

## Contrast Dose Dependence of Arterial-Venous Overlap in High-Grade Glioma

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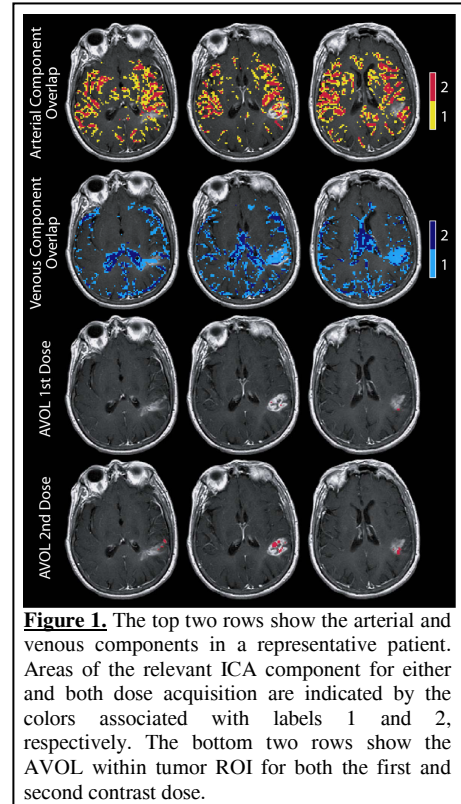
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**INTRODUCTION** High-grade (WHO III-IV) gliomas are malignant brain tumors whose high vascularity provides a focus for qualitative and quantitative characterization with medical imaging<sup>1</sup>. Dynamic susceptibility contrast MRI (DSC-MRI) is perfusion imaging technique where images are dynamically gathered during a rapid bolus dose of contrast agent. Voxel time-series are quantitatively modeled to measure perfusion metrics of tumor vascularity. The introduction of a second contrast bolus has been shown to compensate for an underestimation of tumor vascularity<sup>3,4</sup> caused by contrast leakage into tumor<sup>2</sup>. Independent Component Analysis (ICA) objectively separates major sources of variance in dynamically acquired

MRI data. Applied to DSC data, it has been shown that areas classified by ICA as both arterial and venous (Arterio-Venous Overlap or AVOL) occur in greater proportion within tumor than normal tissue<sup>5</sup>, and that the change in the volume of AVOL within tumor predicts overall survival following treatment with bevacizumab<sup>5</sup>. These recent studies have shown that AVOL has potential value as a non-invasive imaging biomarker for brain tumor vasculature.

Previous AVOL studies have been performed on data gathered during the second contrast dose to alleviate leakage effects. This study measures leakage effect on the AVOL biomarker, and tests whether the second dose is required to utilize this effective biomarker. We first hypothesized that contrast agent leakage in high-grade glioma during the initial dose would generate enough signal variance within brain tumor, that the ICA algorithm would classify leakage as an additional component (not arterial or venous). Second, we hypothesized that the regions of enhancing tumor contain more overlapping arterial and venous contributions (AVOL) in the second dose than in the first dose due to the substantially reduced contrast leakage in the second dose.

**METHODS** Ten patients with high-grade gliomas were enrolled in the study. DSC imaging was gathered during two doses of contrast agent. Between these two doses, conventional post-contrast T1-weighted imaging was obtained. The same DSC imaging parameters were used for both acquisitions<sup>4</sup>. DSC data was then processed using probabilistic ICA as implemented in MELODIC<sup>6</sup>. Three components were extracted from each DSC acquisition. Two independent observers identified arterial, venous, and leakage components based on neuroanatomical landmarks<sup>7</sup>, utilizing the T1+Contrast (T1+C) scan as a reference underlay. A consensus was reached in cases of disagreement. AVOL maps were created by identifying voxels statistically thresholded in both the arterial and venous components. These maps were then masked by a contrast enhancement region of interest manually drawn on T1+C acquisitions acquired in the same slice prescription as the DSC data using AFNI<sup>8</sup>. The percentage of



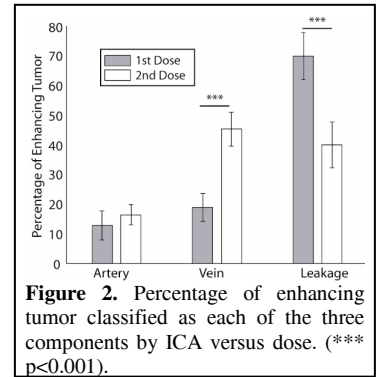
**Figure 1.** The top two rows show the arterial and venous components in a representative patient. Areas of the relevant ICA component for either and both dose acquisition are indicated by the colors associated with labels 1 and 2, respectively. The bottom two rows show the AVOL within tumor ROI for both the first and second contrast dose.

enhancing tumor occupied by each individual independent component was calculated and compared across the two time points. The percentage of AVOL within enhancing tumor was calculated for each dose. Statistical comparisons were made between doses using paired t-tests.

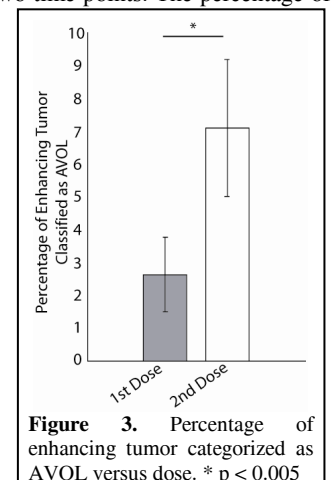
**RESULTS** Figure 1 illustrates the overlap of a representative patient's arterial and venous ICA components between dose, as well as the AVOL maps for each dose within enhancing tumor. Figure 2 compares the percentage of tumor occupied by each of the three ICA components for the first and second doses. As illustrated, the data supports our initial hypothesis that the "leakage" component would be significantly more prevalent in tumor during the first dose scans than the second dose scan ( $p < 0.001$ ). Figure 3 illustrates that the percentage of enhancing tumor occupied by AVOL is significantly different when comparing the first and second dose scans ( $p < 0.005$ ). This data supports our second hypothesis that the ability of ICA to distinguish AVOL is significantly compromised by the contrast leakage effects within tumor.

**DISCUSSION** Our study finds that contrast agent leakage confounds the AVOL biomarker. We find that leakage causes such a significant source of variance in first contrast dose that the ICA algorithm classifies it as an additional component. This variance occurs preferentially in the tumor margin due to the presence of "leakier" vasculature, causing ICA to model the majority of tumor as its own component. The variance caused by leakage effectively masks the vasculature within the tumor margin, and leads to an underestimation of venous ICA component and arterio-venous overlap (AVOL) inside tumor. Acquiring DSC data after administration of a second contrast dose significantly mitigates the contrast leakage effect, and results in a larger portion of AVOL within enhancing tumor. **ACKNOWLEDGEMENTS** Funding: NIH/NCI R01 CA082500, Advancing a Healthier Wisconsin Partnership Program.

**REFERENCES** 1. Louis DN, et al. *Acta Neuropathol* 2007;114(2):97-109. 2. Boxerman JL, et al. *AJNR Am J Neuroradiol* 2006;27(4):859-867. 3. Hu LS, et al. *AJNR Am J Neuroradiol*;31(1):40-48. 4. Paulson ES, et al. *Radiology* 2008;249(2):601-613. 5. LaViolette P.S. *Neurooncology In Press*. 6. FMRIB Tool Library 7. LaViolette PS, et al. *Proc ISMRM, Melbourne, Australia* 2012. 8. AFNI.nimh.nih.gov/AFNI



**Figure 2.** Percentage of enhancing tumor classified as each of the three components by ICA versus dose. (\*\*\*)  $p < 0.001$ .



**Figure 3.** Percentage of enhancing tumor categorized as AVOL versus dose. \*  $p < 0.005$