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Comparing diffusion-weighted and T2-weighted MR imaging for the quantification of infarct size in a neonatal rat hypoxic–ischemic model at 24 h post-injury

Yanxin Wang [a], Pik-To Cheung [b], Gary X. Shen [c], Inderjeet Bhatia [d], Ed Xue Wu [e], Deqiang Qiu [f], Pek-Lan Khong [g,*]

[a] *Diagnostic Radiology, University of Hong Kong, Hong Kong, China*
[b] *Paediatric and Adolescent Medicine, University of Hong Kong, Hong Kong, China*
[c] *MRI Laboratory, Electrical and Electronic Engineering, University of Hong Kong, Hong Kong, China*
[d] *Paediatric and Adolescent Medicine, University of Hong Kong, Hong Kong, China*
[e] *Laboratory of Biomedical Imaging and Signal Processing, Electrical and Electronic Engineering, University of Hong Kong, Hong Kong, China*
[f] *Diagnostic Radiology, University of Hong Kong, Hong Kong, China*
[g] *Diagnostic Radiology, State Key Laboratory of Brain and Cognitive Sciences, University of Hong Kong, Hong Kong, China*

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Abstract

Purpose: In a neonatal rat model of hypoxic–ischemic (HI) brain injury, using T2-weighted imaging (T2WI) and diffusion-weighted imaging (DWI), we aim to determine the best MRI method of lesion quantification that reflects infarct size.
Materials and methods: Twenty 7-day-old rats underwent MRI 24 h after HI brain injury was induced. Lesion size relative to whole brain was measured using T2WI and apparent diffusion coefficient (ADC) maps, applying thresholds of 60%, 70% and 80% contralateral control hemisphere mean ADC, and at day 10 post-HI on pathology with TTC staining. Multiple linear regression analysis was used to study the relationships between lesion size at MRI and pathology.
Results: Lesion size measurement using all MRI methods significantly correlated with infarct size at pathology; using T2WI, $r = 0.808$ ($p < 0.001$), using 80% ADC, 70% ADC and 60% ADC thresholds, $r = 0.888$ ($p < 0.001$), 0.761, ($p < 0.001$) and 0.569 ($p = 0.014$), respectively. Eighty percent ADC threshold was found to be the only significant independent predictor of final infarct volume (adjusted $R^2 = 0.775$).
Conclusion: At 24 h post-HI, lesion size on DWI, using 80% ADC threshold is the best predictor of final infarct volume. Although T2WI performed less well, it has the advantage of superior spatial resolution and is technically less demanding. These are important considerations for experiments which utilize MRI as a surrogate method for lesion quantification in the neonatal rat HI model.

Keywords: Diffusion-weighted; T2-weighted; Apparent diffusion coefficient; Neonatal rat; Hypoxic–ischemic

1. Introduction

Hypoxic–ischemic encephalopathy remains a major cause of infant mortality and morbidity with long-term neurologic sequelae, estimated to occur in approximately 1 to 2 per 1000 live births (Vannucci, 2000). There is intensive on-going research to identify drugs and other physical methods effective in neuroprotection of hypoxic–ischemic injury using animal models (Wagner et al., 2002; Balduini et al., 2001; Xia et al., 2005; Dingley et al., 2006; Shin et al., 2006; Tutak et al., 2005; Adcock et al., 2002; Jatana et al., 2006; Park et al., 2006; Feng et al., 2006; Nedelcu et al., 2000; Albensi et al., 1999). The most common animal model used to evaluate potential neuroprotective therapies is the neonatal rat hypoxic–ischemic (HI) model of unilateral common carotid artery ligation, followed by systemic hypoxia (Albensi et al., 1999; Wagner et al., 2002; Balduini et al., 2001; Xia et al., 2005; Dingley et al., 2006; Shin et al., 2006; Tutak et al., 2005; Adcock et al., 2002; Jatana et al., 2006; Park et al., 2006; Feng et al., 2006; Nedelcu et al., 2000). Unilateral ligation of one carotid artery in

* Corresponding author. Tel.: +852 28553307; fax: +852 28551652.
E-mail address: plkhong@hkucc.hku.hk (P.-L. Khong).

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combination with hypoxia results in a gradual decrease of cerebral blood flow in the middle cerebral artery territory. The affected regions are then exposed to hypoxia which when superimposed on the reduction of cerebral blood flow corresponds to the situation of clinical birth asphyxia with superimposed hypotension (Vannucci and Vannucci, 2005). Magnetic resonance imaging (MRI) is a useful method to determine the evolution of HI injury in a non-invasive way and now plays an increasing role in staging injury progression and developing therapeutic interventions related to HI injury. MRI has been used as a surrogate marker of injury progression at various time-points after neuroprotective intervention (Adcock et al., 2002; Wagner et al., 2002; Nedelcu et al., 2000; Albensi et al., 1999).

The temporal evolution of HI injury in the neonatal rat model has been studied by MRI using both diffusion-weighted MR imaging (DWI) and T2-weighted MR imaging (T2WI) (Tuor et al., 1998; Nedelcu et al., 1999; Miyasaka et al., 2000; Qiao et al., 2001). However, few studies have systematically evaluated and compared the methods of MRI quantification that most accurately reflects infarct size. MRI quantification of lesion size which accurately reflects final infarct size is important for assessing the effectiveness of treatment, selecting the animals for therapy, monitoring results in therapeutic trials and guiding the development of practical treatment protocols. In a previous study, we evaluated lesion size on MRI at an early time-point following HI insult (1–2 h post-HI injury) to determine its relationship with final infarct size and found only a moderate, but significant correlation (Wang et al., 2006). In this follow up study, we evaluate the accuracy of MRI in another cohort of post-HI injury rats at a more chronic stage of injury to determine the accuracy of MRI for predicting final infarct size and also compare the accuracy of lesion size measurement using T2WI and DWI by varying the apparent diffusion coefficient (ADC) thresholds to determine the most accurate method to reflect infarct size at 24 h post-HI.

2. Results

2.1. MRI

Out of 20 HI rats, 18 had lesions and two did not. Therefore, we included 18 rats in the statistical analysis. Using 80% ADC, 70% ADC and 60% ADC threshold values, %LV ranged between 0.03–54.54% (mean, 19.2%, S.D., 16.8%), 0–41.13% (mean, 9.0%, S.D., 11.4%) and 0–14.09% (mean, 2.4%, S.D., 4.4%), respectively. On T2WI, %LV ranged between 0.24% and 41.84% (mean, 16.3%, S.D., 11.2%) (Table 1). By counting the frequency of lesion location, we found the cortex to be the most fragile part, followed by the corpus callosum, caudate nucleus putamen, internal capsule, thalamus and hippocampus.

Table 1
Mean and standard deviation (S.D.) of %LV on pathology, various MRI parameters, and the difference between the %LV on pathology and MRI measurement in 18 neonatal rats

	%LV mean (S.D.)	%LV at pathology − %LV at MRI mean (S.D.)	p
Pathology	23.0 (9.1)	–	–
T2WI	16.3 (11.2)	6.7 (6.6)	<0.001
80% ADC	19.2 (16.8)	20.7 (7.5)	<0.001
70% ADC	9.0 (11.4)	14.0 (7.4)	<0.001
60% ADC	2.4 (4.40)	3.8 (9.6)	0.113

Using paired t-test, mean lesion size measured by all MRI methods was significantly smaller than infarct size on pathology ($p < 0.001$) except when measured by 80% ADC threshold ($p = 0.113$).

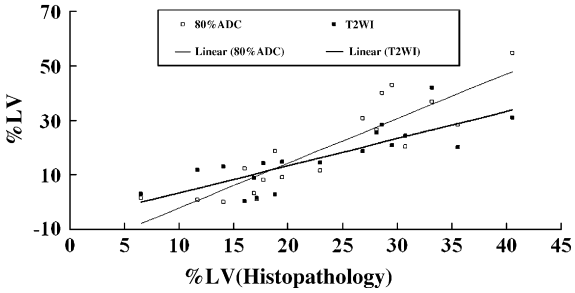

Fig. 1. Scatter plots of %LV on pathology [%LV (histopathology)] vs.; %LV measured on ADC map using 80% contralateral normal hemisphere mean signal intensity and %LV measured on T2WI. The two estimated regression formulae are %LV on pathology = 0.138 + 0.482 × %LV measured by 80% ADC threshold and %LV on pathology = 12.303 + 0.656 × %LV measured by T2WI.

2.2. Pathology

There was large variability in %LV on pathology ranging from 6.51% to 40.55% (mean ± S.D., 23.0 ± 9.1%) (Table 1). The mean %LV measured by DWI and T2WI tended to underestimate the final pathological infarct size at D10 (Table 1).

2.3. Statistical analysis

Using paired t-test, mean lesion size measured by all MRI methods was significantly smaller than infarct size on pathology ($p < 0.001$) except when measured by 80% ADC threshold ($p = 0.113$) (Table 1).

Univariate analysis showed that measurements using all MRI methods significantly correlated with final infarct volume at pathology. Using T2WI, $r = 0.808$ ($p < 0.001$). The estimated predicting formula of T2WI was; %LV on pathology = 12.303 + 0.656 × %LV measured by T2WI (Fig. 1). Using 80% ADC, 70% ADC and 60% ADC thresholds, $r = 0.888$ ($p < 0.001$), 0.761, ($p < 0.001$) and 0.569 ($p = 0.014$), respectively. Multiple linear regression analysis found 80% ADC threshold to be the only significant independent predictor of final infarct volume (adjusted $R^2 = 0.775$). The estimated regression formula was: %LV on pathology = 0.138 + 0.482 × %LV measured by 80% ADC threshold (Fig. 1). Please note that the equations derived from ADC maps may not be generalized as the measurements were made based on DWI and therefore may not truly represent a diffusion measure that is rotationally invariant.

3. Discussion

At 24 h post-HI, we found that lesion size measured by MRI using all methods, i.e. ADC threshold of 80%, 70% and 60%