Perfusion Weighted Imaging of Hyper-vascular Tumors: Implications for Blood Volume and Permeability Measurements.

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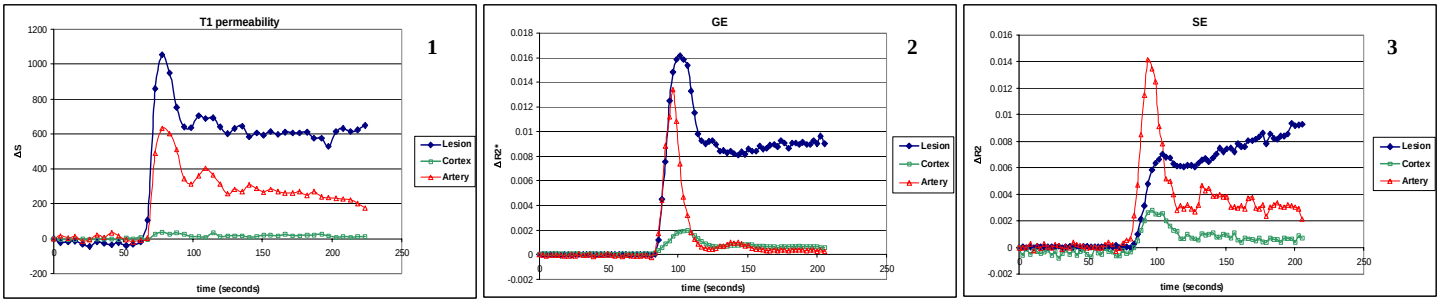
Introduction: Gradient-echo (GE) and Spin-echo (SE) Perfusion Weighted Imaging (PWI) as well as T1 permeability measurements have been used in brain tumor patients to assess tumor vascularity by providing estimates of blood volume, blood flow and permeability.[1] These techniques have been used primarily in the evaluation of glial tumors and there is little experience with other kinds of cerebral neoplasms. We report our findings in patients with Von Hippel Lindau and cerebral hemangioblastomas.[2] To our knowledge, there have been no other studies in the literature on the perfusion and permeability imaging of hemangioblastomas.

Methods: Five Von Hippel Lindau patients diagnosed with cerebral hemangioblastomas were imaged as part of an ongoing protocol of administration of anti-VEGF medication. The patients underwent examination on a 3T Siemens Trio Scanner (Siemens Medical Systems, Erlangen, Germany). Permeability measurements were undertaken using a 3D gradient echo sequence with the following parameters: FOV 192x192x60mm, matrix 128x64x20 with 30% slice oversampling, TR = 5.5ms, TE = 2.89ms, bandwidth 1090Hz/pixel and a 10 degree water excitation pulse. A 75% partial fourier sampling in both phase and slice directions gave a time per image of 5.2 seconds. 44 measurements were acquired with a bolus contrast injection of 0.1mmol/Kg at the 10th image using a power injector at a rate of 5mmol/sec. A subset of the patients was imaged with a similar T1 permeability sequence, but with a time per image of 11 seconds. The T1 weighted sequence was followed by a multislice interleaved T2* / T2 weighted EPI-sequence for PWI. The sequence parameters were: TR 1.3 sec, TE 34 ms (GE), 103 ms (SE), Slice thickness 5mm, Interslice gap 0mm, FOV 220x220, Matrix 128x128, Slices 10, Timepoints 80. An intravenous bolus of 0.3mmol/Kg Gd-DTPA was injected with a power injector at the 20th timepoint and at a rate of 5mmol/sec. ROIs were placed within the lesion, within a major cerebral artery and within normal cerebral cortex. T1 Signal Intensity curves, ΔR2* and ΔR2 changes with time were determined for each ROI.[3,4]

Results: The lesion T1 signal intensity followed that of the artery with a steep initial rise and a second recirculation peak (Figure 1). However, the lesion had a higher peak than the artery and the signal intensity did not gradually decrease like the vessel ROI but it also did not increase to suggest significant contrast accumulation due to a slow leak of Gd. The timecourse of the T1 sequence with 11 seconds per image was similar, but the timepoints were too far apart to well describe the speed of the enhancement. The ΔR2* curve of the lesion follows the steep rise of the arterial curve, but had a higher peak and larger width to the first pass (Figure 2). After the first pass, the lesion curve remains considerably above the baseline unlike the artery and cortex curves which return close to baseline. For the ΔR2 curve the initial rise is lower and slower than the artery and after a smaller first pass it continues to rise slowly until the end of the sequence (Figure 3). This subsequent slow rise was not pronounced in patients with very small lesions. The ΔR2* and ΔR2 curves cannot be used to assess permeability due to the previous injection of Gd for the T1 permeability study.



Discussion: The steep rise of the T1 and ΔR2* curves of the lesion when the contrast agent arrives suggests the existence of a large feeding artery. The higher peaks in the lesion compared to the artery in these curves suggest that in the volume sampled there was a larger volume of feeding vessels which would be expected in a tortuous arterial supply as compared to a single cross section of a normal cerebral artery. The lack of a slow rise in T1 signal intensity over time suggests little accumulation of Gd in the lesion due to a slow leak. The fact that the ΔR2* did not return to baseline suggests that Gd continues to circulate in the large total blood volume in the lesion with persistent T2* effects. The GE and SE perfusion imaging sequences are theoretically sensitive to a different population of vessels, GE to vessels of all sizes and SE to capillary-sized vessels. Therefore the ΔR2 slow rise might indicate the slow filling of small tortuous capillaries within the lesion. These findings are consistent with the known histopathology of hemangioblastomas which consist of a few large muscular arteries feeding the lesion, a large vascular volume with vessels of all sizes and a significant collection of very tortuous small capillaries (Figure 4). The endothelium is unlikely to have tight junctions like in the blood brain barrier, therefore we suspect that Gd did leak into the interstitial space, but it was not detectable in T1 time courses where the signal changes were dominated by the contrast within vessels. The time courses of these curves are unlike those in most glial tumors and therefore the typical models for permeability, relative blood volume and relative blood flow calculations are not valid. On the T1 signal intensity curve, the rapid increase of the signal intensity that is probably attributed to the rapid filling of large vessels and the lack of a slow rise later in the time course makes permeability calculations impossible. The failure of the ΔR2* and ΔR2 curves to return to near baseline makes estimates of rCBV and rCBF inaccurate. In summary the perfusion data provides information about the nature of the vasculature in hemangioblastomas and indicates that the current perfusion models used to calculate relative rCBV, rCBF and permeability are not valid for hypervascular lesions like the hemangioblastomas, and possibly not accurate for the very vascular parts of other more common neoplasms.

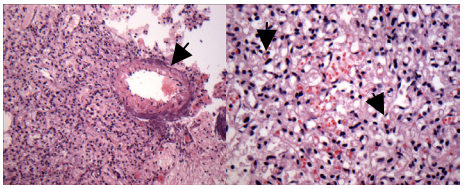


Figure 4. H&E stain of Hemangioblastoma: large muscular artery feeding the lesion on the left (arrow) and collection of capillaries that make up the bulk of the vasculature on the right (arrows).

References: 1. Covarrubias DJ, et al, Oncologist. 2004;9(5):528-37. 2. Lonser RR, et al, Lancet. 2003 Jun 14;361(9374):2059-67. 3. Sorensen AG, et al, Radiology. 1999 Feb;210(2):519-27. 4. Ostergaard L, et al, Magn Reson Med. 1996 Nov;36(5):726-36.

Acknowledgements: The National Center for Research Resources (P41RR14075), The Mental Illness and Neuroscience Discovery (MIND) Institute, and Mary T. Foley. Funding for imaging time by Novartis, Inc.