Quantitative Perivascular Space Analysis at 7T: Exploring a Potential Biomarker for Epilepsy

Jack Rutland[1,2], Lara Marcuse[3], Madeline Fields[3], Brad Delman[2], Priti Balchandani[2], Rebecca Feldman[2]

[1]Wake Forest University, [2]Radiology, Icahn School of Medicine at Mount Sinai, New York, New York, United States, [3]Department of Neurology, Mount Sinai Hospital, New York, New York, United States

Introduction: Epilepsy is a chronic condition, affecting approximately 150,000 in the U.S. (Epilepsy Foundation). Of those afflicted, 15%-30% are refractory, incompletely responsive to pharmacotherapy [1,2]. In many cases, surgery to resect abnormal tissue is the best treatment option, and is most frequently undertaken when a lesion can be identified on a pre-surgical magnetic resonance imaging (MRI) scan that is concordant with EEG and semiology. However, many patients still appear non-lesional on their clinical MRIs. In these cases, conventional imaging is unsuccessful in identifying distinct lesions co-localized with the suspected seizure onset zone (SOZ). Biomarkers can help identify epileptogenic tissue in these nonlesional patients. Ultrahigh field MRI scanners, such as those operating at 7 Tesla (7T) enable higher resolution and contrast in images and permit more effective visualization of small cerebrospinal fluid-filled holes in the white matter of the brain called perivascular spaces (PVSs). Distribution of PVSs may be influenced by conditions such as epilepsy, and could assist in localization of the SOZ in the epileptic brain. To test this, we investigated the distribution of PVSs in the brains of non-lesional epilepsy patients in comparison to the distribution in healthy controls. We also compared the location of PVSs to the subject's suspected SOZ, as determined by semiology and EEG.

Methods: The axial T_2 TSE images (TR 6000 ms, TE 69 ms, voxel 0.4x0.4x2.0mm^3) was obtained on a 7T MAGNETOM scanner (Siemens, Erlangen) as part of a longer epilepsy imaging protocol and used for the identification of perivascular spaces. The images of 10 age and gender-matched non-lesional epilepsy patients (Mean age = 32.4± 6.4 years) and 10 normal healthy subjects (Mean age = 34.7±6.1years) were examined using Osirix software (Pixmeo, Geneva) and prominent PVSs where manually marked (PVS diameter > 0.5mm). 16 common anatomical landmarks were identified in each brain and used to divide the brain into 7 regions as shown in Figure 1. The asymmetry index (AI), weighted by the area of perivascular spaces in the right and left of each region was calculated as $AI = \frac{abs\,(S_r - S_l)}{\frac{1}{2}(S_r + S_l)}$ where S_l and S_r are the sum of the perivascular spaces on the left and right side of each region (respectively) weighted by using $S_j = \sum_{i=1}^{N_{region}} d^2$. N_{region} is total number of PVSs in each region and d_i is the diameter of each individual PVS. AI_{max} , the largest AI calculated from each of the 7 regions in the volunteer's brain. A paired Student's t-test was performed to compare the maximum asymmetry in epilepsy subjects to healthy controls. Finally, the side with the greatest PVSs in the region of greatest asymmetry was compared to the sidedness of the suspected SOZ in the epilepsy subjects.

Results/Discussion: Comparison of the average AI's for each brain region showed no significant difference between epilepsy subjects and controls when analyzed individually, as shown in Figure 2. This is not unexpected, as the SOZ varied between subjects and any localized effect would have been lost in the overall averages. However, the mean AI_{max} (last bar in Figure 2), in epilepsy subjects (mean AI_{max} = 1.0±0.4) is significantly greater than controls (mean AI_{max} = 0.67±0.31) (p = 0.012). Table 1 compares the sidedness of the perivascular spaces (the side on which the greatest number of perivascular spaces exist in the region of AI_{max}) to the suspected SOZ, as determined by EEG and semiology in the 9 out of 10 epilepsy subjects where the SOZ was localized to one side of the brain. In 7 out of these 9 subjects there was a prominence of PVSs contralateral to the suspected SOZ with a high AI_{max} (mean AI_{max} = 1.07 ± 0.44). In 2 out of 9 subjects, the most prominent PVSs were ipsilateral to the suspected SOZ. In these two cases the AI_{max} was lower (AI_{max} = 0.48 and 0.54), and closer to the value seen in controls. These findings suggest that greater asymmetry in the distribution of PVSs exists in patients with epilepsy when compared to healthy controls, and that prominent PVSs are more common contralateral to the suspected SOZ. These findings suggest that PVSs are potential neurological biomarkers of epilepsy and can provide valuable information in localizing SOZ and could assist in surgical treatment for MRI-negative subjects with refractory epilepsy. Future work includes performing this analysis in a larger group of patients and controls and using automated methods of detection for PVSs.

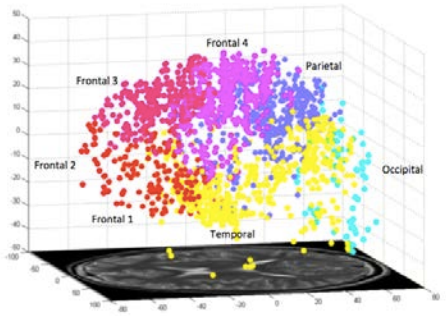

Figure 1. Perivascular Space Distribution. This figure displays the manner in which perivascular spaces were mapped and registered on a coordinate system in one of the epilepsy subjects in this study.

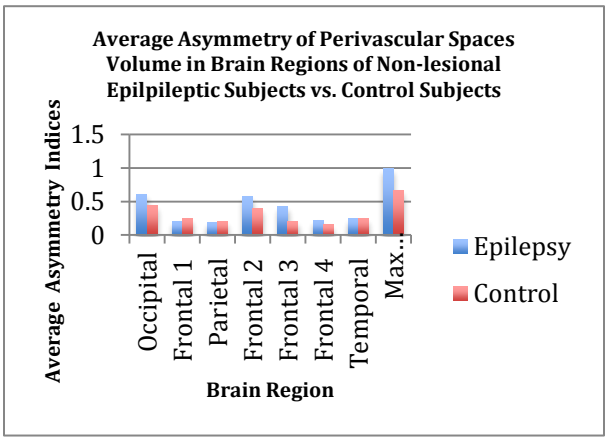

Figure 2. Average Asymmetry of Perivascular Space Volume in Brain Regions of Non-lesional Epileptic Subjects vs. Control Subjects. This graph displays the average asymmetry associated with each of the 7 brain regions for the epileptic subjects compared to the average asymmetry associated with each of the 7 brain regions for the healthy control subjects. The average maximum asymmetry value is also included in this figure.

	Sidedness of PVS (region of greatest AI)		
SOZ		Left	Right
	Left	2	1
	Right	6	0

Table 1. Location of Asymmetry Relative to Location of Epilepsy. This chart shows the location of greater perivascular spaces compared to the SOZ in 9 of the epilepsy subjects.

References: [1] Kwan P, et al (2000) N Engl J Med 342(5):314-9 [2] Mattson R (1992) Epilepsy Res Suppl 5:29-35

Acknowledgments: NIH-NINDS R00 NS070821, Icahn School of Medicine Capital Campaign, Translational and Molecular Imaging Institute and Department of Radiology, Siemens Healthcare