

Improved Differentiation of Brain Tumors by Phase Contrast Calibration of Dynamic Susceptibility Contrast MRI: Combined Use with Extravasation Correction

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INTRODUCTION: Brain tumors are generally classified into four types of increasing biological aggressiveness and malignant behavior by the WHO classification (1). Treatments with novel antiangiogenic therapies are evolving as is the need for quantitative assessment of vascularity in-vivo. Vascular factors correlate with histological tumor grade and histological features such as mitotic activity. Phase-contrast MRA (PC-MRA) is a reproducible way to measure the total cerebral blood flow (tCBF). We have previously demonstrated improved voxel-wise absolute cerebral blood flow (CBF) quantification when PC-MRA is used to calibrate quantitative CBF measurements obtained with dynamic susceptibility contrast MRI (DSC-MRI) (2). The purpose of this study is to implement a PC-MRA calibration for absolute quantification of CBF with DCE-MRI that is clinically feasible in routine examinations and to test the method and compare it with quantitative DCE-MRI CBF measurements (3) with and without enhancement correction (4) in patients with brain tumors.

METHODS: Twenty-six consecutive patients with gliomas (n=15), meningiomas (n=7, 6 WHO I, 1 WHO III), non-neoplastic lesions (n=2; hemorrhage and gliosis) or metastases (n=2) were included. 7 of the 15 patients with glioma had low-grade (all WHO II) gliomas; 8 had high-grade (WHO grades III and IV) gliomas. None of the patients had undergone treatment at the time of the perfusion study. Tissue for histologic analysis was obtained at stereotactic biopsy or during surgical resection. The case of hematoma was diagnosed by imaging criteria and follow-up only. The study was approved by the institutional review board and informed consent was obtained from all patients. All MRI examinations were performed with a clinical 3.0-T imaging unit (Magnetom Trio; Siemens, Erlangen, Germany) as part of the clinical MRI protocol. DSC-MRI (GRE-EPI 2d, 18 slices, 50 phases, 0.1 mmol/kg gadolinium based contrast agent (Multihance) IV, TR 1614 ms, TR 45 ms, 1 average, 5.6 mm slice thickness, 128x128 matrix, 230 mm FOV) data were processed using deconvolution by standard singular value decomposition (sSVD) (5) to generate quantitative cerebral blood flow (CBF) maps. Automated arterial input function detection was used from a single slice at the level of the MCA contralateral to the brain lesion. PC-MRA (fast low angle shot (FLASH) 2D sequence, flip angle 15 degrees, TR 49 ms, TE 7.7 ms, 1 slice above the carotid bifurcation, with cross-sections of right and left vertebral and internal carotid arteries, velocity encoding (VENC) 70 cm/sec, 32 phases, cardiac gated, 256x256 matrix, 5 mm slice thickness, 138 cm FOV) data were analyzed using 'Qflow' software (MEDIS, Leiden, Netherlands) (6) to determine the total cerebral blood flow as the sum of the blood volumetric flow rate of the 4 neck vessels (tCBF-PC). Calculation of tCBF-based correction factor (CF) and tumor CBF correction were performed as described in our previous work (2). In addition, we compared the effect of including enhancement correction by linear least squares fitting of the data to the model of Boxerman et al. (4). Data for 4 combinations of PC calibration and extravasation correction are presented in order: A1: DSC-CBF, A2: Extravasation correction, A3: PC calibration, A4: Both PC calibration and extravasation correction.

RESULTS: Fig. 1 depicts the data before and after correction, visually demonstrating reduced intraclass variation both between WHO grades (left column) and histological subtypes (right column). ANOVA with Tukey's post-hoc test showed, consistent with the existing literature (7), that all approaches were able to differentiate low-grade from high-grade gliomas. Subanalysis showed that all approaches differentiated between grade II and IV gliomas ($p(A1/A2/A3/A4)=0.018/0.019/0.008/0.018$), however no technique differentiated significantly between grade II and III, and grade III and IV gliomas, when oligodendrogliomas and astrocytomas were pooled. However, when separating them, there was a significant difference in CBF between astrocytoma grade II and III for A2/A3/A4 ($p=0.041/0.005/0.001$), but not A1 ($p=0.121$), and between oligodendroglioma grade II and astrocytoma grade II for A3/A4 ($p=0.004/<0.001$), but not for A1/A2 ($p=0.497/0.148$). Also, there was significant difference in CBF between oligodendroglioma grade II and GBM for A3 ($p=0.039$) and marginally for A4 ($p=0.051$), however not for A1 and A2 ($p=0.324/0.375$), and a significant difference between oligodendroglioma grade III and astrocytoma grade II for A3/A4 ($p=0.010/0.001$), but not for A1/A2 ($p=0.189/0.060$). For histological subtype analysis (data in right column of Fig. 1), there was a significant difference in CBF between GBM and astrocytoma (pooled grade II and III) for A3/A4 ($p=0.005/0.005$), but not for A1/A2 ($p=0.144/0.104$). There was a tendency for differentiation between oligodendrogliomas and astrocytomas of all grades with A4 ($p=0.07$), as compared to A1/A2/A3 ($p=0.721/0.453/0.138$).

DISCUSSION: These data indicate that PC-MRA calibration of quantitative DSC-MRI CBF measurements significantly improves the differentiation between brain tumors, compared to quantitative DSC-MRI with or without the use of extravasation correction alone. In addition, all lesions that could be differentiated by the noncalibrated data could also be differentiated by the calibrated data. PC-calibration of quantitative CBF imaging demonstrates the expected increase of mean absolute CBF measurements with increasing WHO grade and reliable differentiation between low-grade and high-grade gliomas, which has been shown by other investigators with different perfusion imaging techniques (7-9). Absolute CBF determination in brain tumor perfusion imaging may have important diagnostic and clinical implications, for instance for tumor diagnosis and grading, and for comparison of serial intra-individual examinations during the course of antiangiogenic therapy.

CONCLUSIONS: PC-MRA calibration of DSC-MRI CBF measurements improves differentiation of brain tumor grade and histology both with and without the use of extravasation correction.

REFERENCES: 1. Burger PC et al. *J Neurooncol* 1995, 24:3. 2. Bonekamp D, et al. *Proc ISMRM* 2009, 725. 3. Ostergaard L et al. *JCBFM* 1998, 18:935. 4. Boxerman JL et al. *AJNR* 2006, 27:859. 5. Ostergaard L et al. *MRM* 1996, 36:726. 6. van der Geest RJ et al. *JMRI* 1999, 10:602. 7. Warmuth C et al. *Radiology* 2003, 228:523. 8. Aronen HJ et al. *Radiology* 1994, 191:41. 9. Donahue KM et al. *MRM* 2000, 43:845.

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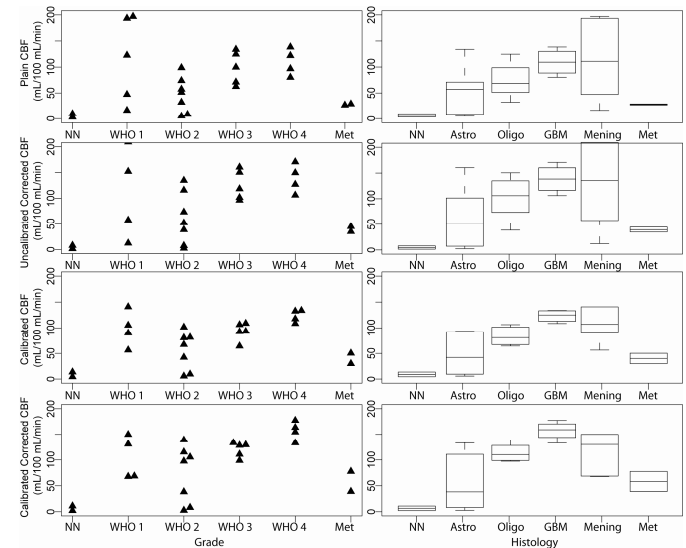


Fig 1: Left column: Scatterplots of absolute CBF for lesions of different grade (NN, non-neoplastic; WHO 1-4, primary brain tumors WHO grade; Met, Metastasis). Right column: Boxplots of absolute CBF for different histologies (NN, Non-neoplastic; Astro, Astrocytoma; Oligo, Oligodendroglioma; GBM, Glioblastoma multiforme; Mening, Meningioma; Met, Metastasis). Both columns: First row, CBF from deconvolution algorithm; Second row, CBF corrected for extravasation; Third row, CBF calibrated by phase contrast method; Fourth row, CBF calibrated by phase contrast method and corrected for extravasation.