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Early prediction of functional outcome using dynamic contrast enhanced magnetic resonance imaging in experimental stroke

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ABSTRACT

Background and purpose: Early prediction of functional outcome in cerebral ischemia stroke using MRI remains a challenge. The aim of this study was to evaluate the predictive value of dynamic contrast-enhanced (DCE) MRI in terms of functional outcome of ischemia stroke.
Methods: Right middle cerebral artery occlusion (MCAO) was performed in male SD rats (n=50), followed by withdrawal of the occluding filament after 3 (n = 10), 4 (n = 10), 5 (n = 10), 6 (n = 10) or 7 (n = 10) h to establish ischemia and reperfusion stroke. DCE and conventional MRI were performed in each animal 60 ± 15 min before and after reperfusion. The outcome was assessed by the modified Neurological Severity Scores (mNSS) (before reperfusion and at 72 h after reperfusion) and the infarct volume. Comparisons of functional prognosis and DCE parameters (K^{trans}, Ve and Kep) were performed using binary logistic regression and operating characteristic (ROC) analysis.
Results: DCE parameters results indicated that blood brain barrier (BBB) permeability increased with prolonged reperfusion timing. Using binary logistic regression analysis on stroke characteristics (reperfusion timing, infarct volume) and BBB permeability parameters ($drK^{trans}_{subcortex}$, drK^{trans}_{cortex}, $drVe_{subcortex}$, $drVe_{cortex}$, $drKep_{subcortex}$ and $drKep_{cortex}$) as covariates , the results demonstrated that reperfusion timing, infarct volume, $drK^{trans}_{subcortex}$ and $drKep_{subcortex}$ were independent factors that were associated with prognosis (OR=0.01, OR=0.23, OR=245.23, OR=1.29). ROC analysis indicated that a $drK^{trans}_{subcortex}$ threshold of 0.88 with a sensitivity of 95.7% and a specificity of 85.2% and a $drKep_{subcortex}$ threshold of -0.25 with a sensitivity of 69.6% and a specificity of 70.4% for differentiation between favourable and unfavourable prognosis.
Conclusions: Quantitative DCE-MRI can be used to predict the functional outcomes of cerebral ischemia injury.

1. Introduction

Early outcome prediction could greatly facilitate clinical treatment decisions for cerebral ischemia. However, due to the complicated and variable courses of ischemic episodes, the prognosis of cerebral ischemia stroke patients is difficult to predict, particularly early after reperfusion. Previous studies have demonstrated that the extent of blood–brain barrier (BBB) breakdown in hyperacute stroke relates to initial stroke severity, stroke evolution and long-term outcome [1,2]. BBB disruption is related to poor prognosis due to vasogenic edema and increased risk of hemorrhagic transformation (HT) [3]. Animal models showed that BBB dysfunction after stroke is biphasic [4,5]. The first signs of increased BBB permeability are found within hours after onset of ischemia [6]. The second phase of BBB injury occurs 24 to 72 h after the infarction particularly after reperfusion [7]. This phase is more complicated and results in greater tissue damage following formation of edema and HT. Moreover, the prognosis and infarct volume correlates with the second step of BBB breakdown [8]. The time window of reperfusion is important. Early reperfusion may be helpful to relieve BBB alterations. Delayed reperfusion will likely aggravate endothelial injury [9].

So far, the evaluation of early BBB disruption in acute stroke has only been performed using MRI. Gadolinium enhancement of cerebrospinal fluid or brain parenchyma as a marker of BBB disruption was observed in 16 to 66% of acute stroke patients [10]. Moreover, BBB disruption occurred more frequently after recanalization therapy and was a predictor of subsequent HT and poor outcome. MRI using a contrast agent and magnetization transfer technique is able to sensitively detect and predict early endothelial

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damage of BBB, which results in small molecule permeability increasing (i.e., Gd-DTPA contrast agent or small proteins) [11].

Enhancement T1 weighted-imaging (T1WI) has been widely used to indirectly and non-quantitatively evaluate the permeability of BBB. However, recent research chooses dynamic contrast-enhanced (DCE) MRI instead, because it could more sensitively indicate the quantitative evaluation of Gd-DTPA contrast agents' leakage across the BBB [12–14].

Based on previous reports, we hypothesized that the extent of BBB breakdown after reperfusion is associated with the functional outcome after acute ischemic stroke, which can be assessed by the DCE parameters. So we observed the change of BBB permeability before and after reperfusion in stroke using DCE. The purpose of our study was to establish the supplemental value of DCE MRI beyond conventional MRI to predict neurologic outcome after acute ischemic stroke.

2. Materials and methods

2.1. Animal models

This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of Fudan Laboratory Animal Public Service Center. The protocol was approved by the Committee on the Ethics of Animal Experiments of the Department of Laboratory Animal Science of Fudan University. All surgery was performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering. Male Sprague–Dawley (SD) rats (n = 50) weighing 250–280 g were anesthetized with halothane (0.7% to 1.5%) in a 2:1 mixture of N_2O/O_2, and the core temperature was maintained at 36°C to 37°C throughout all of the surgical and MRI procedures. The right femoral vein was cannulated with a PE-50 catheter for the infusion of the contrast agent and was cannulated with a PE-50 catheter for measuring blood gases (pH, partial pressures of oxygen, carbon dioxide).

Focal cerebral ischemic stroke was produced using an adaptation of a model that was developed by Longa EZ et al. [15]. Briefly, after a midline skin incision, the right common, internal and external carotid arteries were exposed. Then, right middle cerebral artery occlusion (MCAO) was performed by the intraluminal insertion of a rat special MCAO monofilament (Beijing Sunbio Biotech company, Beijing) from the right external carotid artery into the right internal carotid artery until it blocked the origin of the middle cerebral artery. The monofilament size (diameter 0.34–0.38 mm) depended on body weight. Reperfusion was performed by the careful withdrawal of the occluding monofilament at 3 (n = 10), 4 (n = 10), 5 (n = 10), 6 (n = 10) and 7 (n = 10) h after MCAO.

2.2. Magnetic resonance imaging

MRIs were performed in each animal 60 ± 15 min before reperfusion and after 60 ± 15 min following the withdrawal of the monofilament. The experiments were performed on a human 3T scanner (Verio, Siemens Medical Solutions, Erlangen, Germany) with a 4-channel special animal coil including T1WI, T2 weighted-imaging (T2WI), diffusion-weighted imaging (DWI), DCE and susceptibility weighted imaging (SWI) sequences. Conventional MRI and DWI were used to confirm ischemia model, and SWI was used to detect HT after reperfusion. For each imaging sequence, 12 coronal slices were acquired with a slice thickness of 2 mm and a 0 mm gap.

A conventional spin-echo T1WI with an FOV of 64 × 64 mm^2, matrix of 256 × 256, NEX of 5, and TR/TE of 204/8 ms and a fast spin-echo T2WI with an FOV of 64 × 64 mm^2, matrix of 256 × 256, NEX of 5, and TR/TE of 3500/89 ms were obtained before DCE. Acquisition time was 6.02 min for T1WI and 2.39 min for T2WI.

DWI (TR/TE = 4000 ms/83 ms) was obtained using a 2D echo-planar imaging sequence (SE-EPI) with an FOV of 64 × 64 mm^2 and an imaging matrix of 192 × 96. ADC maps were generated from 2-point analysis based on two different b-values (0 s/mm^2, 1000 s/mm^2). Acquisition time was 2.50 min.

The SWI parameters were an FOV of 64 × 64 mm^2, matrix of 256 × 256, NEX of 8, and TR/TE of 28/20 ms. Acquisition time was 2.33 min.

The DCE-MRIs were performed using the following sequences, and two precontrast datasets were acquired using a T1-vibe (TR/TE: 5.39/2.15 ms, FOV: 64 × 64 mm^2, matrix: 128 × 128, slice thickness: 2 mm) with flip angles of 5° and 15° (acquisition time was 12.8 s). This was followed by a DCE acquisition series using a T1-twist (TR/TE: 5.39/2.15 ms, FOV: 64 × 64 mm^2, matrix: 128 × 128, and slice thickness: 2 mm) with a flip angle of 12°, which consisted of 60 measurements with a temporal spacing of 4.29 s. After the fifth baseline acquisition, a Gadolinium (Gd)-based contrast agent (Gd-DTPA; Omniscan, GE Healthcare, Oslo, Norway) was injected through the femoral vein at a dose of 0.1 mmol/kg of body weight (acquisition time of dynamic contrast sequence was 5.03 min).

The entire MRI protocol lasted approximately 25 min for each animal at each time point.

2.3. Image analysis

Post-processing analysis was performed using workstation software (Syngo Tissue 4D). The Tofts and Kermode pharmacokinetic model was used to model the relationship between tissue concentration of the contrast agent and the blood concentration-time curve of the contrast agent (input function) using linear regression as previously described by Roberts et al. [16]. The whole rat brain was outlined as the region of counting parameters to generate the whole brain K^{trans} map. In total, two round ROIs (2–4-mm diameter) were created at the center of the two side basal ganglia of the section of the lateral cerebral ventricle body to generate the contrast concentration-time curve. DCE analysis was performed on four coronal images that were positioned on MCA brain territory. Two regions of the interest (ROIs) were drawn on the T1W images: one comprised the entire ipsilateral cortex and the other encompassed the ipsilateral subcortex (basal ganglia). Homologous ROIs were also drawn on the contralateral side (Fig. 1). All of these ROIs were copied to the K^{trans} map, and BBB permeability parameter (the volume transfer constant (K^{trans}), extravascular extracellular space per unit volume of tissue (Ve) and the reverse rate constant (Kep)) values were calculated by averaging the ROIs of each cortex and subcortex region.

To eliminate individual animal differences, the relative parameters were calculated.

r-parameter = parameter_ischemic hemisphere/parameter_contralateral hemisphere