly restores normal liver function, little is known about the variation of cerebral hemodynamics and metabolism in patients undergoing liver transplantation [3]. During OLT, hemodynamic instability frequently occurs, particularly after reperfusion of the liver graft. The alteration of the physiological process of autoregulation of cerebral hemodynamics and metabolism may worsen the neurological outcome of patients undergoing OLT [3, 14].

Recent studies show a decreasing frequency of neurologic complications, reflecting improved transplant procedures

Fig. 2 Graph representing mean \pm standard deviation of the ventricular cerebrospinal fluid temperature (LV Temp) expressed in °C in patients before (1) and (2) after orthotopic liver transplantation measured using DWI-based MRI thermometry. No significant difference was observed (38.67 ± 1.76 vs. 38.60 ± 0.99 °C, Mann–Whitney U test: $P=0.6403$, risk of beta-error=0.90)



and advanced management regimens, which have changed the type of neurologic complications from acute post-transplant neurologic complications toward chronic neurologic complications [15]. The etiology of neurologic complications affecting liver transplant recipients is significantly related to immunosuppressant neurotoxicity and opportunistic infections occurring after the transplantation rather than cerebral hemodynamic and metabolic abnormalities occurring during the surgical procedure [14–17].

In this study, we hypothesized that if an alteration of the cerebral blood flow occurs during the transplant that can have a rapid impact on the cerebral metabolisms [3], it may result in a possible fluctuation of the brain-core temperature. In our patient population, brain temperature was stable after liver transplantation, and no acute post-transplant neurologic complications occurred, suggesting that no significant changes in brain metabolism and cerebral blood flow took place during surgery. Other studies have reported that the cerebral hemodynamics and metabolism did not significantly change during liver transplantation. Pere et al. [18] found no changes in cerebral blood flow, cerebral oxygen extraction ratio, and brain metabolism through the insertion of a fiberoptic catheter in the left internal jugular vein, and with the use of transcranial Doppler. Philips et al. [19] found no changes in cerebral metabolic rate during transplantation in cirrhotic patients without hepatic encephalopathy. Larsen et al. [20] showed that cerebrovascular metabolic autoregulation is impaired during liver transplantation because cerebrovascular dilatation uncouples $CMRO_2$ from CBF during the reperfusion phase of the transplant. However, other studies have demonstrated how the CBF is restored after reperfusion of the transplanted liver, particularly in patients with fulminant hepatic failure [21–23].

Brain-core temperature reflects the balance between heat generation and heat removal. Brain metabolism, cerebral blood flow, and body-core temperature are the three principal elements that contribute to cerebral temperature homeostasis [24]. The temperature is produced by the intense cerebral metabolism and neuronal activity, while the CBF and CSF circulation play an essential role in the removing of the heat to maintain a physiological and constant cerebral-core temperature.

DWI thermometry was recently applied in a heterogeneous spectrum of neurological conditions, and detected an increasing or decreasing brain-core temperature in different pathologies. Kuriyama et al. [25] found an increase in brain-core temperature in idiopathic normal-pressure hydrocephalus due to lack of CSF circulation, with insufficient heat removal. Yamada et al. [26] found that the brain-core temperature was higher in moyamoya disease patients than in normal controls. Brain-core temperature increases in patients with Parkinson's disease [27] and schizophrenia [28], while no significant modification in brain-core

temperature was founded in Alzheimer's patients compared with healthy subjects [29].

Conversely, Tazoe et al. [30] found a decrease in brain-core temperature in mild cerebral trauma, and Sai et al. [31] found a lower brain-core temperature in multiple sclerosis patients compared with healthy controls, probably related to decreased brain metabolism. DWI thermometry has also been applied in physiological conditions, showing an increased brain-core temperature in the luteal phase of the menstrual cycle in healthy women [32], and a decreased brain-core temperature with normal aging [33, 34].

Brain thermal response measured with multi-voxel MR spectroscopy was recently found to reflect the interaction between cerebral hemodynamics and metabolism during a dynamic modulation of CBF in patients with steno-occlusive cerebrovascular disease [35]. There is other evidence in the literature of the relationship between brain temperature and CBF and brain metabolism [36, 37]. Our results potentially provide additional support for the hypothesized coupling of the brain-core temperature and cerebral hemodynamics and metabolism, since we found no significant change in brain-core temperature after OLT in our patient population, suggesting that cerebral hemodynamics and metabolism during OLT were stable, and this was indirectly confirmed by the fact that no acute neurological deficits were found after OLT.

Our study has some limitations. First, it was conducted retrospectively in a relatively small number of patients. This was due to the fact that not all liver transplant patients routinely undergo brain MR imaging before and after transplantation; thus, we had a limited number of cases, used for another research project that aimed at assessing the preexistence of cerebral risk factors in patients eligible for OLT at our institute. Another potential limitation of the study is that the results were not compared with a control group of cirrhotic patients, as the study was retrospective and cirrhotic patients do not routinely undergo brain MR; thus, no control group was available. Ideally, DWI thermometry data of patients undergoing OLT should be compared with a control group of patients to show brain temperature change for liver dysfunction. However, brain MR imaging is not routinely used for patients with normal liver function or even for those with liver dysfunction. Moreover, thermometry data can only be compared if calculated from DWI homogeneously obtained with the same MR pulse sequence and the same MR hardware. It was impossible to prospectively collect data from a control group of patients with liver dysfunction, because the MR equipment had been upgraded over time, and we would have had to use only data from patients who undergo brain MR imaging with the same equipment. Future studies on this matter will be needed. Finally, the lack of an invasive monitoring of cerebral blood flow and cerebral metabolism during OLT does not allow a direct correlation of DWI thermometry with measured data of cerebral blood

flow and cerebral metabolism. However, assessment of cerebral blood flow with MR perfusion weighted imaging or arterial spin labeling (ASL) technique could be feasible, but would require an injection of paramagnetic contrast media in the case of PWI, and are both additional time-consuming MR sequences not routinely acquired, and thus beyond the scope of our study.

Though, in other studies [38–40], brain MR spectroscopy was performed before and after OLT to monitor brain metabolic changes, these results refer to the accumulation of a specific metabolite (usually manganese) or metabolite ratio in the brain parenchyma that may recover several months after the transplant [5].

In our study, the brain-core temperature measurement was studied to determine whether it is able to give an estimation of the possible alteration of global brain metabolism and brain perfusion occurring during the transplant procedure with a single routinely standard DWI pulse sequence and an easily reproducible brain-core temperature calculation instead of using additional time-consuming MR spectroscopy sequences, or brain MR perfusion techniques.

Further prospective studies will be necessary to correlate DWI thermometry results with intra-vascular hemodynamic parameters in a large study population, and with a control group of cirrhotic patients, which is not feasible in a retrospective study.

In conclusion, our study found a stable brain-core temperature in patients undergoing OLT. Brain-core thermometry using standard DWI-based MR imaging sequences, routinely utilized for the standard brain MR protocol, is a feasible, non-invasive method to assess brain temperature, and may provide a useful supplementary brain biomarker to confirm that cerebral blood flow and cerebral metabolism are stable in patients undergoing OLT, without additional time-consuming perfusion MR pulse sequences or MR spectroscopy evaluation.

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Compliance with ethical standards

Ethics standards Our retrospective cohort study was reviewed and approved by the Institutional Research Review Board (IRRB) of our institution, and informed consent form was waived; however, informed written consent to the MR was obtained from all patients. We declare that all human studies have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflict of interest The authors declare that they have no conflict of interest.

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