Title: Comparison of Glucose-CEST with Perfusion and Glycolysis Measurements in a C6 Rat Model of Glioma

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Structured Abstract:

Introduction: Glioblastoma is one of the most aggressive brain tumours. The median survival for patients who are diagnosed with glioma remains approximately 12-15 months regardless of technical advances. Chemical exchange saturation transfer MRI using an infusion of glucose (Glucose-CEST) is sensitive to the distribution of glucose in vivo. However, whether glucose-CEST is more related to perfusion or glycolysis is still unknown. In this study, we compared glucose-CEST measurements to computed tomography perfusion and $^{18}$F-fluorodeoxyglucose - positron emission tomography (FDG-PET) to validate if glucose-CEST is a perfusion or glycolysis measurement. In addition, CEST was used to measure changes in intracellular pH (pHi). The change in tumour pHi may provide additional information about tumour cell proliferation.

Methods: 1 million C6 glioma cells were implanted in the brains of Wistar rats (n=11) using stereotactic surgery. Tumours were monitored actively using CT (GE Discovery RCT) starting from Day 7 after the surgery. Isovue was injected after starting a cine CT acquisition of the brain and CTP maps were generated (GE CT perfusion 5). Glucose metabolism was measured in the tumour using the standardized uptake value (SUV) in PET images (Siemens Inveon) acquired 60 minutes after a bolus of FDG (30 ± 2 MBq) 11 to 13 days post-surgery. CTP was measured again immediately after the PET acquisition. Glucose CEST measurements were acquired the following day. CEST spectra were acquired on a 9.4 T Agilent MRI using a continuous wave presaturation pulse preceding a series of fast spin-echo images. Glucose-CEST measurements were analyzed using costumized Matlab script. The effect of glucose infusion on pHi was evaluated using amine and amide concentration-independent detection (AACID). The correlations between CTP measurements, PET measurements and glucose-CEST measurements were evaluated using Pearson's correlation.

Results: The tumour region displayed higher SUV, %CEST, BV and PS than the contralateral normal brain region. Tumour glucose-CEST measurement of %CEST significantly and most strongly correlated with tumour perfusion measurements of blood volume ($p = 0.82, P = 0.02$) followed by the perfusion measurement of permeability surface-area product ($p = 0.79, P = 0.04$). No significant correlation was found between glycolysis measurements of SUV and tumour %CEST. Negative tumour %CEST values were found when AACID values were significantly increased at tumoural and peritumoural regions pre- and post-glucose infusion, corresponding to a drop in pH.

Discussion: Glucose solution in the CEST experiment could be regarded as a perfusion contrast agent and the change in glucose concentration was successfully detected by %CEST measurement. In addition, glucose-CEST signal decreased (negative %CEST) when ACCID values increased after glucose infusion, reflecting the pH-dependence of CEST and the potential for glucose infusions to drive changes in tumour pH.