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The correlation between quantitative T2′ and regional cerebral blood flow after acute brain ischemia in early reperfusion as demonstrated in a middle cerebral artery occlusion/reperfusion model of the rat

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ABSTRACT

Introduction: qT2′-maps are calculated by subtracting T2- from T2*-relaxation rates. They are oxygen-sensitive and depict oxygen extraction. In several studies they have been used to describe the penumbra in patients with acute ischemic stroke. No correlation between rCBF and qT2′ has been performed to date. In this study a correlation between rCBF and qT2′ was performed in a temporary middle cerebral occlusion–reperfusion model of the rat.
Materials and methods: Temporary middle cerebral artery occlusion was performed on seven Sprague–Dawley rats. After 60 min of occlusion and 90 min of reperfusion MRI was performed including DWI, dynamic susceptibility contrast-weighted MR imaging (DSC-MRI) and qT2′. ROIs were placed inside the DWI lesion and transferred to rCBF- and qT2′-maps. rCBF and qT2′ were compared to corresponding tissue in the contralateral hemisphere.
Results: qT2′ was lower in the infarcted areas when compared to the contralateral hemisphere. Correlation between rCBF and qT2′ was $r = 0.41$, $p = 0.14$ (Pearson's correlation coefficient), when corrected for outliers it was $r = 0.58$, $p = 0.04$.
Conclusion: Our results show that there is a moderate correlation between rCBF and qT2′. qT2′-maps could be used to explore cerebral perfusion without the application of contrast agent or radiation.

1. Introduction

Quantitative T2′-maps (qT2′) are calculated by subtraction of T2- from T2*-relaxation rates that are derived from T2- and T2*-weighted multiple echo sequences (Hoppel et al., 1993). They have been used to describe the penumbra in acute stroke patients (Lee et al., 2003; Geisler et al., 2006; Fiehler et al., 2007). This approach is based on a metabolic concept. Hypoperfused tissue adjacent to the infarct core, the so-called penumbra, has an increased oxygen extraction fraction (OEF). Increased OEF leads to decreased vascular oxygen concentration. Tissue with increased OEF and decreased vascular oxygen concentration appears hypointense in qT2′-maps (Geisler et al., 2006; Fiehler et al., 2007).

Early recanalization is the goal of acute stroke management as it saves tissue at risk as demonstrated by magnetic resonance imaging (Jansen et al., 1999). However, this reperfused tissue is often not capable to extract the supplied increased oxygen concentration anymore and still evolves into infarction. Recent data (Geisler et al., 2006) indicates that this hyperperfused tissue appears hyperintense in qT2′-maps. This is in accordance with the above-mentioned theoretical considerations assuming a prolongation of qT2′ in hyperperfused and relatively hypooxygenated tissue (Hoppel et al., 1993). However, a correlation between qT2′ and perfusion was not performed to date. We thus used a rat model with temporary middle cerebral artery occlusion (MCAO) to investigate whether there is a correlation between perfusion values derived from dynamic susceptibility contrast-weighted MR imaging (DSC-MRI) and qT2′ as this novel technique may allow an insight into cerebral perfusion and oxygen consumption/extraction without the need for application of contrast agent or radiation.

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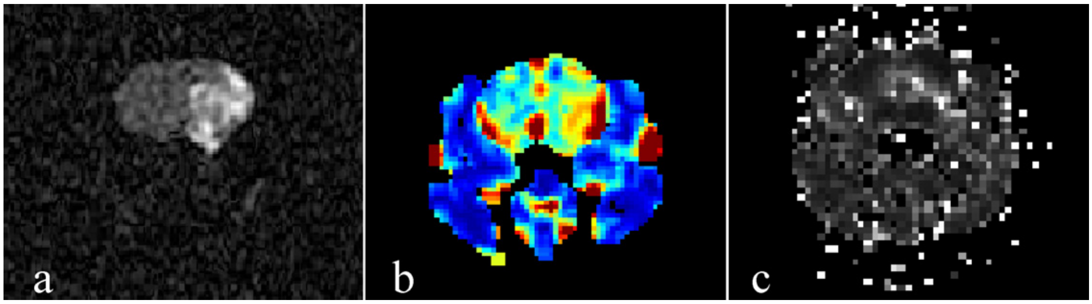

Fig. 1. Example for peripherally hyperintense qT2′-lesion (c) in a hyperperfused area (b) within the DWI-lesion (a). Note that neither the whole DWI-lesion is hyperperfused nor the qT2′-lesion covers the DWI lesion entirely. DWI depicts brain tissue alone while in rCBF- and qT2′-maps the whole head appears.

2. Materials and methods

2.1. Animal preparation

The study was approved by the local Ethics Committee and performed according to local guidelines for animal care. Transient middle cerebral artery occlusion (MCAO) was performed on seven Sprague–Dawley rats (Charles River, Germany, mean body weight = 218.22 ± 27.52 g) for 60 min. They were kept under controlled conditions. The rats were anesthetized with 10% chloral hydrate (400 mg/kg body weight i.p.) for all surgical procedures. During surgery each rat was allowed to breath spontaneously and core body temperature was maintained at 37 °C by a homeothermic blanket. The right middle cerebral artery (MCA) was transiently occluded by a silicone-coated 4–0 nylon filament inserted via the external carotid artery with subsequent reperfusion according to the procedure described in detail elsewhere (Longa et al., 1989). Laser-Doppler flowmetry (Periflux, Perimed) was used to document the surgical success of temporary MCA occlusion by monitoring rCBF before, during and after transient MCAO. The Laser-Doppler-probe was adjusted 5 mm lateral and 1 mm posterior from the bregma over the assumed MCA-territory to monitor occlusion and reperfusion. For DSC-MRI a polyethylene catheter (PP-50) was inserted into the right femoral vein and advanced into the vena cava. The catheter was filled with heparinized saline, passed through a subcutaneous tunnel, sealed, and secured at the back of the neck.

2.2. MR imaging

Ninety minutes after removal of the filament and cerebral reperfusion MRI was performed including a diffusion weighted sequence (DWI, TR/TE = 2399/165 ms, slice thickness = 1.3 mm, gap = 0.2 mm, 64 × 64 matrix, FOV = 50 × 50 mm, flip angle = 90°, *b*-values 0 and 2000) and a dynamic susceptibility weighted GE-EPI sequence (DSC-MRI, TR/TE = 24/12 ms, slice thickness = 1.5 mm, FOV = 64 × 48 mm, 64 × 48 matrix, 40 dynamics) using an Achieva, 3 T scanner (Philips, Best, The Netherlands) equipped with a dedicated solenoid rat coil (Philips, Hamburg/Germany). For the dynamic contrast-enhanced susceptibility-weighted perfusion sequence a suspension of 0.3 ml Gd-DTPA (Gadovist, 1 mmol/ml, Schering, Germany) and 0.7 ml NaCl was injected into the femoral vein via the venous catheter as a bolus with a flow rate of 1 ml/3 s after an initial rest phase of 2 s (Ulmer et al., 2008).

To obtain qT2′-maps T2- and T2*-weighted sequences with multiple echoes were recorded. (T2: 5 echoes, TE = 20/40/60/80/100 ms, TR = 1403 ms, slice thickness = 1.3 mm, gap = 0.2 mm, 64 × 64 matrix, FOV = 48 × 48 mm, flip angle = 90°; T2*: 8 echoes, TE = 16/26.3/36.6/46.9/57.2/67.5/77.8/88.1 ms, TR = 1251 ms, slice thickness = 1.3 mm, gap 0.2 mm, 64 × 64 matrix, FOV = 48 × 48 mm, flip angle = 18°). Overall scanning time was approximately 30 min.

2.3. Data analysis

qT2′-maps were calculated using the modified Philips T2 analysis tool (Philips, Best, The Netherlands, 2006) by first determining qT2 and qT2* using Eq. (1) (Hoppel et al., 1993)

$$\mathrm{SI}(t) = \mathrm{SI}_0 e^{-t/\mathrm{qT2}} \text{ and } \mathrm{SI}(t) = \mathrm{SI}_0 e^{-t/\mathrm{qT2}*} \quad (1)$$

Inserted into $1/\mathrm{qT2}' = 1/\mathrm{qT2}^* - 1/\mathrm{qT2}$ allows to rewrite to $\mathrm{R2}' = \mathrm{R2}^* - \mathrm{R2}$ or $\mathrm{qT2}' = 1/\mathrm{R2}'$ (with R = relaxation rate) and to obtain qT2′ (Hoppel et al., 1993). The correction with spin-spin effects is necessary since qT2 also undergoes changes in acute cerebral ischemia (Gröhn et al., 2000).

The size of the infarction was determined using the DWI sequence on a slice-by-slice basis. The area of infarction was outlined manually using the ImageJ-software (Abramoff et al., 2004). These outlines were transferred to the qT2′- and rCBF-maps and mirrored to the non-infarcted hemisphere. As reperfused ischemic tissue is often not capable to extract the oxygen from the blood, OEF should be diminished. The infarction core should thus appear hyperintense in qT2′ maps, should have increased perfusion values but still undergo infarction. Furthermore, the infarction core is clearly outlined by DWI. Therefore, only the infarction core was used for further analysis. Mean rCBF (in l/100 g/min) was calculated using the PENGUIN (Wu et al., 2003; Ostergaard et al., 1996) software (http://www.cfin.au.dk/software/penguin). Mean values of qT2′ and rCBF of the infarct core defined by DWI were compared to the contralateral non-affected hemisphere and as DSC-MRI only offers relative values ratios were created. A ratio of $\mathrm{rCBF}_{\mathrm{infarcted}}/\mathrm{rCBF}_{\mathrm{not\text{-}infarcted}} < 0.9$ was considered hypoperfusion, a ratio >1.1 was considered hyperperfusion. A ratio between 0.9 and 1.1 was considered normoperfusion. A two-sided *t*-test for unpaired samples was used for statistical analysis with a *p*-value of 0.05 or less being considered statistically significant.

3. Results

Three of the examined rats showed hypoperfusion ($p < 0.002$, $p < 0.002$ and $p < 0.02$), three showed normoperfusion and one showed hyperperfusion ($p < 0.002$, Fig. 1) based on rCBF maps calculated from DSC-MRI (Table 1). Values of qT2′ – except for the animal with hyperperfusion – were lower in the infarction compared to the contralateral hemisphere. In one of the animals with hypoperfusion this was significant ($p < 0.02$). In the three animals with normoperfusion again the values of qT2′ were lower compared to the unaffected hemisphere; however, this was not statistically significant. The rat with hyperperfusion in DSC-MRI showed a significant increase of qT2′ compared to the unaffected hemisphere ($p < 0.02$, Table 1).

Pearson's correlation coefficient between qT2′ and CBF was $r = 0.41$ ($p = 0.14$), when corrected for outliers (rat number 2) it was 0.58 ($p = 0.04$).