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Translational Research in Stroke

Determining Stroke Onset Time Using Quantitative MRI: High Accuracy, Sensitivity and Specificity Obtained from Magnetic Resonance Relaxation Times

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Key Words
Quantitative MRI · Ischaemia · Wake-up stroke

Abstract
Many ischaemic stroke patients are ineligible for thrombolytic therapy due to unknown onset time. Quantitative MRI (qMRI) is a potential surrogate for stroke timing. Rats were subjected to permanent middle cerebral artery occlusion and qMRI parameters including hemispheric differences in apparent diffusion coefficient, T_2-weighted signal intensities, T_1 and T_2 relaxation times (qT_1, qT_2) and f_1, f_2 and $V_{overlap}$ were measured at hourly intervals at 4.7 or 9.4 T. Accuracy and sensitivity for identifying strokes scanned within and beyond 3 h of onset was determined. Accuracy for $V_{overlap}$, f_2 and qT_2 (>90%) was significantly higher than other parameters. At a specificity of 1, sensitivity was highest for $V_{overlap}$ (0.90) and f_2 (0.80), indicating promise of these qMRI indices in the clinical assessment of stroke onset time.

Introduction

Ischaemic stroke patients are ineligible for thrombolytic treatment if time of symptom onset is unknown. Common reasons include lack of witness, being unaware of symptoms or wake-up stroke. MRI is sensitive to hydrodynamic changes in brain parenchyma caused by

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ischaemia [1]. A growing body of evidence suggests quantitative data from these changes could be informative of tissue status, aiding decision-making for clinical treatment [1, 2]. Low sensitivity and ambiguity associated with relying on visual assessment of MR images prompted investigation into the potential utility of quantitative MRI (qMRI) for clinical needs [3].

Hemispheric differences in the apparent diffusion coefficient (ADC) [4], signal intensities of T_2-weighted (T_2-w) images (with and without FLAIR) [4–6] and quantitative T_1 (qT_1) [7] and T_2 (qT_2) relaxation times [5, 7] correlate with time from stroke onset. This relationship is attributed to changes in tissue-water dynamics due to cytotoxic and/or vasogenic oedema [1] and enabled onset time to be determined with varying levels of accuracy [3–8]. In rat focal ischaemia, the spatial distribution and volume of abnormal qT_1 or qT_2 tissue is initially smaller than total ischaemia volume (delineated by decreased ADC) but increases with ischaemia duration [5, 7]. We therefore proposed qMRI surrogates for stroke timing including f_1, f_2 and $V_{overlap}$, where f_1 and f_2 are the volume of tissue with elevated qT_1 or qT_2 as a percentage of total ischaemia volume, respectively, and $V_{overlap}$ is the volume with both elevated qT_1 and qT_2 normalised by the whole brain volume [7].

From a clinical perspective, a surrogate with high specificity is essential to minimise potential adverse events of thrombolysis. High sensitivity is also important to stratify as many patients as possible for thrombolysis. Accuracy of the above qMRI surrogates for stroke assessment has been reported in preclinical and clinical settings [3–8]. The objective of this study was to compare the accuracy and sensitivity of ADC, T_2-w, qT_1, qT_2, f_1, f_2 and $V_{overlap}$ in a defined rat model of ischaemic stroke.

Methods

qMRI data from our previous studies [5, 7] were used. Although qT_1 and qT_2 are dependent on magnetic field strength, combining data from 4.7 T and 9.4 T, was not considered problematic as the net magnitude of qT_1 and qT_2 change due to ischaemia is independent of field strength during the initial hours of stroke [7].

Animal Model

Animal procedures were conducted according to European Community Council Directives 86/609/EEC guidelines and approved by the Animal Care and Use Committee of the University of Eastern Finland. Rats were anaesthetised with isoflurane (1.5–2%). Twelve male Wistar rats (300–400 g) underwent permanent middle cerebral artery occlusion (MCAo) to induce focal ischaemia (see online supplementary information, available at www.karger.com/doi/10.1159/000448814). During MRI, breathing rate and rectal temperature were monitored and core temperature maintained at 37°C with a water heating pad. After MRI, rats were sacrificed [5, 7].

MRI

Rats were scanned at 4.7 T (n = 7) or 9.4 T (n = 5) for 7 or 5 h post MCAo, respectively [5, 7]. Every hour, axial slices of FLASH T_1 (9.4 T only), trace of diffusion tensor (D_{av}) for ADC quantification and multi-echo T_2 were acquired. 4.7 T data was single-slice and 9.4 T was multi-slice (n = 12). The online supplementary information provides details of MRI data acquisition parameters.

Image Postprocessing and Data Analyses

Image postprocessing and data analysis, including quantification of ADC, T_2-w, qT_1, qT_2, f_1, f_2 and $V_{overlap}$, was carried out on all MR data acquired from each rat at every hour post

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Table 1. Sensitivity of qMRI parameters for discriminating between scans performed within and beyond 3 h of stroke onset, when specificity is set at 1

Parameter	Threshold	Specificity (95% CI)	Sensitivity (95% CI)
$V_{overlap}$	1.83%	1 (0.65–1)	0.90 (0.57–1.00)
f_2	69.71%	1 (0.65–1)	0.80 (0.48–0.95)
f_1	84.09%	1 (0.65–1)	0.50 (0.24–0.76)
qT_2	0.99	1 (0.85–1)	0.39 (0.24–0.56)
T_2-w	1.00	1 (0.85–1)	0.29 (0.16–0.47)
qT_1	0.99	1 (0.65–1)	0.10 (0.00–0.43)
ADC	0.79	1 (0.77–1)	0.00 (0.00–0.12)

CI = Confidence interval. Thresholds for f_1, f_2 and $V_{overlap}$ are percentages, where f_1 and f_2 are the volume of qT_1 or qT_2 elevation within the ADC-defined ischaemic lesion as a percentage of the size of ischaemic volume, and $V_{overlap}$ is the percent of voxels with both qT_1 and qT_2 elevation within the ischaemic volume relative to the whole-brain size. ADC, qT_1, qT_2 and T_2-w are ischaemic/nonischaemic ratios.

MCAo. Matlab (MathWorks, Natick, Mass., USA) scripts written in-house or MRI data software 'Mango' (Research Imaging Institute, UT Health Science Centre at San Antonio, Tex., USA) were used. qT_1 and qT_2 maps were computed using a monoexponential approximation. Images for quantification of signal intensities were the sum of weighted images acquired at each echo time.

Ischaemic regions were identified as hypointense areas on D_{av} images, all within the striatum, which is 100% grey matter [7]. Regions of interest (ROIs; 3 mm diameter) were placed in the ischaemic and homologous regions. ROIs were loaded onto corresponding weighted and relaxometry images. For 9.4 T data, a representative central slice from the comparable brain region to the 4.7 T data was chosen for analyses. Relative differences in ADC, T_2-w, qT_1 and qT_2 were calculated by dividing the average value of the ischaemic ROI by the average nonischaemic ROI. Use of nonischaemic values was to eliminate intersubject variation. f_1, f_2 and $V_{overlap}$ values from our previous study [7] were used including all slices of the 9.4 T dataset (methods described in the online suppl. information). Signal-to-noise ratio (SNR), the key image quality characteristic, was computed for maps and summed weighted images using the dual acquisition approach (see online suppl. information).

Statistical Analysis

Areas under receiver operating characteristic (ROC) curves (AUCs) were calculated for each qMRI parameter for identification of scans acquired ≤3 h post MCAo. ≤3 h was chosen for comparison as both data sets contained this time point. Nonparametric pairwise comparisons of AUCs were performed (see online suppl. information) and sensitivity levels at a specificity of 1 determined.

Results

SNR was higher for weighted images but comparable across field strengths. SNR at 4.7 T was 31.4 (SD = 7.1) for qT_2, and 90.5 (SD = 19.2) for T_2-w. At 9.4 T, SNR was 19.1 (SD = 3.9) for qT_2, and 59.2 (SD = 23.0) for T_2-w. Figure 1 shows ROC curves and AUCs. $V_{overlap}$, f_2 and qT_2 had comparable accuracy ($p > 0.05$) and were more accurate than ADC, T_2-w, qT_1 and f_1 ($p < 0.05$). Table 1 shows that at a specificity of 1, $V_{overlap}$ and f_2 were most sensitive. Thresholds

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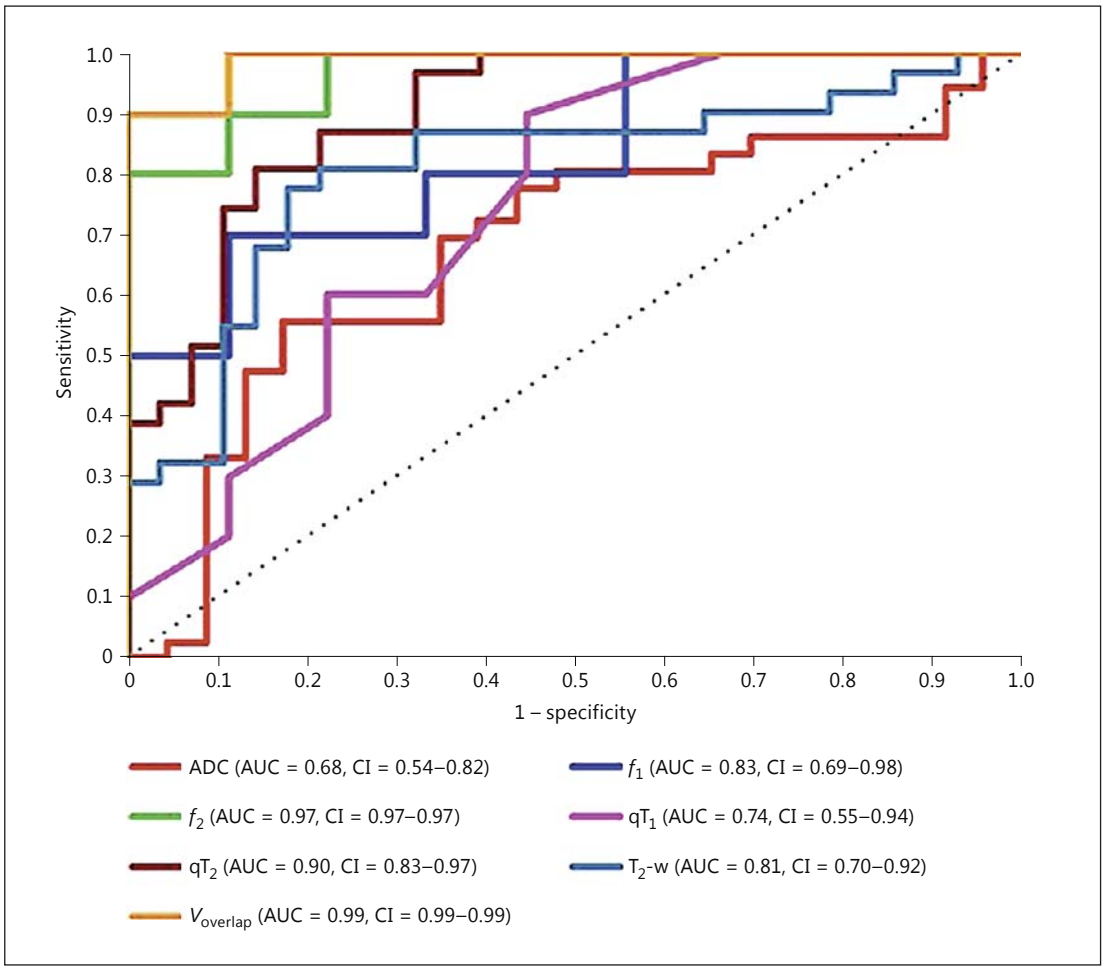

Fig. 1. ROC curves and AUC of qMRI parameters for discriminating between scans performed within and beyond 3 h of stroke onset. CI = 95% confidence interval.

for identifying strokes ≤3 h at these specificity and sensitivity levels are also shown. For example, a $V_{overlap}$ measurement of ≤1.8 indicates the scan was performed within 3 h of onset (due to specificity of 1), and most measurements of >1.8 indicate onset >3 h; however, due to sensitivity of 0.9, 10% of >1.8 measurements could be <3 h.

Discussion

We compared accuracy and sensitivity of qMRI parameters for discriminating between strokes scanned within and beyond 3 h of onset. $V_{overlap}$, f_2 and qT_2 are far more accurate than T_2-w, f_1, qT_1 and ADC. Our data suggest qMRI is a potential tool for identifying ischaemic stroke patients with unknown onset still within the treatment window, which may aid decision making for pharmacotherapy.

This study agrees with our previous study that quantitative MR relaxation times are more accurate for stroke onset determination than signal intensities in respective relaxation-weighted images [5]. High accuracy of relaxation times is likely due to the fact that fitting

signal intensities to the MR relaxation equations removes inherent variations caused by technical factors such as magnetic field inhomogeneities and proton density [4]. A further benefit of $V_{overlap}$, f_1 and f_2 is their insensitivity to magnetic field variation within the ischaemic lesion [7]. SNR was higher for summed weighted images suggesting poor SNR cannot account for inferior performance of signal intensities.

Our results suggest quantitative volumes of tissue with elevated relaxation times ($V_{overlap}$, f_2) may perform better in onset time estimation than hemispheric differences of qT_1 or qT_2. Sensitivity was zero for ADC and low for T_2-w. Indeed, in clinical acute stroke cases, ADC was deemed to carry no timing information, but rather serves as an early MRI index of ischaemia per se [5]. Similarly, low sensitivity of T_2-w was reported clinically [3]. Thus, ADC or T_2-w alone can be regarded as poor indices for stroke timing, but instead are important for stroke diagnosis. It should also be recognised that as the rat brain is comprised mainly of grey matter [7] and ischaemic lesions extend differentially within tissue types [9], present findings are representative only of grey matter.

A common concern regarding qMRI for stroke timing in clinical settings includes the long scan times required for T_1 and T_2 quantification, which increases the possibility of motion-induced artifacts and would delay treatment. However, fast qT_1 and qT_2 mapping is currently possible in clinical systems, and with the recent advent of MR fingerprinting, which provides many quantitative MR results simultaneously, the future of qMRI for clinical use is promising [10].

To conclude, from the multiple qMRI parameters studied here, $V_{overlap}$, f_2 and qT_2 quantified in the low ADC lesion provide the most accurate stroke onset times. The current preclinical data encourage investigation of $V_{overlap}$, f_2 and qT_2 as surrogates for stroke timing in clinical settings.

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