

## Clinical utility of cerebrovascular reactivity mapping in patients with low grade gliomas

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### Abstract

**AIM:** To evaluate neurovascular uncoupling (NVU) associated with low grade gliomas (LGG) using blood oxygen level dependent (BOLD) cerebrovascular reactivity mapping.

**METHODS:** Seven patients with low grade gliomas referred by neurosurgeons for presurgical mapping were included in this pilot study. Cerebrovascular reactivity (CVR) mapping was performed by acquiring BOLD images while patients performed a block-design breath-hold (BH) hypercapnia task. CVR mapping was expressed as BOLD percentage signal change (PSC) from baseline associated with performance of the BH hypercapnia task. Standard T2\* Dynamic Susceptibility Contrast perfusion imaging was performed and relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) maps were generated. Structural T1 weighted MR images were also acquired. A correlation

analysis between intratumoral normalized (*via* ratio with contralateral homologous regions) BOLD BH PSC [referred to as ( $n_{CVR}$ )] and intratumoral normalized resting state rCBV (rCBF) values (i.e.,  $n_{CBV}$  and  $n_{CBF}$ , respectively) was performed.

**RESULTS:** No significant correlation was seen between the normalized BOLD BH PSC (i.e.,  $n_{CVR}$ ) and  $n_{CBV}$  or  $n_{CBF}$ . However, the average  $n_{CVR}$  (median = 0.50,  $z = -2.28$ ,  $P = 0.01$ ) was significantly less than 1.0, indicating abnormally reduced vascular responses in the tumor regions relative to normal contralateral homologous regions, whereas the average  $n_{CBV}$  (median = 0.94,  $z = -0.92$ ,  $P = 0.375$ ) and  $n_{CBF}$  (median = 0.93,  $z = -1.16$ ,  $P = 0.25$ ) were not significantly higher or lower than 1.0, indicating iso-perfusion in the tumor regions relative to normal contralateral homologous regions. These findings suggest that in LGG, hyperperfusion that is seen in high grade gliomas is not present, but, nevertheless, abnormally decreased regional CVR is present within and adjacent to LGG. Since the patients all demonstrated at least some residual function attributable to the cortical regions of impaired CVR, but were incapable of producing a BOLD response in these regions regardless of the tasks performed, such regionally decreased CVR is indicative of NVU. The low  $n_{CVR}$  ratios indicate high prevalence of NVU in this LGG cohort, which is an important consideration in the interpretation of clinical presurgical mapping with functional magnetic resonance (MR) imaging.

**CONCLUSION:** Our preliminary study shows that BH CVR mapping is clinically feasible and demonstrates an unexpectedly high prevalence of NVU in patients with LGG.

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**Key words:** Blood oxygen level dependent; Brain tumor; Cerebrovascular reactivity; Functional MRI; Neurovascular uncoupling; Presurgical mapping

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## INTRODUCTION

Presurgical localization of brain sensorimotor, visual and language regions in patients with brain tumors or epilepsy who are candidates for surgical resection currently represents the most mature clinical application of blood oxygen level dependent (BOLD) functional MR imaging (fMRI)<sup>[1-3]</sup>. Presurgical mapping with fMRI can assist neurosurgeons by providing useful information for: (1) pre-operative risk assessment; (2) planning the safest surgical trajectory; (3) selection of patients for asleep *vs* awake craniotomy; and most importantly; and (4) optimization of efficiency, exposure and technique of intraoperative mapping. However, despite its many advantages in presurgical planning that have resulted in widespread clinical utilization over the last decade, some limitations of clinical fMRI do exist<sup>[4-9]</sup>. One such limitation is the frequent inability to distinguish essential from nonessential participatory activated (i.e., “eloquent”) cortex involved in performance of a particular cognitive, sensorimotor or visual task, thus leading to lower than ideal specificity of activation maps<sup>[10]</sup>.

Another limitation is the problem of decreased sensitivity for detection of actual electrically active eloquent cortex in areas of impaired cerebrovascular reactivity (CVR); this phenomenon is referred to as neurovascular uncoupling (NVU)<sup>[11,12]</sup>. NVU can result in false negative BOLD activation, which constitutes a major hazard with respect to interpretation of clinical fMRI examinations; such false negatives within or adjacent to tumor boundaries can result in undesirable resection (in the absence of intraoperative electrophysiologic confirmation) of essential electrically active eloquent cortex that is incapable of demonstrating a BOLD response due to impaired CVR. Such eloquent cortical resection may lead to serious permanent postoperative neurological deficits. Thus, the phenomenon of NVU is not merely a theoretical issue of scientific interest, but is rather an issue of considerable clinical relevance and importance. NVU has been documented in the immediate vicinity of high grade gliomas (HGG), mostly due to tumor angiogenesis, which is associated with abnormal vascular permeability, abnormal hyperperfusion (elevated relative cerebral blood volume [rCBV]) related to increased vascular density, and impaired regional CVR<sup>[13,14]</sup>. However, it is not clear how high the prevalence of impaired CVR (and resultant NVU) is in low grade gliomas (LGG), in which

**Table 1** Age, sex, tumor location and histology for seven brain tumor cases included in the study

Age	Sex	Tumor location	Histology/tumor grade
25	F	Left frontal lobe	Oligoastrocytoma grade II
27	M	Right cingulate gyrus	Oligodendroglioma grade II
42	M	Left temporal lobe	Astrocytoma grade II
25	M	Right temporal lobe	Diffuse astrocytoma grade II
54	M	Left frontal	Oligodendroglioma grade II
27	F	Left hemispheric (primarily insular and inferior frontal)	Pilocytic astrocytoma grade I
41	M	Left insular	Oligoastrocytoma grade II

F: Female; M: Male.

hyperperfusion is unusual. In this study, we investigated regional CVR, using a BOLD breath-hold (BH) hypercapnia task, within LGG, which are known to infiltrate, rather than destroy or displace, eloquent cortex, in order to determine whether the same NVU potential exists in these tumors as in HGG. In this study we report our initial experience using BH CVR mapping in 7 patients with LGG (6 patients with grade II gliomas and 1 patient with grade I glioma) as a quality control tool for detecting risk of NVU, and we compare these results to those of T2\* DSC perfusion imaging that was also performed during the same scan sessions as part of a comprehensive clinical presurgical mapping protocol. The findings of this study are discussed in the context of current literature pertaining to brain tumor-related NVU.

## MATERIALS AND METHODS

Seven patients (mean age  $34 \pm 11$  year, 5M/2F) with histopathologically proved grade I and II intra-axial primary brain tumors (Table 1) underwent our institutional clinical BOLD fMRI protocol for presurgical planning which included multiple T2\* BOLD fMRI sequences during performance of motor, language or visual tasks and a BH task, a T2\* Dynamic Susceptibility Contrast perfusion sequence and a structural T1-weighted 3D MPRAGE sequence after Gadolinium injection. Details of these three sequences are reported in Table 2. Images were acquired on a 3T MRI scanner (Magnetom Trio, Siemens Medical Solutions, Erlangen, Germany). The block design BH task consisted of four cycles of 40 s each of normal breathing (baseline) alternating with blocks of 4 s of inhalation and 16 s of breath-holding<sup>[15]</sup>. Instructions for task performance were delivered visually using Prism Acquire Software (Prism Clinical Imaging, Elm Grove, WI, United States).

The study was approved by our Institutional Review Board. Images for each patient were first transferred to an external workstation. Perfusion and raw BOLD BH images were coregistered to the T1 MPRAGE images using DynaSuiteNeuro software (DynaSuiteNeuro, InVivo Corporation, Pewaukee, WI, United States). Perfusion image analysis included the generation of rCBV and rCBF maps. rCBV was calculated by adding a correction

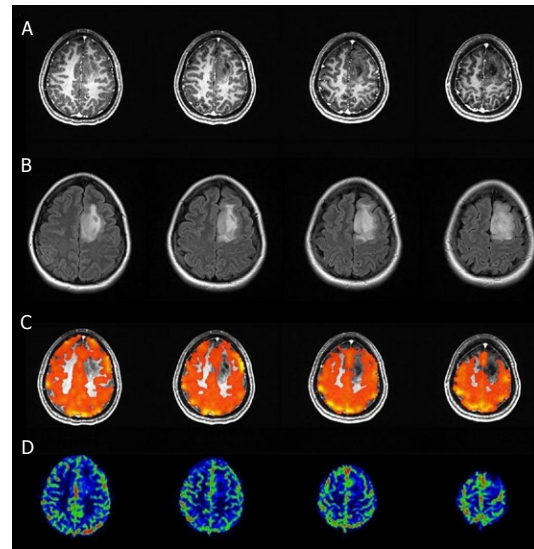
**Table 2** Main parameters for the sequences of interest in the study

Sequence	TR (ms)	TE (ms)	FA	FOV (cm <sup>2</sup> )	Acquisition matrix	Slice thickness (mm)
T1 MPRAGE	7	3.5	9°	24 × 24	256 × 256	1
T2* DSC	2450	45	90°	24 × 24	128 × 128	4
T2* BOLD	2000	30	90°	24 × 24	64 × 64	4

DSC: Dynamic susceptibility contrast; BOLD: blood oxygen level dependent; FOV: Field of view.

factor to take into account the contrast leakage through the disrupted blood-brain barrier<sup>[16]</sup>. BOLD BH data analysis was carried out using AFNI software (afni.nimh.nih.gov) and included slice timing correction, realignment, spatial smoothing followed by generation of PSC maps<sup>[17]</sup>. Subsequently, a Region of Interest (ROI) analysis was carried out using MIPAV (mipav.cit.nih.gov) (Medical Image Processing, Analysis and Visualization) software. For each patient, two independent raters [JJ (a board-certified neuroradiologist with 14 years of neuroimaging experience) and DZ (an imaging scientist with a PhD in functional imaging and 3 years of postdoctoral neuroimaging experience)] selected on the high resolution T1 MPRAGE images a ROI that included the tumor entirely, defined as the entire hypointense component. This ROI encompassing the entire lesion shall be referred to as the “ipsilesional ROI.” This T1 hypointense region corresponded exactly to the areas of tumor T2/FLAIR hyperintensity seen on other sequences acquired as part of the overall clinical fMRI examination, but T1 MPRAGE images were selected for ROI delineation because of their higher resolution compared to the standard FSE T2 and T2 FLAIR sequences. A mirror homologous contralateral hemispheric (referred to as “contralesional”) ROI was generated in a semi-automated fashion, with particular attention paid to trying (to the greatest extent possible) to ensure a similar degree of contribution from gray and white matter structures in the contralesional ROI as in the ipsilesional ROI, considering the degree of anatomic distortion resulting from the tumor. The following metrics were then calculated: a normalized rCBV ( $nCBV$ ), expressed as the ratio between the mean rCBV value (of all included voxels) in the ipsilesional ROI and the mean rCBV value in the contralesional ROI; a similarly computed normalized rCBF ( $nCBF$ ), defined as the ratio between the mean rCBF value in the ipsilesional ROI and the mean rCBF value in the contralesional ROI; a normalized PSC ( $nCVR$ ) expressed as the ratio between the mean BOLD PSC in the ipsilesional ROI and the mean BOLD PSC in the contralesional ROI.

Correlation analysis was performed between  $nCBV$  and  $nCVR$  as well as between  $nCBF$  and  $nCVR$ . Mean values among the raters were used. A one sample Wilcoxon test was also performed to assess whether the PSC normalized ratio was significantly lower than 1.0. An identical statistical test was also performed on  $nCBV$  and  $nCBF$  to determine whether there were any significant differences in perfusion metrics



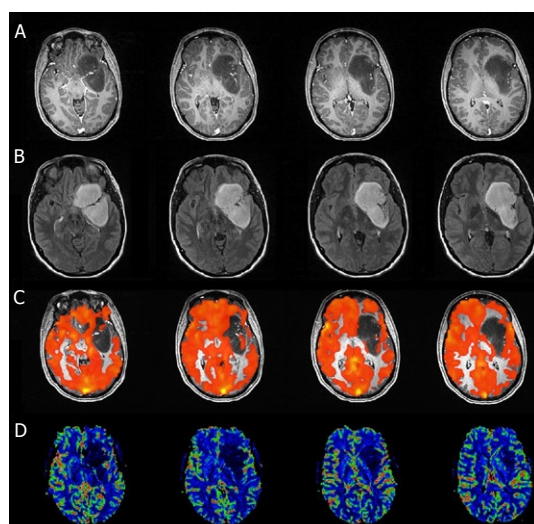
**Figure 1** Axial T1 postcontrast 3D MPRAGE and T2 FLAIR images (A and B) breath-hold cerebrovascular reactivity maps (C) and relative cerebral blood flow maps (D) in a patient presenting with a left frontal lobe lesion, classified as grade II oligoastrocytoma after surgical resection, are displayed. Breath-hold cerebrovascular reactivity (BH CVR) maps were fused with axial T1 post Gadolinium images, and the threshold was set to 0.35 for blood oxygen level dependent PSC. Decreased CVR is present within and at the anterosuperolateral margin of the lesion (involving the infiltrated cortex of the left superior frontal gyrus) relative to contralateral hemispheric normal tissue. This represents an area of tumor-induced neurovascular uncoupling. Perfusion imaging did not provide equivalent information because the same area does not demonstrate any definite regional perfusion abnormality.

between the ipsilesional and contralesional ROIs. Statistical analysis was performed using OriginPro 8.0 software.

## RESULTS

T1 MPRAGE and T2 FLAIR images, perfusion maps and BH PSC maps for two cases are shown in Figures 1 and 2. Reduced PSC is clearly visible in the ipsilesional ROI compared to the contralesional ROI, whereas in both cases the lesion appears iso-perfused relative to the contralesional ROIs. Intraclass Correlation Coefficients (ICC) among the raters were excellent (0.88 for  $nCVR$ , 0.98 for  $nCBV$ , 0.98 for  $nCBF$ ). In this group of 7 patients, none of the cases demonstrated a  $nCVR$  that was greater than 1.0 (Figure 3A). The fact that all 7 cases demonstrated  $nCVR$  values less than 1.0 indicated that every one of the LGG cases demonstrated abnormally decreased CVR in the ipsilesional ROI compared to the contralesional ROI, suggesting a high risk of NVU in all cases in areas of cortex where regionally decreased CVR were noted. Correlation with the patients' clinical status confirmed that these areas of regionally decreased cortical CVR corresponded to areas of actual NVU, since preservation of residual motor and language function was noted clinically despite absent expected task-based activation in these regions of decreased CVR on task-based fMRI activation maps obtained as part of the concurrent clinical fMRI examinations. Based on group

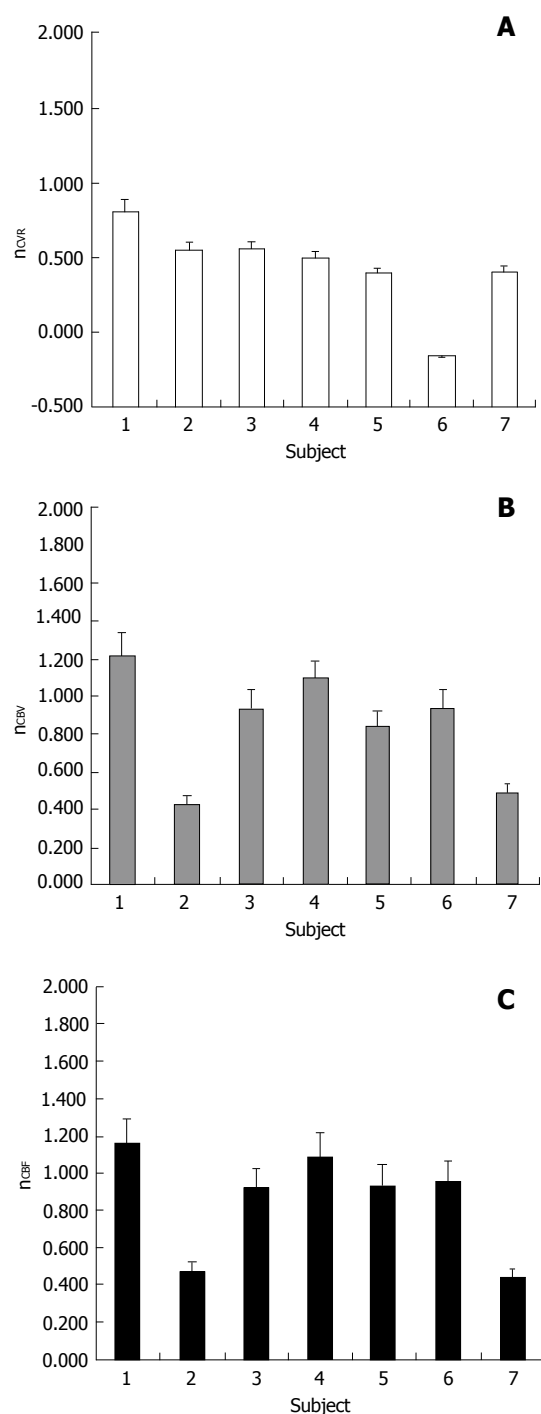




**Figure 2** Axial T1 postcontrast 3D MPRAGE and T2 FLAIR images (A and B), breath-hold cerebrovascular reactivity maps (C) and relative cerebral blood flow maps (D) in a patient presenting with a left hemispheric lesion, classified as pilocytic grade I astrocytoma after surgical resection, are displayed. Breath-hold cerebrovascular reactivity (BH CVR) maps were fused with axial T1 post Gadolinium images, and the threshold was set to 0.45 for blood oxygen level dependent (BOLD) signal. Decreased CVR is present within the lateral margin of the lesion (involving the adjacent cortex of the left superior temporal gyrus) relative to contralateral hemispheric normal tissue. This represents an area of tumor-induced neurovascular uncoupling. Perfusion imaging did not provide equivalent information because the same area does not demonstrate regional perfusion abnormality.

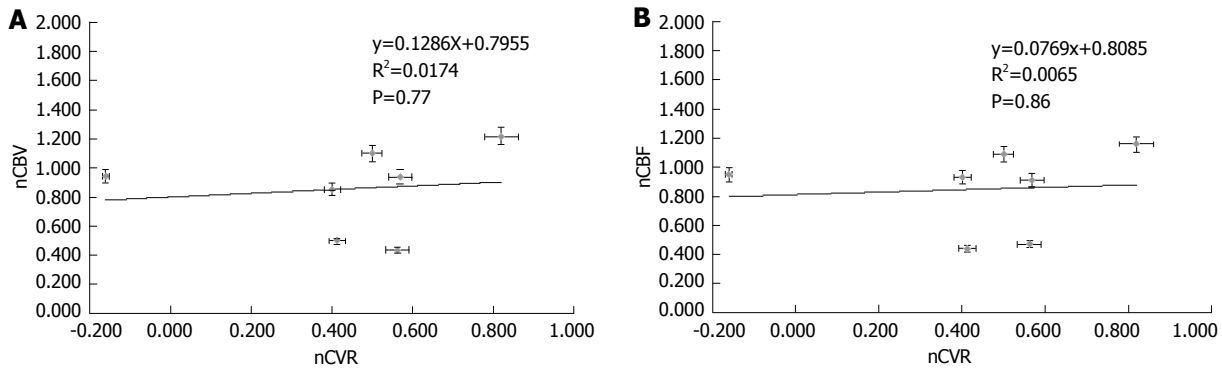
analysis, the overall distribution of  $n_{CVR}$  in this cohort of patients was statistically significantly lower than 1.0 (median = 0.50,  $z = -2.28$ ,  $P = 0.01$ ).  $n_{CBV}$  (median = 0.94,  $z = -0.92$ ,  $P = 0.375$ ) and  $n_{CBF}$  (median = 0.93,  $z = -1.16$ ,  $P = 0.25$ ) were not significantly higher or lower than 1.0 at a group level, indicating the absence of any substantial hyperperfusion or hypoperfusion in the ipsilesional ROI compared to the contralesional ROI (Figure 3B and C). We did not find any significant correlation between the perfusion and CVR metrics (Figure 4A and B), indicating that perfusion imaging by itself is not a valid predictor of vascular reactivity, and therefore an indicator of NVU in this particular cohort of LGG patients.

The use of a semi-automated approach to contralesional ROI placement helped to ensure that similar contributions to the contralesional ROI from gray and white matter structures were obtained as in the ipsilesional ROIs. This avoided spuriously high contralateral perfusion and CVR values related to greater contributions from normal gray matter in the contralesional ROIs. This was especially important considering that all of the lesions were gliomas, and as such involved mostly white matter rather than cortical gray matter. None of the 7 LGGs demonstrated any appreciable contrast enhancement on Gadolinium-enhanced T1 weighted images, and none demonstrated any internal areas of necrosis by histopathology or imaging features, although some very small regions of internal cystic change were noted in some of the oligodendrogliomas in this group. It is im-



**Figure 3** Cerebrovascular reactivity ratio ( $n_{CVR}$ ) (A), cerebral blood volume ratio ( $n_{CBV}$ ) (B) and cerebral blood flow ratio ( $n_{CBF}$ ) (C) distribution for the group of seven patients with classified grade I and grade II tumors included in this study. In all cases  $n_{CVR}$  is less than 1.0 and the median value is significantly less than 1.0 according to the one sample Wilcoxon test.  $n_{CBV}$  and  $n_{CBF}$  median values are not significantly lower or higher than 1.0.

portant to note that no internal necrosis or enhancement was present, since such features may result in spuriously decreased or increased mean perfusion, respectively, in ipsilesional ROIs. In the patients with oligodendrogliomas in our cohort, the known propensity toward relatively higher tumor perfusion than comparable low grade astrocytomas is balanced by propensity for internal cystic



**Figure 4** Normalized relative cerebral blood volume ratio ( $n_{CBV}$ ) vs normalized cerebrovascular reactivity ratio ( $n_{CVR}$ ) (A) and normalized relative cerebral blood flow ratio ( $n_{CBF}$ ) vs normalized CVR ratio ( $n_{CVR}$ ) (B) in our cohort of low grade gliomas. As described in the Methods section, these normalized ratios were calculated by dividing the mean voxel values obtained in ipsilesional regions of interest (ROIs) by those obtained in mirror contralateral ROIs. Neither  $n_{CBF}$  nor  $n_{CBV}$  demonstrated significant inverse correlation with  $n_{CVR}$  in this LGG group. LGG: Low grade gliomas; CVR: Cerebrovascular reactivity

change, thus not resulting in overall mean voxel hyperperfusion within the ipsilesional ROIs. By using overall mean perfusion metrics computed from all voxels within the ROI rather than simply voxels with maximal perfusion metrics within the ROI, we avoided the risk of spuriously high perfusion values contributing to artifactually high perfusion ratios.

## DISCUSSION

All of the LGG cases in our study demonstrated reduced CVR in the tumor (i.e., ipsilesional) ROI compared to the normal contralateral hemispheric mirror (i.e., contralateral) ROI. Such regionally abnormally reduced CVR, despite the presence of clinically intact, albeit impaired, motor or language function in all of these patients is direct evidence of tumor-related NVU. The fact that no substantial corresponding regional perfusion abnormality was present in any of these cases is reflected in the absence of significant correlation between the normalized (i.e., ipsilesional to contralateral) perfusion ratios and normalized CVR ratios. The absence of tumor hyperperfusion is expected in this cohort of LGG, since such tumors, unlike HGG, are not associated with angiogenesis<sup>[18,19]</sup>. Although reports of NVU associated with hyperperfusion in HGG exist in the literature<sup>[20,21]</sup>, few reports of NVU related to LGG exist<sup>[22,23]</sup>. We have shown in our study that the phenomenon of NVU, as detected by regionally decreased CVR, in LGG is much more prevalent than previously thought<sup>[24]</sup>. We have also shown the clinical feasibility of the performance of such BH CVR mapping in such a patient population. Our results suggest that BH CVR mapping should be considered in all brain tumor patients regardless of tumor grade.

The coupling mechanism between neuronal firing and blood flow changes results from a complex sequence (which we can consider as the NVU cascade) of cellular, metabolic and vascular processes involving neurons, glial/astrocytic components, neurotransmitters, chemical mediators and eventually vascular smooth muscle cells. The currently accepted explanation is that during neuro-

nal activity, synaptic release of neurotransmitters, such as glutamate, that bind to receptors on other neurons, may trigger the secondary release of vasodilatory mediators such as nitric oxide, which in turn increase CBF and CBV. These neurotransmitters such as glutamate can also act on astrocytes through different receptors, thus resulting in the release of compounds such as arachidonic acid and prostaglandin E2, which in turn result in vasoconstriction or vasodilatation, respectively, by acting on arteriolar smooth muscle<sup>[25]</sup>. It is possible that while in HGG, aberrant neovascularity with abnormal permeability and vasoactivity may be primarily responsible for the NVU, in LGG, abnormal astrocytic function or dysfunction involving other elements of the NVU cascade may be responsible. However, little is known about the pathophysiologic mechanisms underlying such NVU in LGG.

The need to detect NVU, when present, is critical in the interpretation of clinical fMRI examinations because regional cortical NVU will result in an inability to elicit BOLD activation in the affected cortex regardless of the nature of the particular fMRI task performed. Thus, false negative activation in these cortical regions may result during performance of sensorimotor, visual, language or other cognitive tasks that are expected to activate such regions based on a priori knowledge of functional anatomy. Such false negatives may not only result in incorrect language lateralization, but also incorrect localization or underestimation of the true extent of localization of eloquent cortex, as well as possibly incorrect inferences regarding tumor-induced cortical functional reorganization<sup>[11]</sup>. Such erroneous interpretations of task-related fMRI activation maps can result in unexpected and tragic postoperative neurological deficits related to inadvertent resection of eloquent cortex that is “BOLD-silent” directly due to NVU. The added value of BH CVR mapping in this setting lies in the additional confidence in assignment of function to areas of activation on fMRI maps in cases where no regional CVR abnormality results, as well as in proper exercising of caution in cases where functional activation is expected on a particular task in a particular cortical region where absent activation

is seen on task-based fMRI with corresponding abnormally decreased regional CVR. In the latter case, such as in this LGG cohort, one needs to acknowledge the limitation of clinical fMRI and needs to inform the referring neurosurgeon that complementary intraoperative electrophysiologic mapping will be necessary to exclude eloquent cortex in these regions of impaired CVR adjacent to or within the LGG. Such knowledge is very useful, in our clinical experience, in neurosurgical planning as well as in counseling of patients regarding the potential risks of tumor resection.

Thus, in conclusion, although our results are preliminary and based on a fairly small sample size, they suggest that BH CVR mapping in patients with LGG is both clinically feasible and capable of detecting NVU, which is a critical limitation of clinical fMRI. We furthermore note an unexpectedly high prevalence of NVU in LGG, suggesting that NVU is a commonly encountered phenomenon in brain tumors of all grades, and not just in HGG as previously thought.

## COMMENTS

### Background

Cerebrovascular reactivity (CVR) mapping using a breath-hold (BH) technique is a method of evaluating how responsive the microvasculature in the brain is to external stimuli. Although the mechanism for BH CVR mapping is related to transient mild increases in pCO<sub>2</sub> (i.e., hypercapnia), resulting in vasodilatation, this can be applied to the evaluation of standard clinical blood oxygen level dependent (BOLD) functional MRI (fMRI) examinations, where sensorimotor, visual or language/cognitive stimuli result in transient blood flow changes in brain microvasculature adjacent to activated neurons. If CVR is impaired for any reason, such as aberrant tumor neovascularity or astrocytic dysfunction due to tumor infiltration, then no BOLD response is possible on standard clinical fMRI activation studies because the BOLD response relies on intact CVR.

### Research frontiers

It has been determined that CVR is impaired within or adjacent to low grade gliomas (LGG), thus compromising our ability to accurately map eloquent cortex for surgical planning using fMRI. It has already been established that such impaired CVR is present in high grade gliomas (HGG) due to tumor angiogenesis as reflected in hyperperfusion on MR perfusion imaging.

### Innovations and breakthroughs

Very little is currently known about CVR in LGG. Most of the work to date relating to CVR mapping in brain tumor patients relates to applications in HGG. It is clear that tumor hyperperfusion, as detected on T2\* DSC (standard clinical) MR perfusion imaging, is related to tumor angiogenesis, but in LGG, angiogenesis typically does not occur. Astrocytic dysfunction, however, is known to occur due to tumor infiltration and primary astrocytic and/or oligodendrocyte involvement by all LGGs.

### Applications

The findings of a high prevalence (100% in our cohort) of abnormal CVR in LGG is of immense clinical value, because this is a potentially serious limitation of standard clinical BOLD fMRI examinations that may result in false negatives which adversely impact surgical planning. The recognition of this pitfall of fMRI is critical for proper surgical planning and counseling of patients prior to surgical resection of LGG. Further studies with larger sample sizes will need to be performed to evaluate the true prevalence of such findings in LGG of different histologic subtypes.

### Terminology

Cerebrovascular reactivity mapping and BOLD fMRI have been described in the Background section above. BOLD fMRI is a method of noninvasively evaluating sensorimotor, visual, language and other cognitive functions and mapping eloquent cortical regions prior to neurosurgical intervention, particularly in brain tumor patients and patients with other conditions such as epilepsy.

## Peer review

The manuscript is well written and authors are reporting a valuable research. Methods and material section is well described and results are defined well.

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