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Non-parametric intravoxel incoherent motion analysis in patients with intracranial lesions: Test-retest reliability and correlation with arterial spin labeling

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ABSTRACT

Intravoxel incoherent motion (IVIM) analysis of diffusion imaging data provides biomarkers of true passive water diffusion and perfusion properties. A new IVIM algorithm with variable adjustment of the b-value threshold separating diffusion and perfusion effects was applied for cerebral tissue characterization in healthy volunteers, computation of test-retest reliability, correlation with arterial spin labeling, and assessment of applicability in a small cohort of patients with malignant intracranial masses. The main results of this study are threefold: (i) accounting for regional differences in the separation of the perfusion and the diffusion components improves the reliability of the model parameters; (ii) if differences in the b-value threshold are not accounted for, a significant tissue-dependent systematic bias of the IVIM parameters occurs; (iii) accounting for voxel-wise differences in the b-value threshold improves the correlation with CBF measurements in healthy volunteers and patients. The proposed algorithm provides a robust characterization of regional micro-vascularization and cellularity without a priori assumptions on tissue diffusion properties. The glioblastoma multiforme with its inherently high variability of tumor vascularization and tumor cell density may benefit from a non-invasive clinical characterization of diffusion and perfusion properties.

1. Introduction

In spite of aggressive therapy consisting of surgical resection, radiotherapy, and/or chemotherapy, patients with malignant brain tumors have a poor prognosis with a median survival around 8 to 17 months for glioblastoma multiforme (GBM) (Li et al., 2011) and 18 to 31 months for anaplastic astrocytoma (AA) (Paravati et al., 2011). Both tumor types present heterogeneous lesions (Furnari et al., 2007; Yamashita et al., 2016).

The characterization of both, vascularization (Akgoz et al., 2014) and cellularity (Chenevert et al., 2006), of enhancing (Parker et al., 2015) and non-enhancing (Jain et al., 2014) lesions may provide potential prognostic indicators. Pathological alterations of blood flow and volume can be monitored in MRI using both, dynamic contrast enhanced MRI (Piludu et al., 2015) and techniques of arterial spin labeling (ASL) (Jarnum et al., 2010). In addition to perfusion-weighted MRI, the use of diffusion-weighted MRI has been proposed for the quantification of indirect indicators of tumor cell density and cell proliferation (Chenevert et al., 2006).

The intravoxel incoherent motion model in MRI isolates diffusion- and perfusion-related effects on the MR signal attenuation with growing diffusion-weighting of image contrast for increasing *b*-value (Le Bihan et al., 1988). Perfusion-related effects can be detected at low b-values, while further signal attenuation at high b-values is expected to be mainly dominated by diffusion. A few studies have recently investigated the clinical potential of IVIM-indexes for differentiation of brain lesions (Shim et al., 2015), preoperative grading (Hu et al., 2014), or for an assessment of tumor microcirculation (Bisdas et al., 2014). While IVIM promises to yield information on diffusion and microcirculation from a single scan, an important limitation is the robustness of standard fit algorithms, which is jeopardized by the high number of fit parameters and, for most algorithms, by an a priori separation of the perfusion and the diffusion components, with a fixed b-value threshold

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(Wurnig et al., 2015). The use of fixed-threshold multi-step algorithms for IVIM has been proposed in the attempt to improve the stability of the multi-parametrical fit (Luciani et al., 2008). Only few studies focused on the dependence of the IVIM-indexes from the b-value threshold in the separation of the diffusion and the perfusion components (Wurnig et al., 2015). However, a dependence of the b-value threshold from tissue type, functional state, or from pathological alteration of tissue microcirculation can be hypothesized (Pazahr et al., 2014) and was proven for abdominal organs (Wurnig et al., 2015). A novel algorithm proposed by Wurnig et al. (Wurnig et al., 2015) addressed the issue of the organ-specific adaptation of the b-value threshold with a variable-threshold IVIM algorithm, which determines the optimal b-value threshold for each voxel based on the fit residuals, independent of assumptions regarding the underlying tissue characteristics.

The aims of this study were to: (i) investigate the repeatability of the variable-threshold algorithm for brain tissue in healthy volunteers by test-retest measurements; (ii) to test the validity of the algorithm for the assessment of the perfusion correlates in patients with malignant intracranial lesions by comparison to quantitative ASL perfusion data.

2. Material and methods

2.1. Subjects

Eleven healthy volunteers (4 men, 7 women; mean age ± standard deviation: 31 ± 6 years, range: 24–39 years) and nine patients with malignant intracranial masses (6 men, 3 women; mean age ± standard deviation: 45 ± 14 years, range: 27–73 years) were included in this prospective study. The study was approved by the local ethics committee. All participants gave written informed consent to the MR examination and the scientific evaluation of the data sets. For the patients, a summary of tumor diagnosis and treatment is reported in Table 1.

2.2. MR protocol

All MR data were acquired on a 3 Tesla whole-body scanner (Ingenia, Philips, Best, The Netherlands) with a 15-channel head coil (Philips, Healthcare, Best, The Netherlands) and using the built-in body transmit coil for spin excitation.

For anatomical orientation, a 3D T1-weighted gradient-echo pulse sequence (TR/TE = 4.5 ms/2.0 ms; flip angle = 8°, echo train length 123, TI = 314 ms, sensitivity encoding factor 2) and a driven equilibrium fast spin echo sequence (TR/TE = 3000 ms/80 ms; echo train length 15, sensitivity encoding factor 2) were acquired.

Diffusion-weighted images for IVIM were acquired using an Echo Planar Imaging (EPI) sequence with spin echo diffusion preparation (TR = 1065 ms; TE = 63 ms; water-fat separation bandwidth = 25.9 Hz; bandwidth in EPI readout direction = 2852.7 Hz/px, sensitivity encoding factor 2; halfscan = 0.677; voxel size = 2.20 × 2.20 × 5.00 mm^3; b-values: 0, 10, 20, 40, 80, 160, 320, 640, 1280 s/mm^2, number of averages 4, three orthogonal diffusion-encoding directions). Depending on the anatomy of the subject ten till twelve slices were acquired resulting in slight variations of the TR of the sequence. Spectral Pre-saturation with Inversion Recovery (SPIR) was used for fat signal saturation. Range and distribution of b-values were selected considering the following points: (i) for b-values above 150–200 s/mm^2 the perfusion effects on the quantification of the diffusion estimates are considered negligible in the brain (Le Bihan, 2011); (ii) five measurement points in the low range of b-values (i.e., below 160 s/mm^2) were selected in order to improve the quality of the perfusion estimates (Lemke et al., 2011); (iii) a b-value above 1000 s/mm^2 should minimize the relative root mean square error in the estimation of the diffusion coefficient (Freiman et al., 2012).

Arterial spin labeling was performed using a balanced pseudo-continuous ASL (pCASL) single-shot gradient echo EPI sequence (Aslan et al., 2010). Imaging parameters were the following: voxel size 3.00 × 3.00 × 5.00 mm^3, 10 slices, TR/TE = 3497 ms/12 ms, flip angle = 40°, sensitivity encoding factor 3, post labeling delay = 1465 ms, labeling duration 1650 ms, label gap 20 mm, RF duration = 0.5 ms, pause between RF pulses = 0.5 ms, labeling pulse flip angle = 18°, bandwidth = 2.0 kHz, echo train length = 29, number of control/tagged pairs = 50. A control volume for cerebral blood flow (CBF) quantification was acquired using the same sequence by setting the labeling delay to 2500 ms.

For each healthy subject, data sets for quantification of diffusion and perfusion estimates (using IVIM and ASL models) were acquired twice. Before acquisition of the second trial, subjects were allowed to adjust the position of the own head within the coil. Volumes acquired during the two trials slightly differed in slice positioning and orientation.

For each patient, T1-weighted images (3D gradient-echo sequence, TR/TE = 1700 ms/2.6 ms, TI = 900 ms, flip angle = 9°, voxel size = 0.47 × 0.47 × 0.90 mm^3) acquired after the administration of Gadolinium-DTPA were available from clinical examinations performed immediately before or after the study examination.

2.3. Post-processing and computation of parametrical maps

The IVIM model (Le Bihan et al., 1988) presumes the MR signal attenuation for increasing strength of the diffusion weighting (i.e. for increasing b-values) to depend on diffusion and perfusion according to the following equation (Eq. 1):

$$\frac{S(b)}{S_0} = f_P \cdot exp(-b \cdot D^*) + (1-f_P) \cdot exp(-b \cdot D). \quad (1)$$

In Eq. 1, $S(b)$ and S_0 represent the signal intensity for a given b-value and for the b-value set to 0 s/mm^2, respectively. The term f_P (fraction of perfusion) is a dimensionless index (between 0 and 1), which mainly reflects the blood volume (Le Bihan et al., 1988). The pseudo-diffusion D^* (in units of mm^2/s) is a perfusion related component of the signal attenuation, which mimics the diffusion process, while D (in units of

Table 1
Summary of patients' data.

Patient	Status*	Gender	Age	Diagnosis	LC (month)	Therapy before MRI	Therapy after MRI
1	Deceased	M	73	GBM	No (5)	Biopsy	6cTMZ, RT, 3× Bevacizumab
2	Deceased	M	32	GBM	No (3)	Operation, RCT, 6cTMZ, bevacizumab	Bevacizumab bevacizumab + CCNU
3	Alive	M	47	AA	No (6)	Operation	RT, operation, 3cTMZ
4	Lost in follow-up	F	55	GBM	No (1)	Biopsy	RT
5	Deceased	F	43	AO	No (5)	Operation, RT, 6cTMZ, bevacizumab	Bevacizumab, RT
6	Alive	M	52	AA	No (3)	Biopsy, 2c TMZ	RT
7	Alive	F	31	AA	No (7)	Operation	RT
8	Alive	M	26	GBM	Yes (7)	Operation	RCT, 3cTMZ
9	Alive	M	50	Met	No (6)	Vandetabib	RT, sorafenib

AA: anaplastic astrocytoma, AO: anaplastic oligodendroglioma, c: cycle, CCNU: lomustine, GBM: glioblastoma multiforme, LC: local control; RCT: radiochemotherapy, RT: radiotherapy, TMZ: temozolomide.

* Status at the time point of the manuscript preparation.