Cerebral Metabolic Rate of Oxygen Consumption in Human Brain Tumors: A pilot ^{17}O MRI study

Sebastian C. Niesporek[1], Armin M. Nagel[1,3], Reiner Umathum[1], Nicolas GR Behl[1], Mark E. Ladd[1], Heinz-Peter Schlemmer[2], and Daniel Paech[2]

[1]Medical Physics in Radiology, German Cancer Research Center (DKFZ), Heidelberg, Germany,[2] Division of Radiology, German Cancer Research Center (DKFZ), Heidelberg, Germany, [3]Institute of Radiology, University Hospital Erlangen, Erlangen, Germany

TARGET AUDIENCE Scientists and physicians interested in techniques for functional and metabolic brain analysis via MRI

PURPOSE The oxygen (O_2) metabolism plays a vital role in the human brain and can serve as a diagnostic quantity in various diseases such as cancer ('*Warburg effect*') **[1]**, Parkinson's **[2],** or Alzheimer's disease **[3]** where the functional parameter of cerebral metabolic rate of oxygen consumption ($CMRO_2$) contains information about tissue viability. The $CMRO_2$ parameter can be measured via dynamic ^{17}O MRI of the stable oxygen isotope ^{17}O employing an inhalation procedure where enriched $^{17}O_2$ gas is administered during continuous imaging **[4]**. Recently, the reproducibility and reliability of $CMRO_2$ determination via ^{17}O MRI with additional partial volume (PV) correction was demonstrated in a small volunteer cohort **[5]**. The presence of strong PV effects in ^{17}O-MRI is caused by low spatial resolution and rapid transverse relaxation (T_2~5ms), requiring an efficient correction procedure to separate signal contribution from different compartments. In the presented work the verified method from **[5]** was applied in a clinical research setting to three patients (one glioma WHO grade II, two glioblastoma WHO grade IV) to quantify $CMRO_2$ values in tumor regions and normal appearing brain tissue.

METHODS A three-phase inhalation experiment **[4]** (t_1 baseline-phase; t_2 ^{17}O-inhalation-phase; t_3 decay-phase) was performed with a MR-compatible breathing system in which a $^{17}O_2$-bolus is administered in a closed circuit. In this ongoing IRB approved study one untreated glioma-patient (male, 26y.-o. astrocytoma WHO grade II) and two untreated glioblastoma-patient (male, 34 y.-o./ 76 y.-o., WHO grade IV) were included. ^{17}O MRI was conducted at a 7 Tesla whole-body scanner (Siemens Healthineers, Erlangen, Germany) with a nominal spatial resolution of $(7.5\text{mm})^3$ employing a density-adapted radial sequence **[6]** with a Golden Angle acquisition scheme **[7]** (TR/TE= 20/0.56ms, acquisition time 30:00min). Data were reconstructed with a temporal resolution of Δt=1:00min. Per experiment 3.8±0.1L of 70%-enriched $^{17}O_2$ gas (NUKEM Isotopes Imaging GmbH, Alzenau, Germany) were administered. High-resolution T_1 MPRAGE $(0.6\text{mm})^3$, T_2 TSE $(0.4\text{x}0.4\text{x}0.5\text{mm})^3$ at B_0=7T were additionally acquired. Proton data were utilized for tumor or normal brain segmentation (normal appearing gray and white matter (NGM, NWM), CSF, tumor) as well as for the employed PV correction algorithm **[8,9]** and signal quantification. Contrast-enhanced (CE) MPRAGE images were available from routine clinical imaging (B_0=3T, $(0.5\text{x}0.5\text{x}1.25\text{mm})^3$). Prior to patient examinations the imaging protocol was optimized utilizing dynamic numerical signal simulation of the human brain: the impact of shortening of the baseline- and decay-phases on the accuracy of quantification was investigated and the final patient protocol was adjusted accordingly.

Tab. 1 *Results of $CMRO_2$ determination of the patient study with and without applied PVC. Tumor volumes in both tumor types (WHO II, WHO IV) were segmented differently: WHO II patient, one volume (tumor volume, **TV**) and contralateral normal appearing brain tissue (**CL**). WHO IV-patient tumor segmentation into three separate masks (necrotic region (**NE**), contrast-enhancing region (**CE**), peritumoral edema (**PE**)) and CL volume.*

volume	mask	$CMRO_2$ values in µmol/g/min			
		WHO II -patient		WHO IV-patient 1 & 2	
		w/o PVC	w/ PVC	w/o PVC	w/ PVC
NGM		1.21±0.21	2.34–2.58±0.20	0.70–1.55±0.36	1.81–2.55±0.12
NWM		0.98±0.15	0.56–0.62±0.06	0.72–1.33±0.15	0.64–0.85±0.08
CL[2]		1.02±0.08	1.10–1.22±0.08	0.75–0.82±0.09[1]	0.59–0.85±0.09[1]
	TV[2]	0.85±0.07	0.59–0.66±0.16	0.29–0.55±0.06	0.20–0.22±0.08
Tumor	CE	-	-	0.30–0.41±0.06	0.19–0.21±0.08
	NE	-	-	0.23–0.32±0.10	< 0.09
	PE	-	-	0.55–0.60±0.19	0.25±0.17

[1]*control volume contains CSF*
[2]*separate evaluation of combined volume TV=CE+NE and contralateral control volume*

RESULTS The available fit information in individual breathing phases (t_1, t_3) was systematically reduced in two considered simulated compartments (NGM, NWM). Only a minor dependence is seen for variation of t_1 and a deviation >5% for t_3<15min. With this information the patient inhalation protocol was set to: t_1= 5:00min, $t_2 \leq$ 10:00min (depending on available $^{17}O_2$ bolus), $t_3 \leq$ 15:00min. Results of the glioma WHO II patient revealed significantly decreased $CMRO_2$ in tumor tissue (0.59–0.66±0.16µmol/g/min) compared to contralateral normal appearing brain tissue (CL, 1.10–1.22±0.08 µmol/g/min, **Tab.1**). Further, $CMRO_2$ was significantly increased in gray matter (2.34–2.58±0.20µmol/g/min) compared to white matter tissue (0.56–0.62±0.06µmol/g/min) after application of PVC. $CMRO_2$ determination in both glioblastoma patients, revealed an even more pronounced metabolization drop in the tumor tissue, with lowest values in the necrotic (NE) as well as contrast enhancing (CE) tumor region (**Tab.1**). Here, the CL volume indicated also a largely elevated $CMRO_2$ value in both patients. A map of relative ^{17}O signal increase that visualizes the decrease of oxygen metabolization in the tumor and edema region is shown in **Fig.1**.

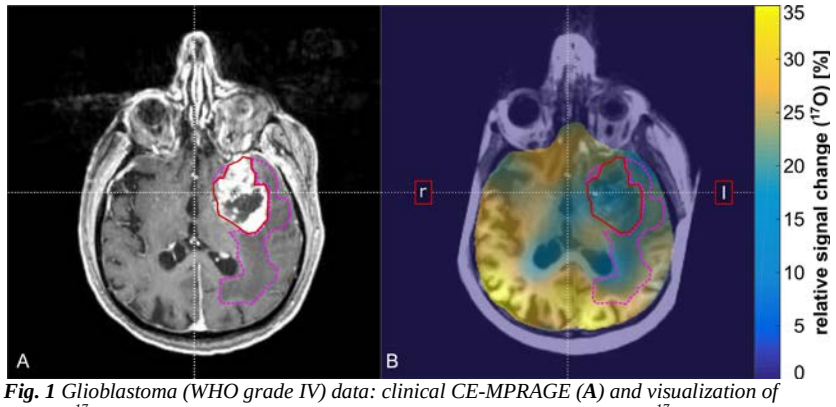

Fig. 1 *Glioblastoma (WHO grade IV) data: clinical CE-MPRAGE (**A**) and visualization of relative ^{17}O signal increase (**B**) in a representative transversal slice. In (**B**), ^{17}O data are shown as an overlay on anatomical T_1 MPRAGE $(0.6\text{mm})^3$. The tumor volume (TV, solid) as well as edema compartment (PE, dashed) was segmented manually and is indicated in both images.*

DISCUSSION Application of a simulation tool allowed protocol optimization and estimation of expected fitting errors due to information reduction in individual breathing phases. The protocol and utilized inhalation setup allowed measurements in three patients and demonstrated the feasibility of transferring the suggested method to a clinical environment. The drop in quantified functional parameters observed in all three patient experiments in the malignant tissue (CE, NE, PE) may correspond to the *Warburg effect*, which describes decreased $CMRO_2$ in tumors due to the shift in glucose metabolism from oxidative phosphorylation to lactate production for energy generation as firstly reported for ^{17}O MRI data in the feasibility study by Hofmann et al. **[10]**. Overall functional parameters are in good agreement with previous reports **[10, 11]**. Due to large voxel volumes and rapid transverse relaxation, the quantified $H_2{}^{17}O$ concentrations might be underestimated despite the application of a dedicated PVC algorithm. Uncertainties in the prior ^{17}O enrichment factor as well as limitations of the PVC as discussed in **[5]** are the main sources of error in the suggested method. However, $CMRO_2$ values of healthy tissue (NGM, NWM) and cerebrospinal fluid (CSF) are in correspondence with previous work **[4,5]**. Variation in functional parameters of contralateral control volumes in all three patients is due to the individual mixture (fraction of NGM, NWM and CSF) and size of the corresponding mask.

CONCLUSION This work presents the first results of an ongoing study investigating brain tumor metabolism in patients with the help of dynamic ^{17}O MRI. Further application may provide new insights into tumor pathophysiology through the visualization of the cerebral metabolic rate of oxygen consumption.

ACKNOWLEDGMENT The authors thank NUKEM Isotopes Imaging GmbH for their generous supply of ^{17}O gas and support of this project.

REFERENCES [1] Miles KA, Williams RE., Cancer Imaging 2008 (8):81-86; **[2]** Beal MF., Ann Neurol; 1992 (2):119-130; **[3]** Maurer I, Neurobiology of Aging 2000;21(3):455-462; **[4]** Atkinson IC, Neuroimage 2010 (51):723-733; **[5]** Niesporek SC, Magn Reson Med 2017, doi: 10.1002/mrm.26952; **[6]** Nagel et al., Magn Reson Med 2009 (62):1565-73; **[7]** Chan, R.W. et al., Magn Reson Med 2009(61): p. 354–363; **[8]** Rousset et al., J Nucl Med 1998(5):904-911, 1998, **[9]** Niesporek et al., NeuroImage, 2015(112): 353–363; **[10]** Hoffmann et al., MAGMA 2014(27):579-87; **[11]** Ito, M., Neuroradiology 1982 (23): 63–74