Comparison of different leakage-correction methods for DSC-based CBV measurement in human gliomas

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Introduction: Cerebral blood volume (CBV) is an important parameter for the characterization of brain tumors. CBV measurement in clinical routine often relies on dynamic susceptibility contrast (DSC) MRI, using Gd-DTPA as intravascular contrast agent (CA). One issue of Gd-DTPA is its leakage into the extravascular extracellular space (EES) in regions with disrupted blood brain barrier, where it induces T1 and T2* shortening. Depending on the dominating effect this could lead to an under- or overestimation of CBV. In consequence several correction methods have been developed. One robust technique uses a pre-bolus (PB), to saturate the tissue with CA [1]. However, this only reduces T1 effects and can increase T2* effects. Therefore, several additional pre- and post-processing methods were developed for leakage correction. The method of Boxerman et al. [2] is based on the assumption that relaxation curves of tumorous pixels are scaled versions of a mean tissue curve. Hence, leakage can be estimated using linear combinations of this reference curve, but if the mean transit time (MTT) differs between normal and malignant tissue this method fails. Leigh et al. [3] accounted for this by introducing an arrival time correction, allowing shifting and temporal scaling of the reference curve. For both methods, CBV is calculated from the area under the corrected relaxation curve (AUC). A third approach, of Bjørnerud et al. uses the central volume principle to calculate CBV [4]. The leakage is estimated from the residue function, obtained via singular value decomposition (SVD), so it should be independent of MTT. The aim of this study was to investigate the influence of CA leakage on relative CBV, as received with different correction methods [2, 3, 4], using routine clinical scanning protocols.

Methods: 26 patients (60 ± 14 years, 14 male) with confirmed high grade glioma (WHO °IV) were examined, with a dynamic single-shot GRE EPI protocol (10 without PB: 3 T Philips Achieva, TR=1576 ms, TE=40 ms, α=75°, 40 dynamics; 16 with PB: 3 T Siemens mMR Biograph, TR=1500 ms, TE=30 ms, α=90°, 60-80 dynamics). A bolus of 15 ml Gd-DTPA (0.5 mmol/ml) was injected; the PB dose was 7.5 ml. For improved leakage correction, three post-processing methods were implemented in Matlab R2013a (MathWorks, Natick, US), based on the approaches of Boxerman et al. [2] – method 1, Leigh et al. [3] - method 2 and Bjørnerud et al. [4] - method 3. All methods provide a second parameter (K2), related to permeability. For comparability, all CBV's of one patient were normalized to the same healthy white matter region assuming CBV_{WM}=1.5 %. For VOI evaluation, contrast enhancing tissue (CET) was determined by thresholding post-contrast T1w data.

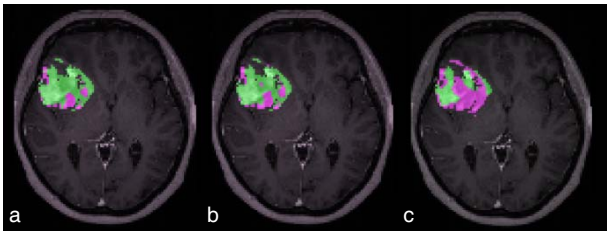

Fig. 1: Tumor heterogeneity in a patient acquired with PB - distribution of areas affected by T1 (K2 > 0, magenta) and T2 (K2 < 0, green) effects in CET. (a) method 1, (b) method 2, (c) method 3.*

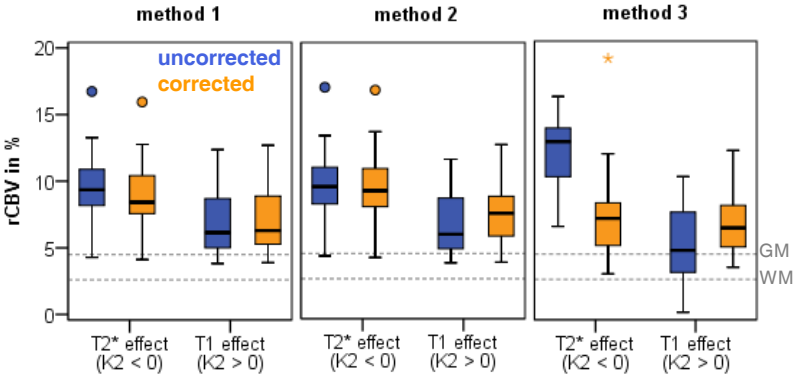

Fig. 2: Relative CBV (acquired with PB), in CET regions with K2 < 0 and K2 > 0. GM = mean rCBV in grey matter (4.5 ± 1.0 %), WM = mean rCBV in white matter (2.6 ± 0.5 %)

Results: Fig. 1 exemplary shows the heterogeneity within CET, with respect to T1 (K2 > 0) and T2* (K2 < 0) effects. Distributions of method 1 and 2 are similar, while method 3 shows more tissue with T1 effect. This is consistent with observations in the entire patient group. The average percentage of CET with T1 effect increases from 28 ± 19 % (method 1) to 40 ± 29 % (method 3), for data with PB. In contrast, data without PB, showed a higher percentage of T1 effects and a broader variance (method 1: 49 ± 33 %, method 2: 52 ± 32 %, method 3: 48 ± 37 %). CBV values were analyzed separately for CET with T1 and T2* effect (Fig. 2). Method 1 showed stronger correction for T2* effects while in method 2 T1 effects are stronger corrected. Over whole CET this resulted in a slightly decreased CBV for method 1 and increased CBV for method 2. Method 3 indicated the largest corrections for both regions in CET. A pixel-wise correlation of the different K2's showed for all patients a linear relationship between methods 1 and 3 (R > 0.8), whereas between method 1 and 2 there was usually a bend in correlation between K2 values greater and smaller than zero. Further all K2 values still depend on MTT, where K2 of method 1 disclosed, as expected, the strongest dependency.

Discussion: In summary all correction methods modify CBV as expected. Method 1 was supposed to underestimate T1 and overestimate T2* effects if tissue response curves are altered by differences in MTT [4]. This was also confirmed in our data and partially explains the discrepancies between method 1 and 2. Another explanation could be the fact, that only a user defined range of values was used, to optimize the temporal scaling. In general AUC based correction approaches induced only small changes in mean CBV, while CBV calculated via SVD seemed to be more affected by leakage, probably because it is more sensitive to noise and the selection of the arterial input function. Here, correction stabilized results, what could be additionally improved with prior time shifting of the tissue curve [5]. Anyway corrected CBV and K2 values of method 3 were in good accordance with method 1. Even though K2-distributions of the three methods are not absolutely consistent, most values showed strong correlation, so it may be useful as a qualitative parameter for further tumor characterization similar to k_{trans} as previously suggested [2, 3, 4]. To get quantitative statements about permeability in DSC, further developments are necessary. For more precise CBV estimation, a combination of method 2 and 3, similar to the method proposed by Quarles et al. [6], is probably the best solution, but a more detailed analysis taking into account tumor heterogeneity is currently under way.

References: [1] Boxerman et al. AJNR Am J Neuroradiol. 2012;33:1081-7. [2] Boxerman et al. AJNR Am J Neuroradiol. 2006;27:859-67. [3] Leigh et al. PLoS One. 2012;7:e52656. [4] Bjørnerud et al. J Cereb Blood Flow Metab. 2011;31:2041-2053. [5] Ibaraki et al. J Cereb Blood Flow Metab. 2007;27:404-13. [6] Quarles et al. Magn Reson Med. 2005;53:1307-16.