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Michael H. Lev and Leonardo Vedolin

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COMMENTARY

Permeability versus Cerebral Blood Volume Measurement in Brain Tumor Evaluation: Comparative Clinical Value and Advice to Authors

In this issue of the *AJNR*, 2 different methods of MR blood-brain barrier permeability evaluation—first-pass T2*-weighted susceptibility (fpT2*) and steady-state T1 (ssT1) weighted imaging—are compared to each other and to dynamic susceptibility relative cerebral blood volume (rCBV) maps, in both gliomas and meningiomas.[1] With fpT2*, the first-pass susceptibility effect of a standard gadolinium bolus is tracked on a pixel-by-pixel basis, by using a cine echo-planar gradient-echo technique during the initial 45–60 seconds of circulation. With ssT1, a lower dose of gadolinium is tracked (typically about 10% standard) by using a conventional T1-weighted sequence for a longer time period (5–10 minutes). With both methods, mathematical models are constructed on the basis of assumptions regarding tracer kinetics, resulting in maps of "K^{trans}"—the transfer coefficient, proportional to the permeability surface area product—a measure of the degree of endothelial permeability. The reliability of these maps is largely dependent on how well the assumptions fit reality. Cha et al conclude that K^{trans} values derived from both methods are "more predictive of glioma grade" than is rCBV and that—for gliomas but not meningiomas—the K^{trans} values from both methods are highly correlated.

These conclusions are noteworthy in several respects. Perfusion imaging, which considers the time course of contrast enhancement, has indisputable advantage over the static "snapshot" provided by routine postcontrast MR imaging. Despite this, and the implication of the word "conventional" in the title of Cha et al's manuscript, permeability imaging remains a research tool, used intermittently at a small number of centers. As such, the technical parameters of acquisition and postprocessing are not standardized, potentially limiting generalization of the study results. The devil is in the details—eg, is CBV mathematically corrected for leakiness, is an arterial input function measured or inferred? With permeability measurement, size matters: different tracers, including commercially available gadolinium chelates of varying molecular weight and charge, pass the blood-brain barrier differently, again limiting generalization, quantification, and comparison with prior studies. Indeed, nongadolinium tracers can be used to obtain MR permeability data. For example, magnetic iron oxide nanoparticles (MIONs) have recently been applied to noninvasively detect the autoimmune induced microvascular permeability changes of pancreatic islet cells that accompany the development of diabetes in mice.[2]

Moreover, the conclusion that the K^{trans} values derived from both methods are "more predictive of glioma grade" than is rCBV, although supported by the data (and of clear utility in drug trials), begs the question which of these techniques is the most clinically relevant. The answer is that it is the distinction between "low"-grade (WHO I/II) and "high"-grade (WHO III/IV) lesions that typically has the greatest impact on management and prognosis, rather than the distinction between anaplastic astrocytoma (WHO III) and glioblastoma multiforme (GBM; WHO IV). It is important to note that Cha et al's Fig 5 and Table 2 clearly demonstrate that it is rCBV—and not ssT1 or fpT2*—that in this small cohort most accurately distinguishes WHO grade II from grade III tumors. One wonders whether the statistically significant difference in mean K^{trans} between anaplastic astrocytoma and GBM can simply be attributed to the necrosis that, by definition, is present in GBM but not in lower-grade malignancy.

Implicit in Cha et al's report is the concept that ssT1 provides a more accurate measure of K^{trans}, by virtue of its longer temporal sampling of the contrast time course curve, than does fpT2*, but that fpT2* is more convenient. This does much to explain the reported poor correlation between K^{trans} values for highly permeable meningiomas (the "leakiness" of which may not be fully characterized by only 45–60 seconds of cine perfusion imaging) compared with the strong correlation for less-permeable gliomas. The fact, however, that even for gliomas, the calculated K^{trans} values are scaled differently for the 2 techniques (the slope of regression line is 0.5 in Fig 6*A*), underscores the point that these methods are not interchangeable.

The limitations discussed by Cha et al are instructive for future authors. Arguably the most important of these is the homogeneity of the study population: a heterogeneous cohort can unduly dilute the statistical power of the results. Specifically, the inclusion of mixed brain tumor histologies, notably low-grade oligodendrogliomas alongside astrocytomas, is known to confound the calculation of mean rCBV—and possibly K^{trans} as well—because of the "false-positive" high blood volume of many of these lesions.[3] With regard to image analysis, selection of maximally abnormal regions of interest is crucial to accurately mirror histologic findings. In another study, Provenzale et al sampled the mean highest permeability on 3 images through the tumor, as well as the single highest value of any region of interest within the tumor.[4] Also, because gray and white matter have different baseline perfusion values, it is important to distinguish these carefully when selecting regions of interest, particularly when they will be used for normalization of perfusion values to that of nonmalignant regions.

Finally, steroid use is an important confounder of both tumor permeability and blood volume measurement and must be noted when describing patient demographics. Even as early as 1 hour following administration, steroids can dramatically alter the K^{trans} and rCBV values of astrocytomas. One MR study revealed a mean gray matter reduction of 53% in blood-brain barrier permeability and 15% in rCBV at approximately 2.7 hours after treatment.[5] A PubMed search of all peer-reviewed, primary research articles published between 1990 and 2004 in which untreated human brain tumors were studied by using dynamic first-pass MR rCBV mapping surprisingly resulted in only 3 publications that had specifically investigated the effect of steroids on perfusion parameters and only 8 that had reported in their methods sections whether steroids had been administered to their study cohorts.

In conclusion, this article addresses a timely, novel, and potentially important topic - that of permeability imaging of brain tumors. For clinical trials in particular, the monitoring of K^{trans} as a surrogate marker for treatment response is likely to be valuable, especially because some tumor angiogenesis factors, among them vascular endothelial growth factor, double as potent permeability factors.[4]

Michael H. Lev and Leonardo Vedolin
Massachusetts General Hospital (M.H.L.)
Boston, Mass; and
Mae de Deus Hospital (L.V.)
Porto Alegre, Brazil

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